Blood and immune disorders

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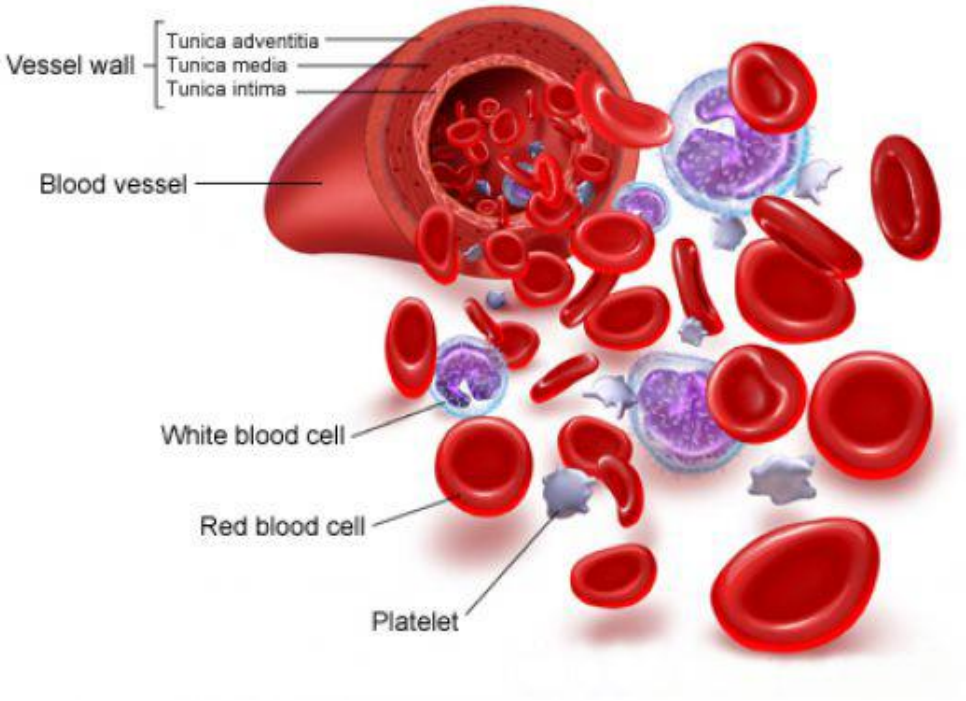
Blood

- 4-6 L
- Hematopoetic system



- Formed blood elements:
  - **Erythrocytes**
  - **Leukocytes**
  - **Thrombocytes (platelets)**

- pH 7.35-7.45

Plasma vs. Serum

- Blood clot
  - Blood cells + fibrin
  - yellow liquid = *serum*

- Anticoagulants:
  - heparin
  - citrate
  - EDTA

Li Heparin

K_3EDTA

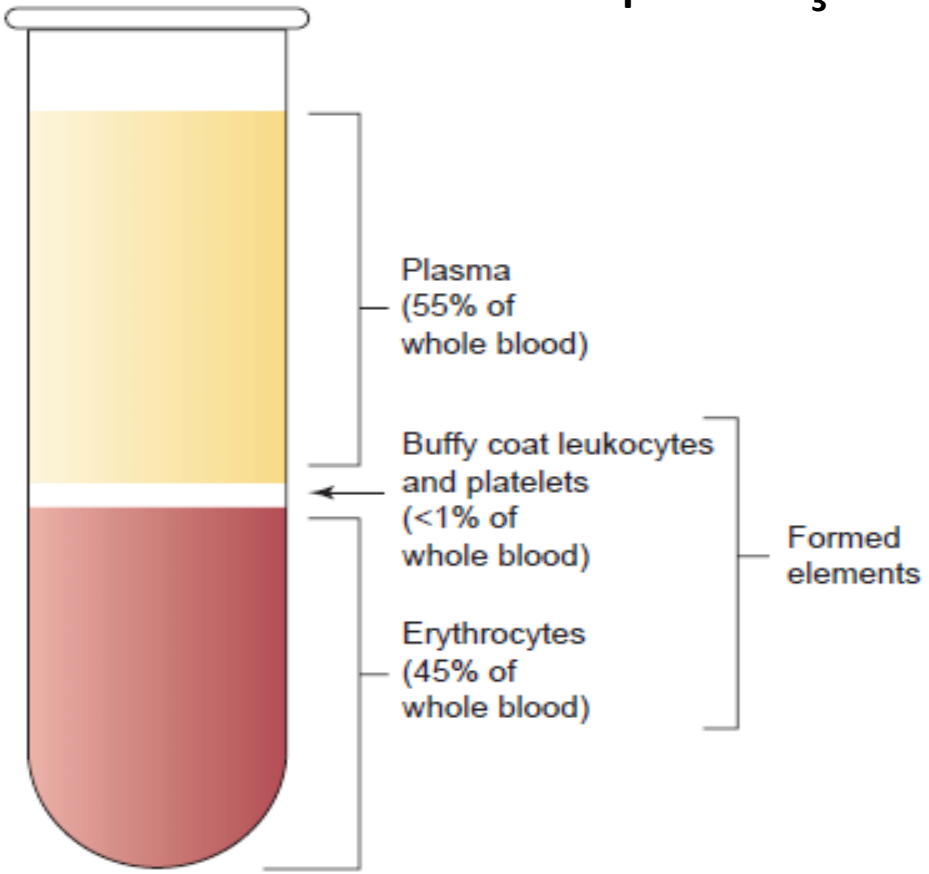


FIGURE 14-1 Layering of blood components in an anticoagulated and centrifuged blood sample.

Plasma

TABLE 14-1 Plasma Components

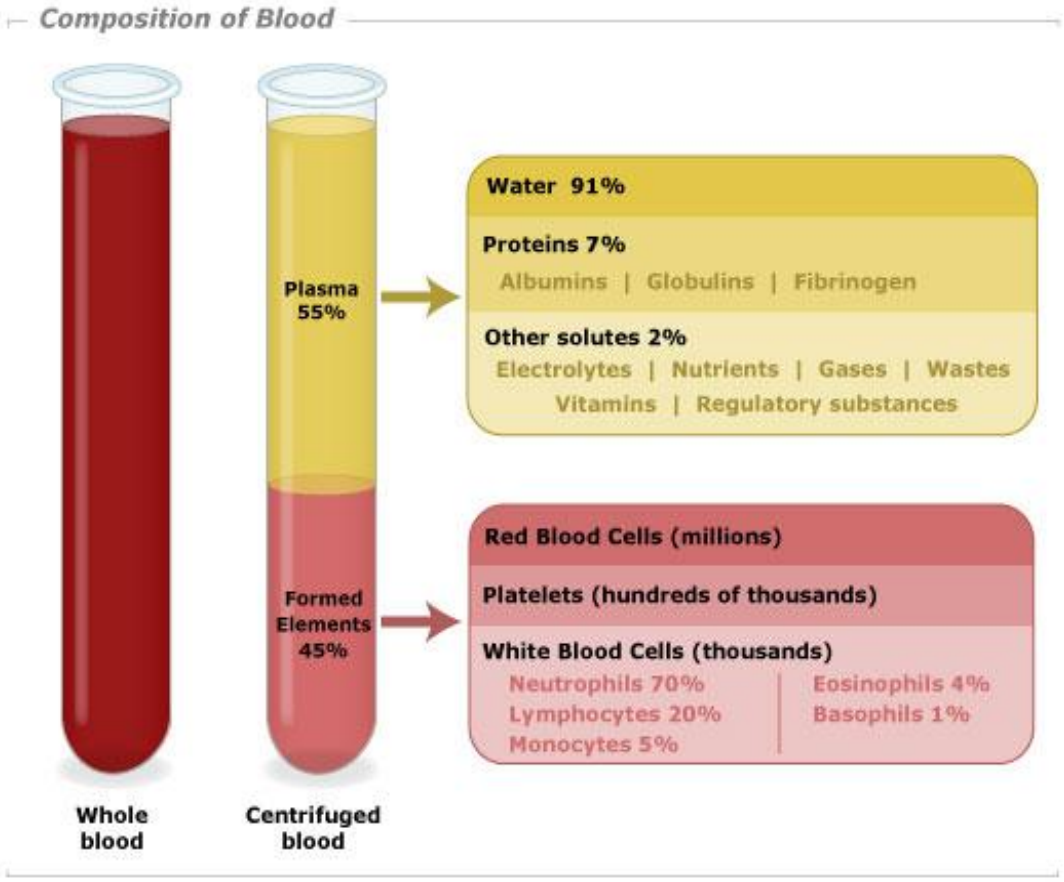
Plasma	Percentage of Plasma Volume	Description
Water	90–91	
Proteins	6.5–8	
Albumin		54% Plasma proteins
Globulins		38% Plasma proteins
Fibrinogen		7% Plasma proteins
Other substances	1–2	Hormones, enzymes, carbohydrates, fats, amino acids, gases, electrolytes, excretory products

Albumin

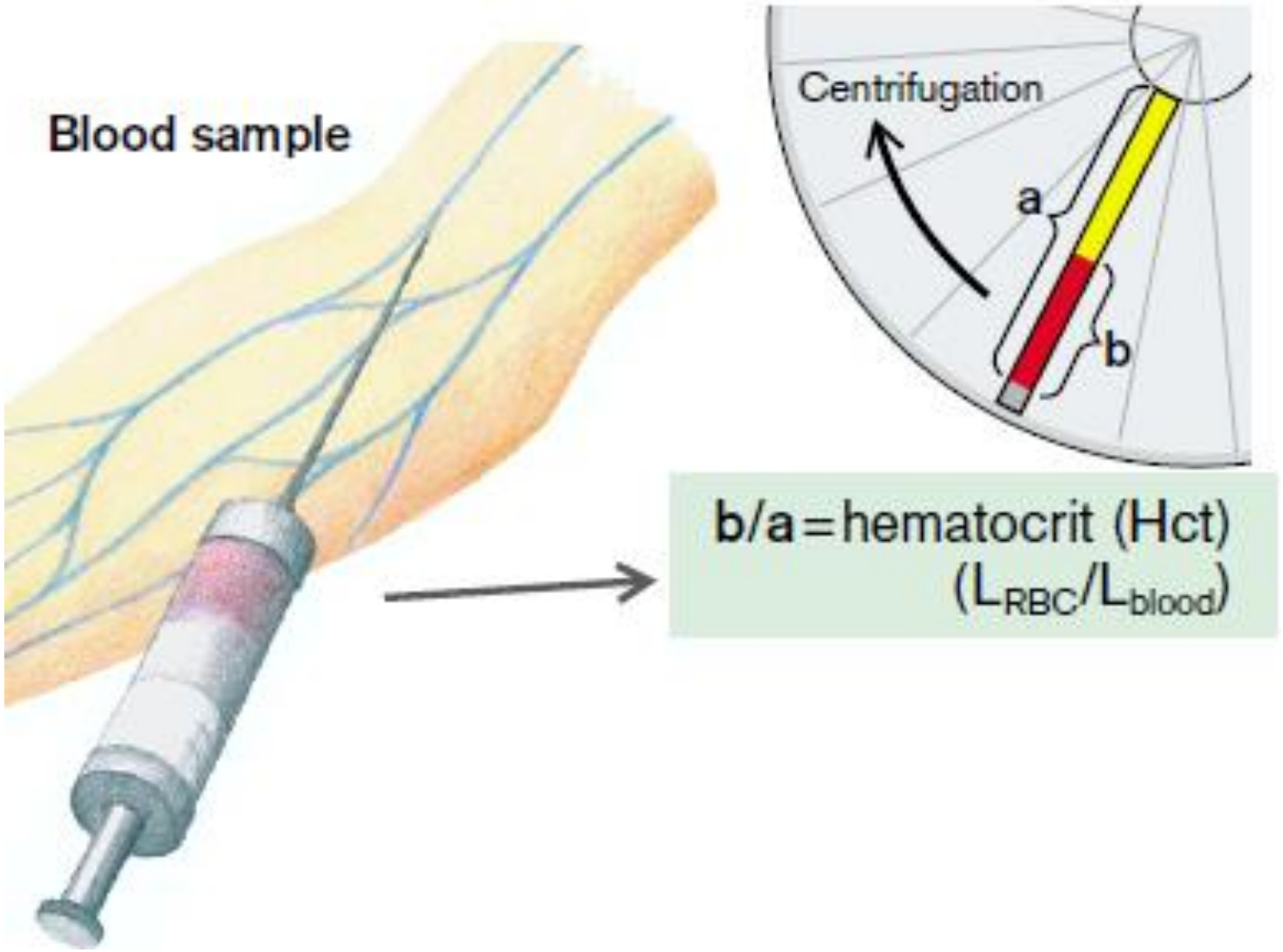
Globulins

- **alpha globulins**
- **beta globulins**
- **gamma globulins**

Fibrinogen



- **Hematocrit (Hct)**
- **♀:39±4%**
- **♂:44±5%**



Functions of the blood

- **Transport of various substances:**
  - gases: O2, CO2
  - nutrients
  - metabolic products
  - vitamins
  - hormones
- **Termoregulation**
- **Immune response**
- **Hemostasis**

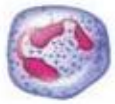
Regulation of hematopoiesis

- hormone-like growth factors = ***cytokines***

- production:
    - **bone marrow stromal cells**
    - **liver and kidney**

Hematopoietic growth factors (colony-stimulating factors: CSF)

1. **Erythropoietin**
2. **Granulocyte-monocyte colony-stimulating factor**
3. **Granulocyte colony-stimulating factor**
4. **Macrophage colony-stimulating factor**
5. **Thrombopoietin**

Cell Type	Illustration	Description*	Number of Cell per mm^3 (µl) of Blood	Duration of Development (D) and Life Span (LS)	Function
ERYTHROCYTES (red blood cells; RBCs)		Biconcave, anucleate disc; salmon-colored; diameter 7–8 µm	4–6 million	D: 5–9 days LS: 100–120 days	Transport oxygen and carbon dioxide
LEUKOCYTES (white blood cells, WBCs)		Spherical, nucleated cells	4800–11,000		
Granulocytes		Nucleus multilobed; inconspicuous cytoplasmic granules; diameter 12–14 µm	3000–7000	D: 7–11 days LS: 6 hours to a few days	Destroy bacteria by phagocytosis
• Neutrophils					
• Eosinophils		Nucleus bilobed; red cytoplasmic granules; diameter 12–15 µm	100–400	D: 7–11 days LS: about 5 days	Turn off allergic responses and kill parasites
• Basophils		Nucleus bilobed; large blue-purple cytoplasmic granules; diameter 10–14 µm	20–50	D: 3–7 days LS: a few hours to a few days	Release histamine and other mediators of inflammation
Agranulocytes		Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 µm	1500–3000	D: days to weeks LS: hours to years	Mount immune response by direct cell attack (T cells) or via antibodies (B cells)
• Lymphocytes					
• Monocytes		Nucleus U- or kidney-shaped; gray-blue cytoplasm; diameter 14–24 µm	100–700	D: 2–3 days LS: months	Phagocytosis; develop into macrophages in tissues
PLATELETS		Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 µm	150,000–500,000	D: 4–5 days LS: 5–10 days	Seal small tears in blood vessels; instrumental in blood clotting

Hemoglobin (Hb)

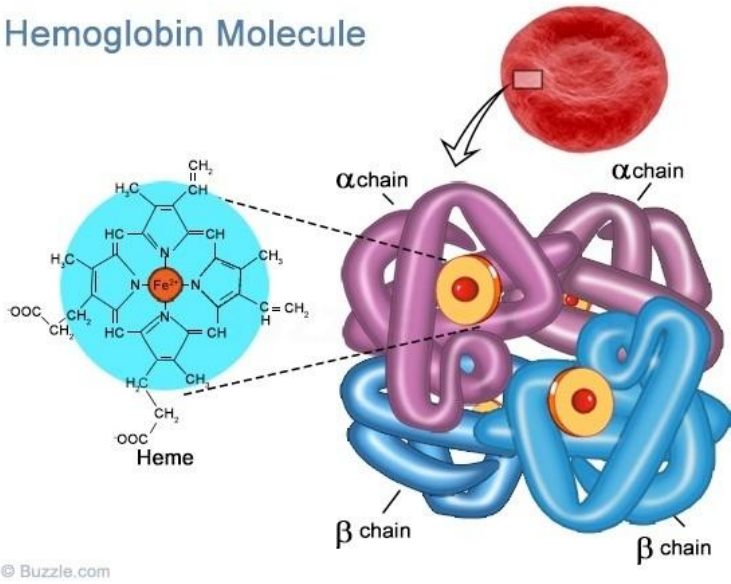
•an oxygen-carrying protein

•tetramer:
-2 types of subunits (α + β) - heme - Fe^{2+} atom

•oxygen-binding capacity: 1.34 mL O_2/g Hb

Hemoglobin A1: 2α and 2β subunits ($\alpha_2\beta_2$) – 97%.
Hemoglobin A2: 2α and 2δ (α2δ2) – 3%
Hemoglobin F: α2 and γ2 (α2γ2) – 1%

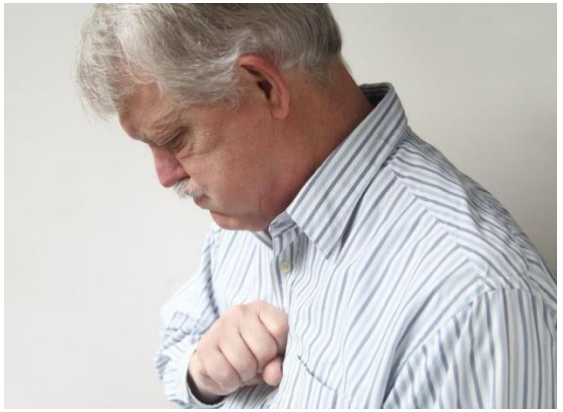
Concentration in blood: 130 – 160 g/l



Anemia

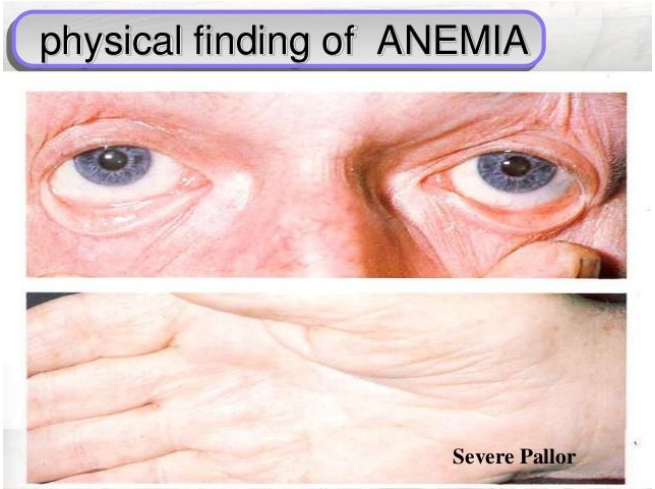
- a ↓ in the total amount of RBCs or Hb in the blood, or both
- lowered ability of the blood to carry O_2

- ♂: **Hb < 130-140g/L**
- ♀: **Hb < 120-130 g/L**



Anemic syndrome

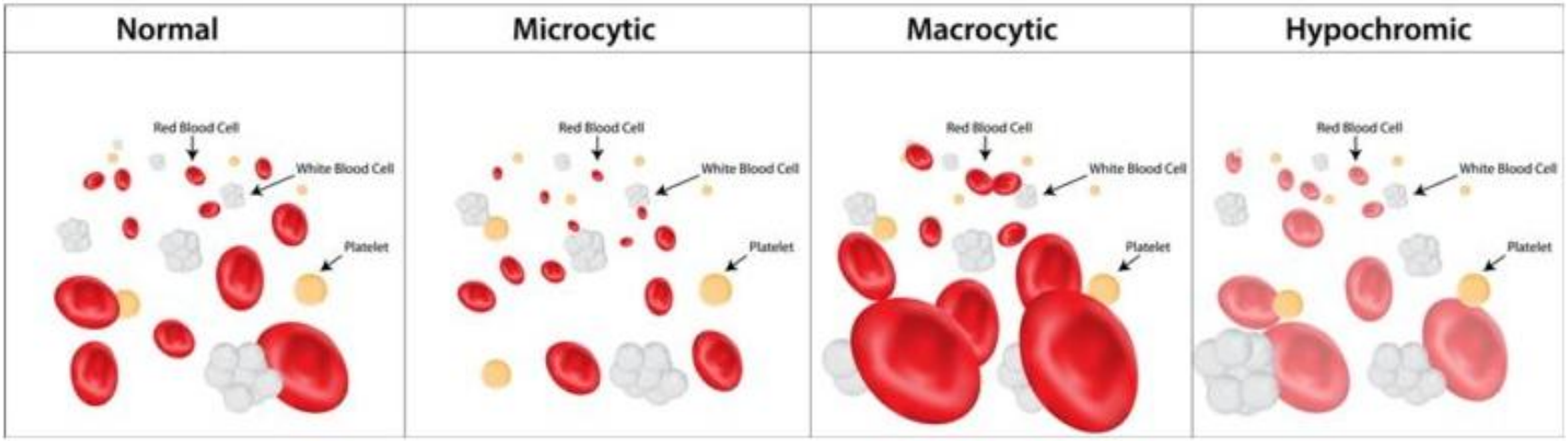
- Pallor
- Fatigue
- Dyspnoe
- Tachycardia and palpitations
- Headache, faintness, dim vision



Causes of anemia

1. loss of blood (RBCs)
2. increased red blood cell breakdown
3. decreased RBC production

Classification according to the size of RBCs and amount of Hb:



1. Blood loss anemia

- **Acute (rapid):**
  - trauma or surgery
  - GIT bleeding – peptic ulcers
  - (normocytic, normochromic)

- **Chronic (slow)**:
  - Gynecologic disturbances (menstruation, fibroids)
  - (microcytic, hypochromic)

2. Increased red blood cell breakdown Hemolytic anemia

- Premature destruction of RBC
- ↑ erythropoiesis
- ↑ reticulocytes in the circulation
- Mild jaundice
- Mostly normocytic & normochromic

- <u>Hemolysis:</u>
  - Intravascular (transfusion, mechanic injury, toxins)
  - Extravascular (spleen phagocytosis of abnormal RBS)

Types of hemolytic anemia

- **Hereditary (inherited):**

a) Defects of RBCs membrane

b) Enzyme defects

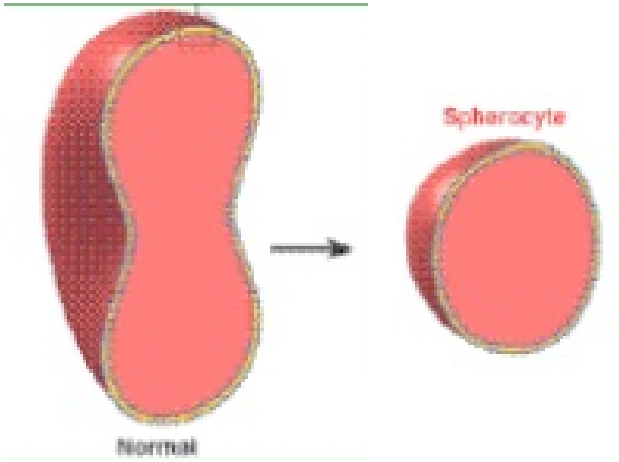
c) Defects in hemoglobin production (hemoglobinopathies)

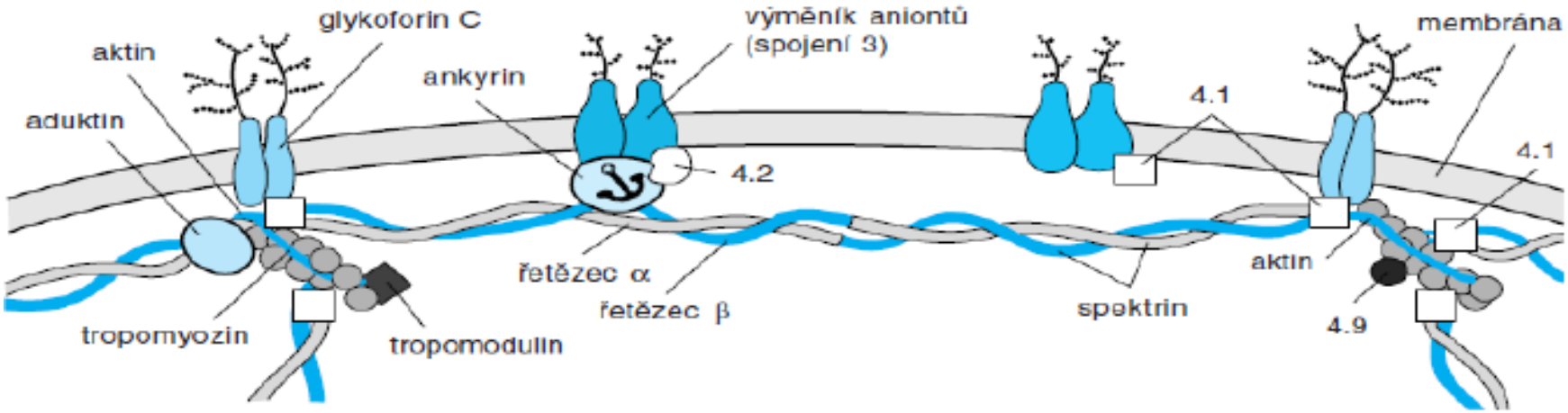
- **Acquired:**
- drugs, bacterial or other toxins, antibodies, trauma

a) Inherited: Defects of RBCs membrane

HEREDITARY SPHEROCYTOSIS

- Deficiency of membrane proteins:
  - ankyrin and spectrin
- Treatment: splenectomy





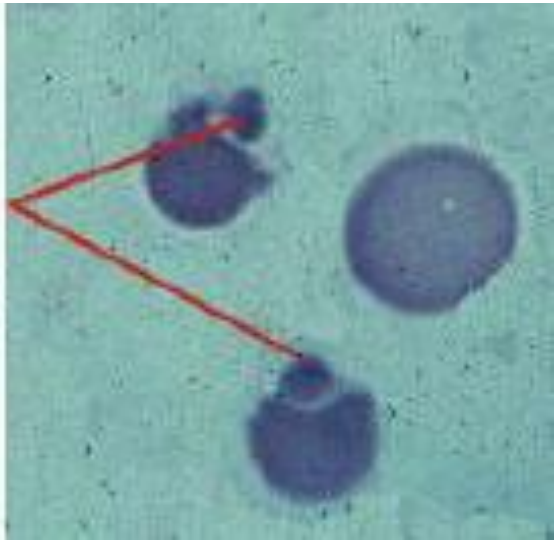
b) Inherited: Enzyme defects

- **Glucose-6-phosphate dehydrogenase** (G6PD) deficiency

- RBC more vulnerable to oxidants → direct oxidation of Hb to **methemoglobin** & denaturing of Hb → **Heinz bodies**

Heinz bodies

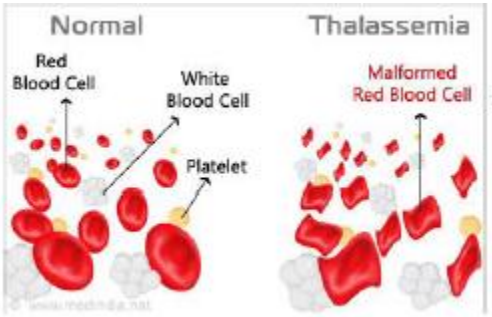
(dense bodies composed of precipitated Hb)

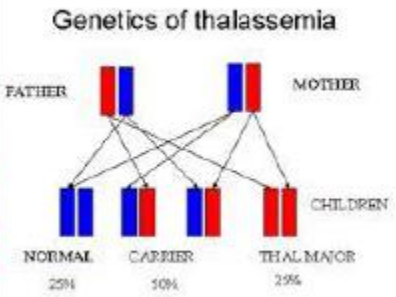


c) Defects in Hb production (Hemoglobinopathies)

THALASSSEMIA

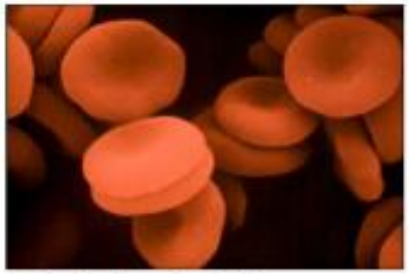
- Deficit in synthesis of α or β chains of Hb
- β-thalassemia ⟶ HbA1 deficiency
- Minor vs major
- α -thalassemia





SICKLE CELL ANEMIA

- Point mutation in the β-chain of Hb
- Causes: hemolytic anemia & vessel occlusion
- Treatment: BM transplantation



Red Blood Cells

Acquired Hemolytic anemias

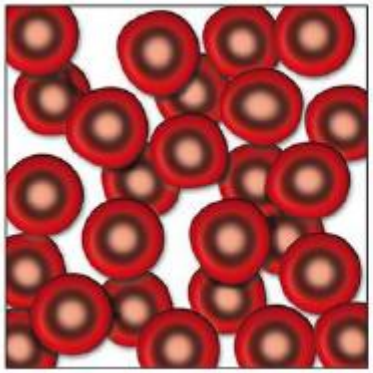
- nonhereditary acute or chronic anemia
- external factors leading to hemolysis:
  - ❑ direct membrane destruction – drugs, chemicals, toxic materials from plant and animal forms (snake venoms), infections

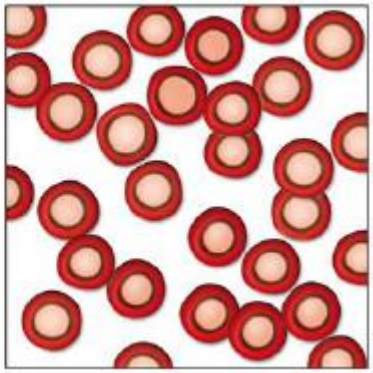
3. Anemias from deficient RBC production

- Deficiency of nutrients for synthesis of **Hb** (iron) or **DNA** (folic acid, cobalamin) → decreased production of erythrocytes by the BM

  - **Iron deficiency anemia**
  - **Megaloblastic anemias**

Iron-deficiency anemia





- **Dietary deficiency**
- **Loss of iron through bleeding** (Metrorrhagia, menorrhagia)

- Iron – a component of heme – iron deficiency → ↓ hemoglobin synthesis → impaired O2 delivery

- Iron-deficiency :
  - ↓ hemoglobin + Hct + iron stores
  - RBCs = microcytic & hypochromic

SIGNS AND SYMPTOMS OF IRON DEFICIENCY

Fatigue and Tiredness

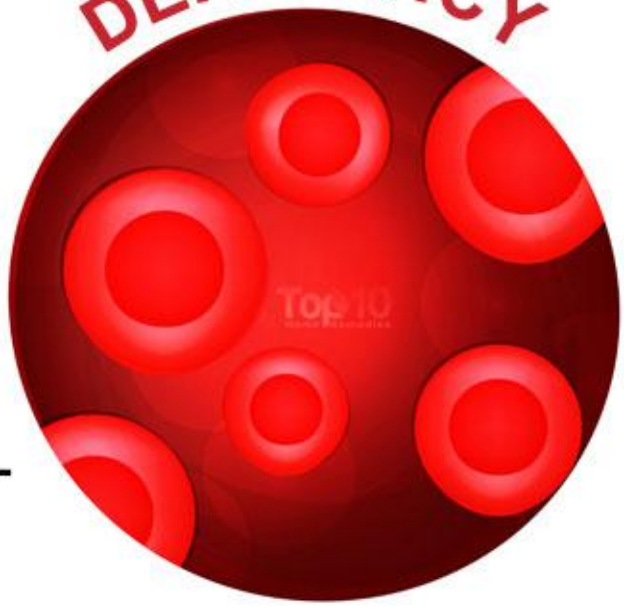
Restless Leg Syndrome

Shortness of Breath

Frequent Headaches

Depression

Increased Sensitivity to Cold



Hair Loss

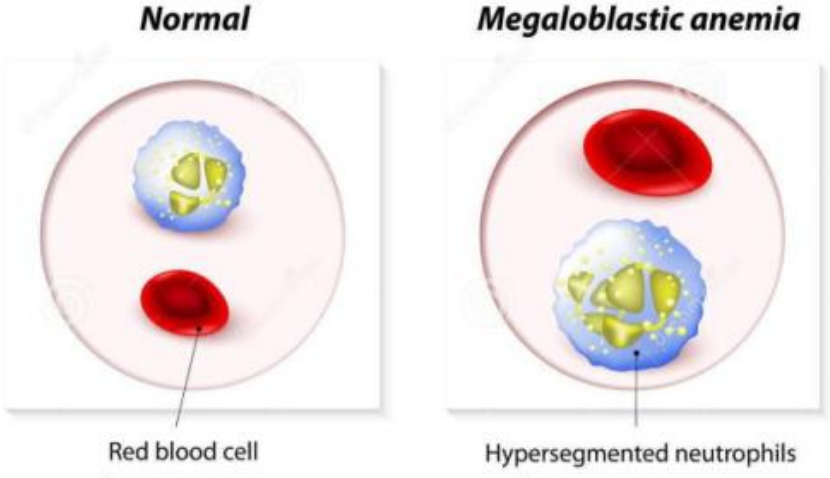
To explore more, visit

Top 10 Home Remedies

www.Top10HomeRemedies.com

Brittle Nails

Megaloblastic anemia



Cobalamin (B_{12}) deficiency anemia

- Impaired DNA synthesis

- Vitamin B12 – essential for DNA synthesis
- Deficit of B12 – nuclear maturation and cell division fail to occur

- dietary deficiency
- IF deficiency
- Ileal resection
- Inflammation of the ileum
- Defective transcobalamine II (TCII)

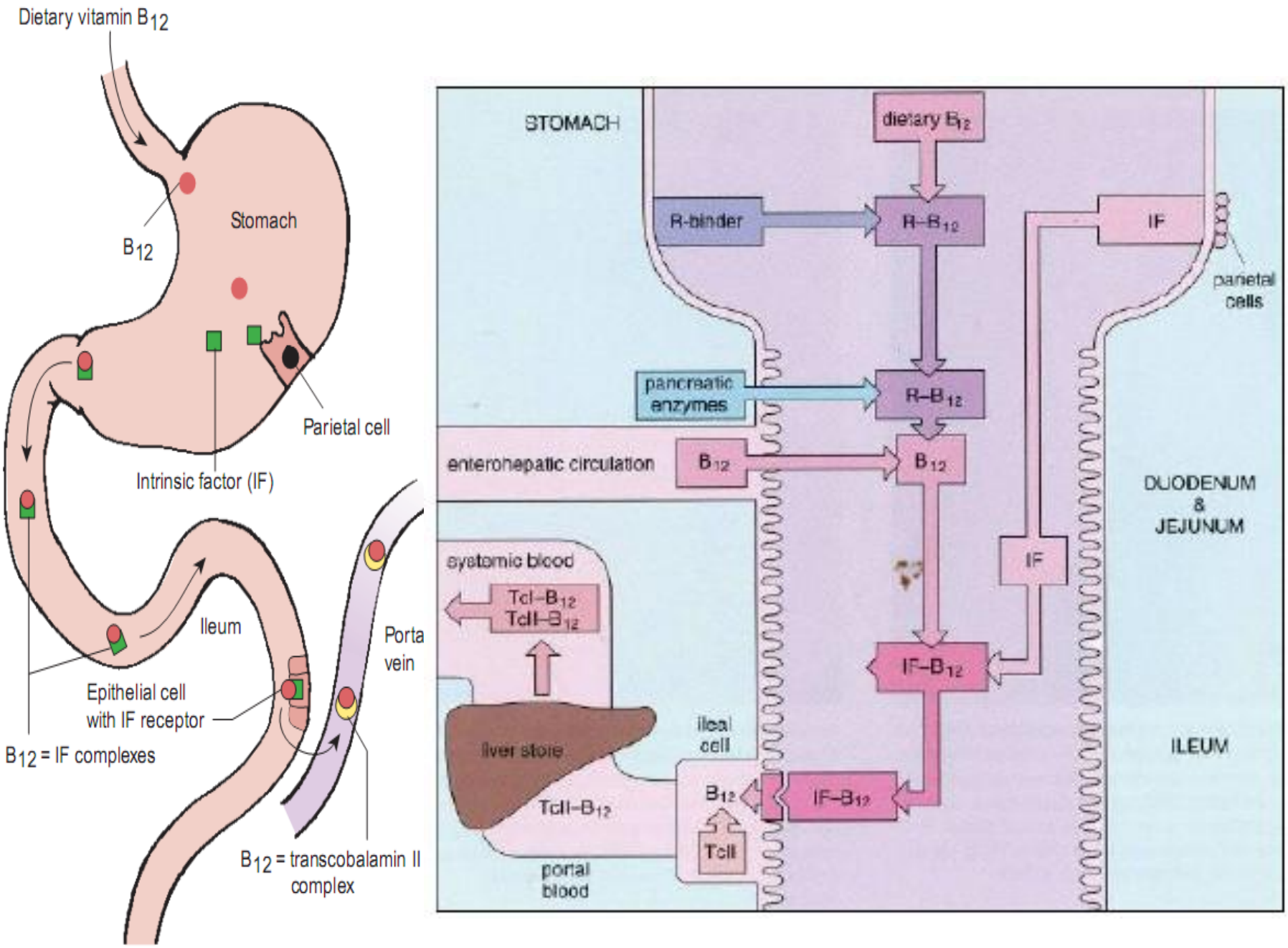


FIGURE 16-8 Absorption of vitamin B_{12}.

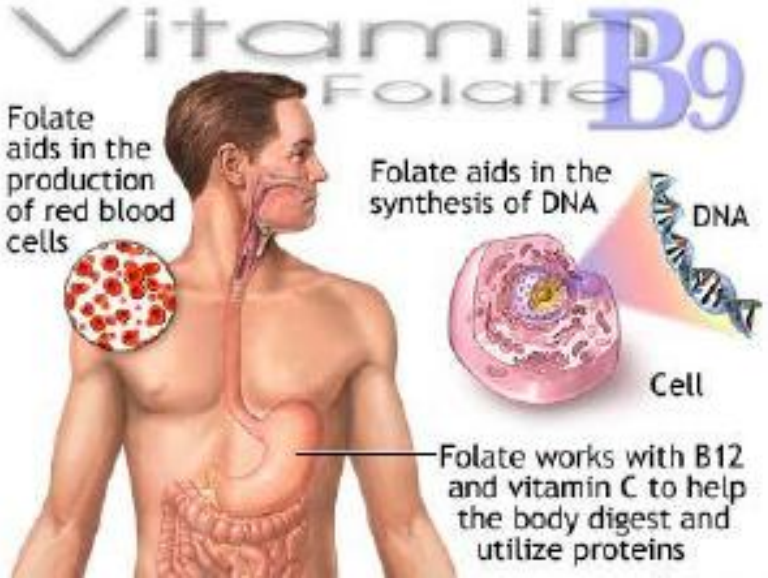
Megaloblastic anemia

Folic acid deficiency

- impaired DNA synthesis

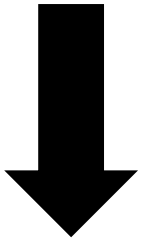
- similar manifestation as in previous

- malnutrition/dietary lack (elderly)
- pregnancy (increased requirement)



Animal models of anemia

- Chronic posthemorrhagic anemia
- Anemia of chronic inflammation
- **Erythropoietin-deficiency anemia**
  - —***Epo*$^{KO/flox}$ mice**



HOMEWORK ☺

Inflammation

- **Defense reaction** of the organism
- Aim: repair or at least limit the damage
- **Destroying, diluting or neutralizing the primary course**
- Damaged tissue is replaced by:
- **regeneration of parenchymal cells**
- filling in the residual defects with **fibrous scar tissue**

Acute inflammation

- short duration - few minutes to several days

Chronic inflammation

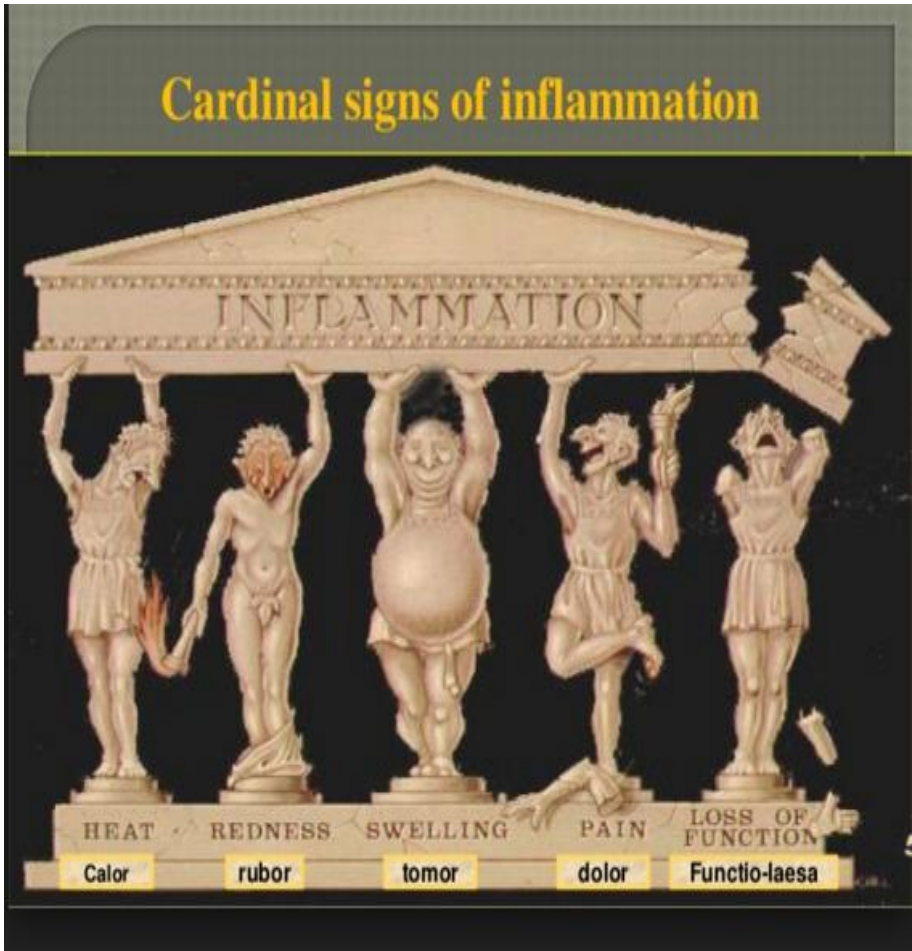
- longer duration – weeks to years

Acute inflammation

- Early response (few minutes – several days)
- Nonspecific

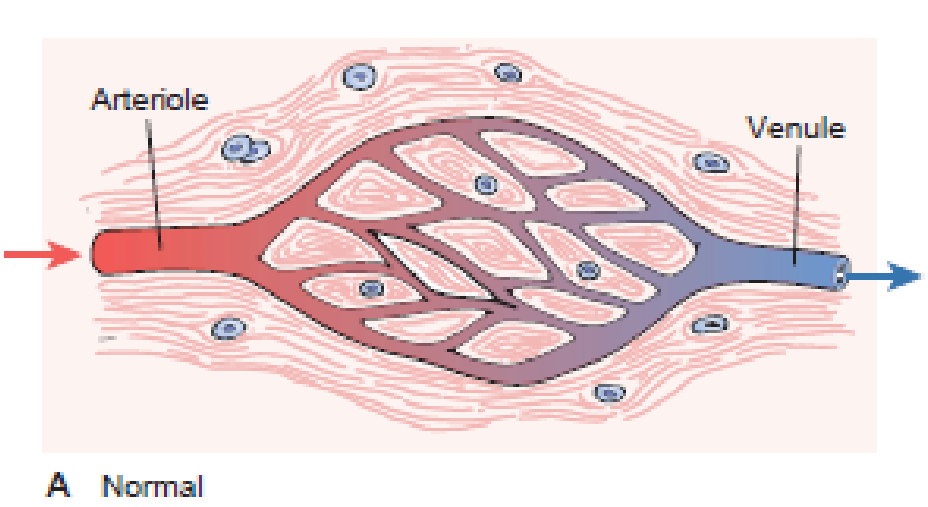
- **Signs:**

➢ **Rubor (reddening)**
➢ **Calor (warmth)**
➢ **Tumor (swelling)**
➢ **Dolor (pain)**
➢ **Functio laesa (loss of function)**

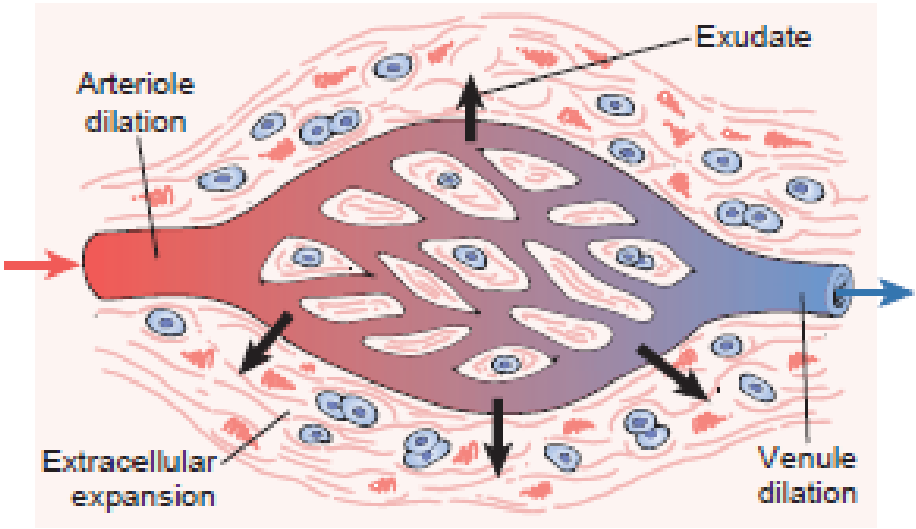


Acute Inflammation

- **Vascular stage**



A Normal

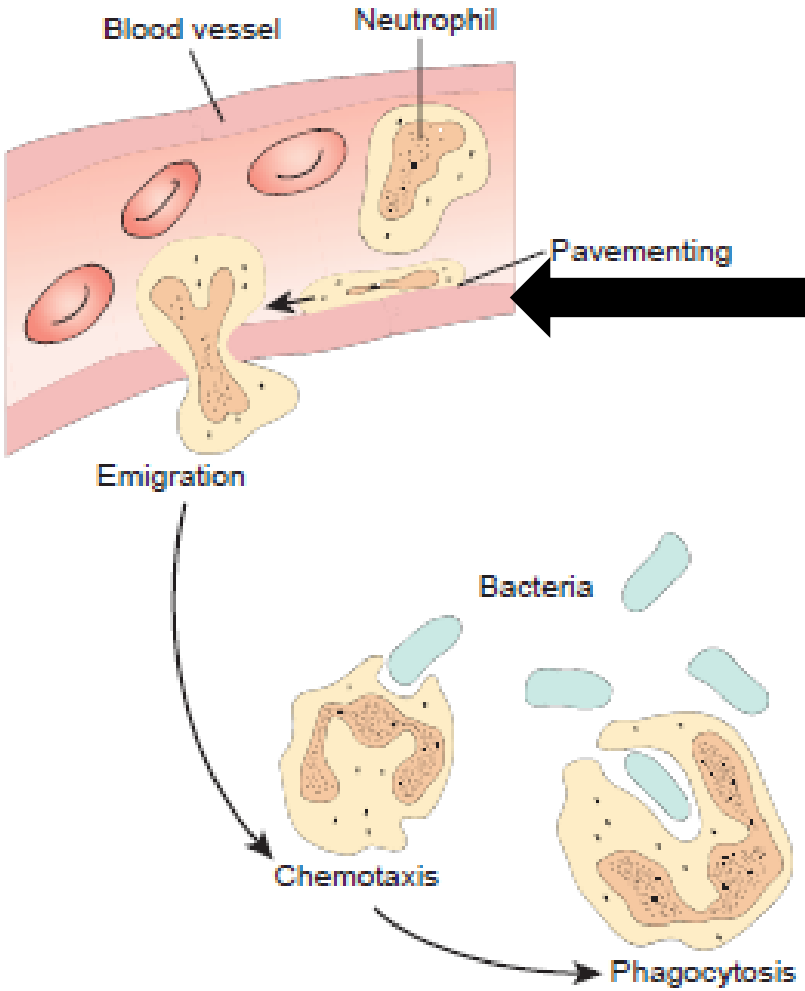


B Acute inflammation

FIGURE 20-1 Vascular phase of acute inflammation. (**A**) Normal capillary bed. (**B**) Acute inflammation with vascular dilation causing increased redness (erythema) and heat (calor), movement of fluid into the interstitial spaces (swelling), and extravasation of plasma proteins into the extracellular spaces (exudate).

Acute inflammation

- **Cellular stage**



Granulocytes + monocytes

Mastocytes + macrophages - **cytokines**

FIGURE 20-3 Cellular phase of acute inflammation. Neutrophil margination, emigration, chemotaxis, and phagocytosis.

Chronic inflammation

- Self – perpetuating (weeks, months ... years)
- Result of a **recurrent or progressive acute inflammatory response**
- Infiltration by **mononuclear cells (macrophages) and lymphocytes**
- **Proliferation of fibroblasts**

Causes:

- silica, asbestos, surgical suture materials, viruses, certain bacteria, fungi

Local manifestation of acute inflammation

A) Exudate

- **Serous**
- **Hemorrhagic**
- **Fibrinous**
- **Purulent**

B) Abscess

C) Ulcer

D) Edema

Systemic manifestation of inflammation

- inflammatory mediators are released to circulation
- **Acute phase response**

➢ hours or days after inflammation

➢ **IL-1, IL-6, TNF-α**

⬇

➢ **[c] plasma proteins,**

➢ **↑ ERY sedimentation rate**

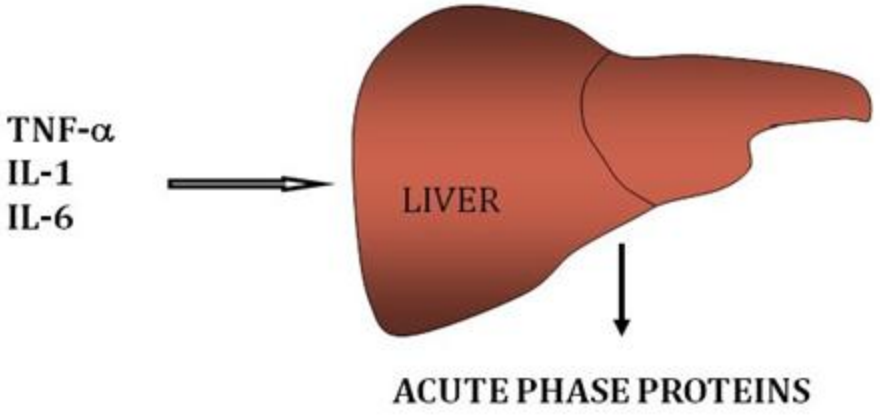
➢ **fever, lethargy**

➢ **↑ leukocytes**

➢ **Acute phase proteins**

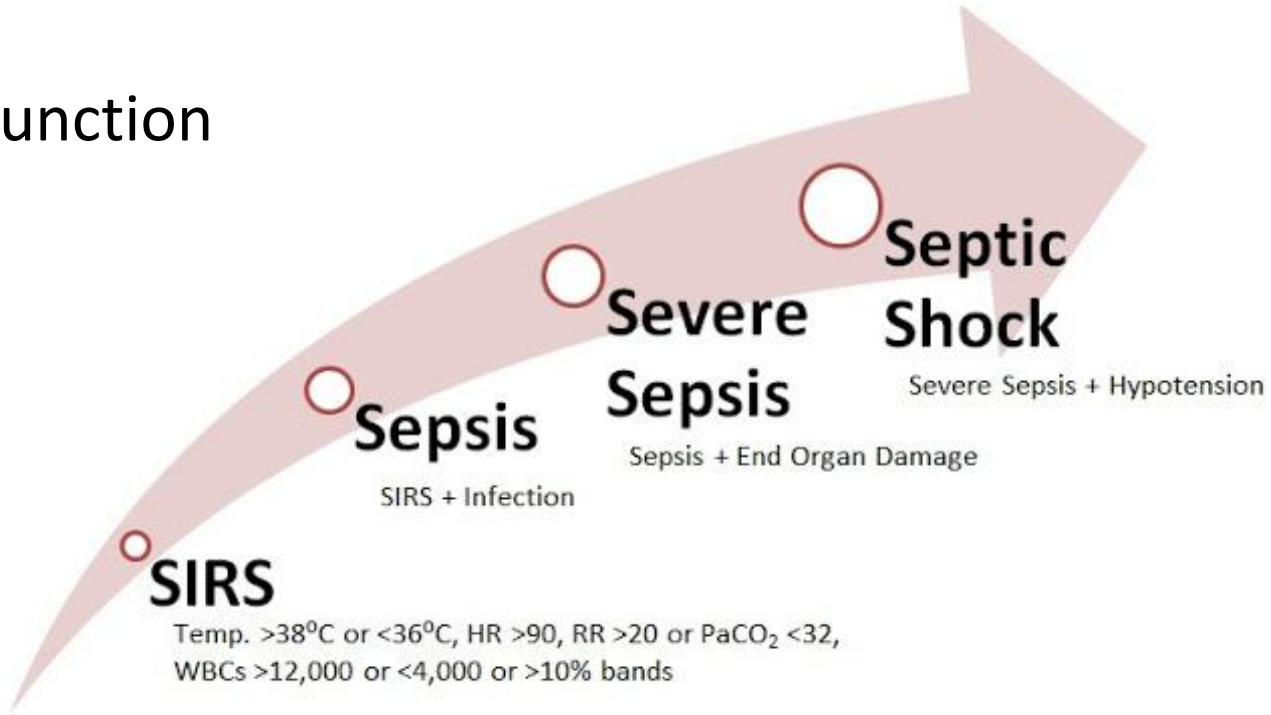
↑ CRP, fibrinogen

CRP [mg/l]	Meaning
up to 6	normal
6-35	**Infection - virus**
35 – 50	Uncertain range
nad 50	**Infection - bacteria**



Systemic manifestation of inflammation

- SIRS = systemic inflammatory response syndrome - nonspecific
- Multiple organ dysfunction

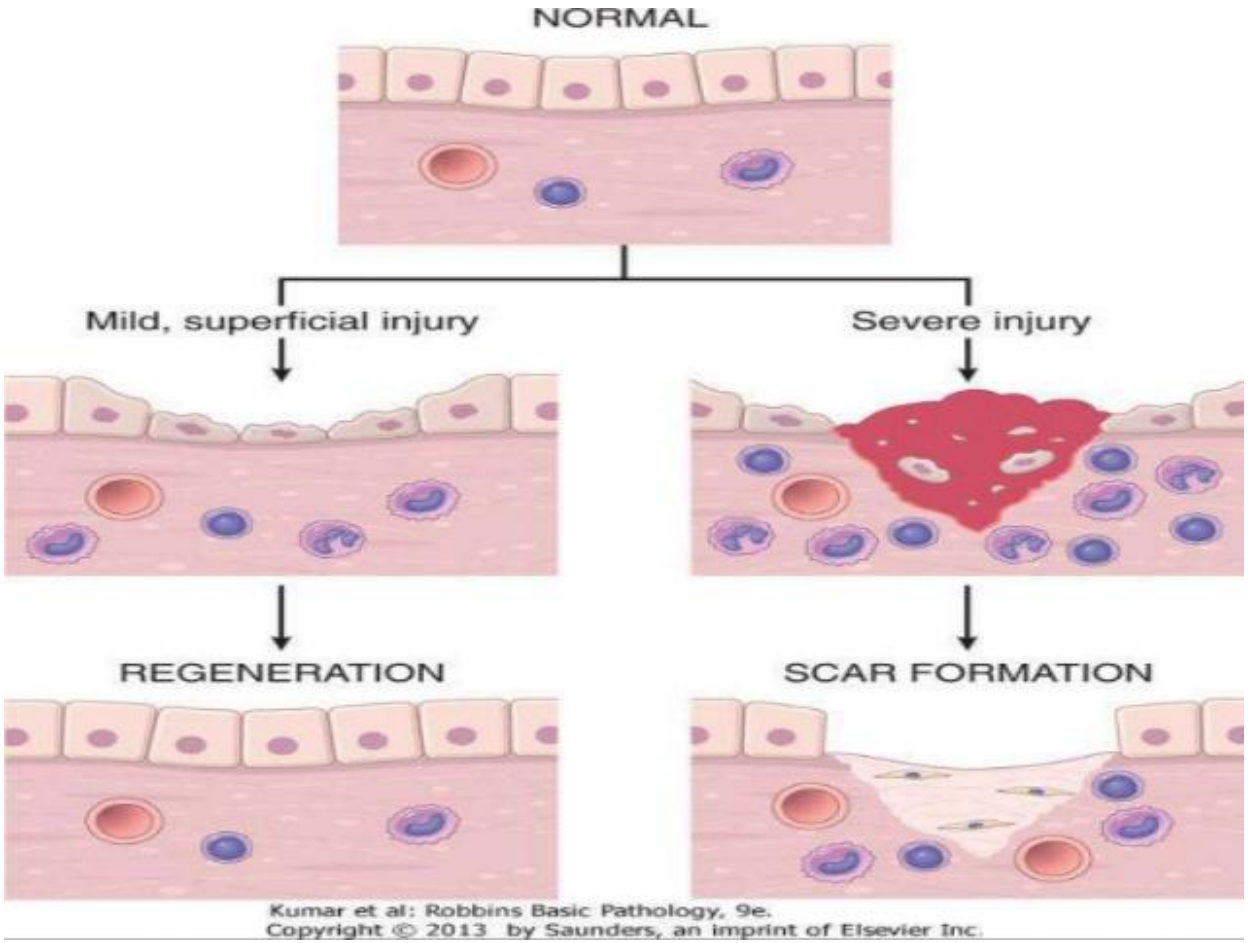


SIRS:

- ❑**Temperature >38°C or <36°C**
- ❑**Heart rate >90 beats per minute**
- ❑**Respiratory rate >20 breaths per minute /or PaCO2 <32 mm Hg (pH <4.3)/**
- ❑**WBC >12,000 cells/mm3, <4000 cells/mm3**

Tissue repair

- **Tissue regeneration** (replacement by the same cells)
- **Replacement by connective tissue** (scar/fibrosis)
- Cell migration, proliferation, and differentiation as well as interaction with the extracellular matrix



Animal models

- LPS, bacteria, fungi, viruses, chemicals
- Locally – e.g. periodontitis
- Systemically – sepsis (LPS, bacteria)

Alterations in the immune response

- **Immunodeficiency disorders**
- **Hypersensitivity disorders**
- **Autoimmune diseases**

Immunodeficiency disorders

By affected component:

1. **Humoral immune deficiency** (B cell deficiency)

•hypogammaglobulinemia (decrease of one or more types of antibodies)
•agammaglobulinemia (lack of all or most antibody production)

2. **T cell deficiency** →acquired immune deficiency syndrome (AIDS)

3. **Granulocyte deficiency** (granulocytopenia, agranulocytosis, neutropenia)

4. **Asplenia**

5. **Complement deficiency**

Primary immunodeficiences (congenital or inherited)

- Genetic diseases
- **Either present at birth or become apparent shortly after birth**
- Many of these disorders (hereditary and autosomal recessive, or X-linked)

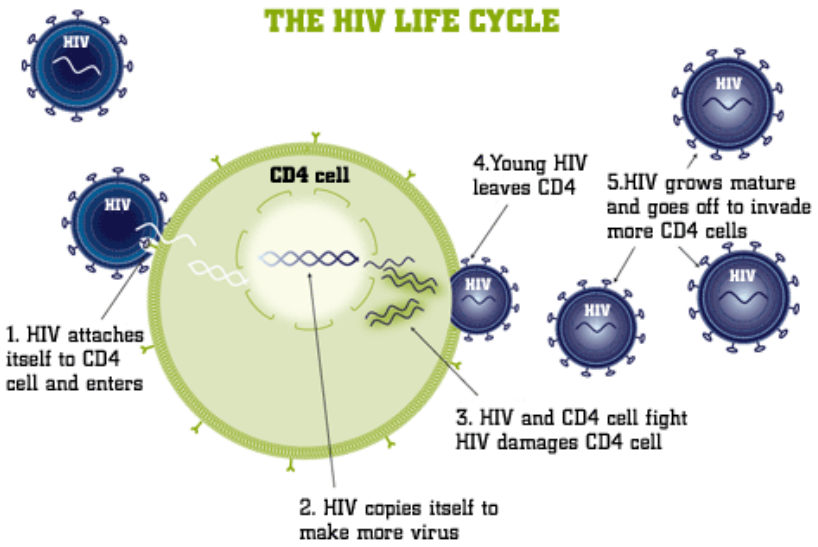
- **Antibody-mediated** (X-linked agamaglobulinemia) – 50%
- **T-cell mediated** (Di George syndrome)
- **Combined** (SCID = severe combined immunodeficiency syndrome)
- **Complement** (Hereditary angioedema)
- **Fagocytic** (chronic granulomatosis)

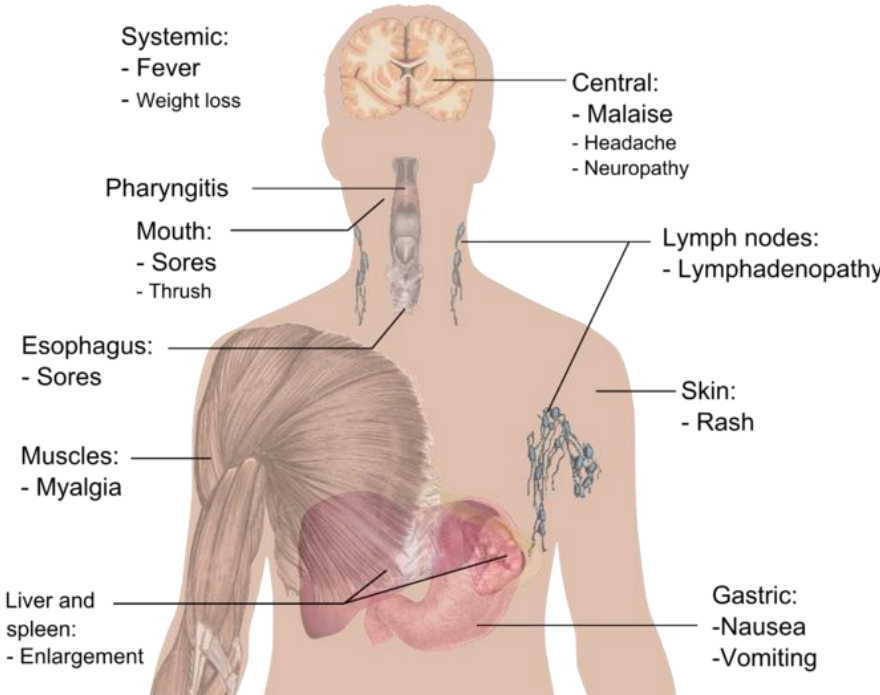
- Treatment:
    - depends on the nature of the defect
    - involve antibody infusions
    - long-term antibiotics

Secondary immunodeficiences (acquired)

- **when the immunodeficiency is acquired later in life**
- **<u>more common than primary disorders of genetic origin</u>**
- **result from various immunosupressive agents**

- Infections
- Malnutrition
- Immunosuppressive therapy (HIV - **AIDS**)
- Neoplasms
- Mediacations (chemotherapy)
- Environmetal toxins (mercury, heavy metals, pesticides)
- Aging





Animal models

- Athymic nude mouse / Nu (T-cell deficient)

- Nude Rat

Nu/J

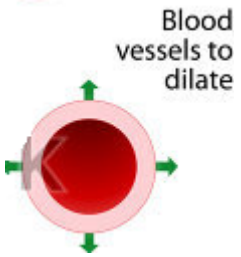
Nude rat

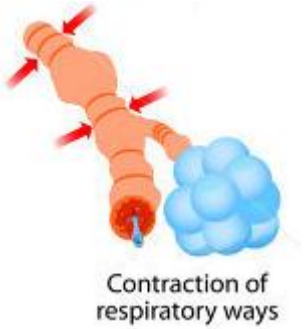
Hypersensitivity disorders

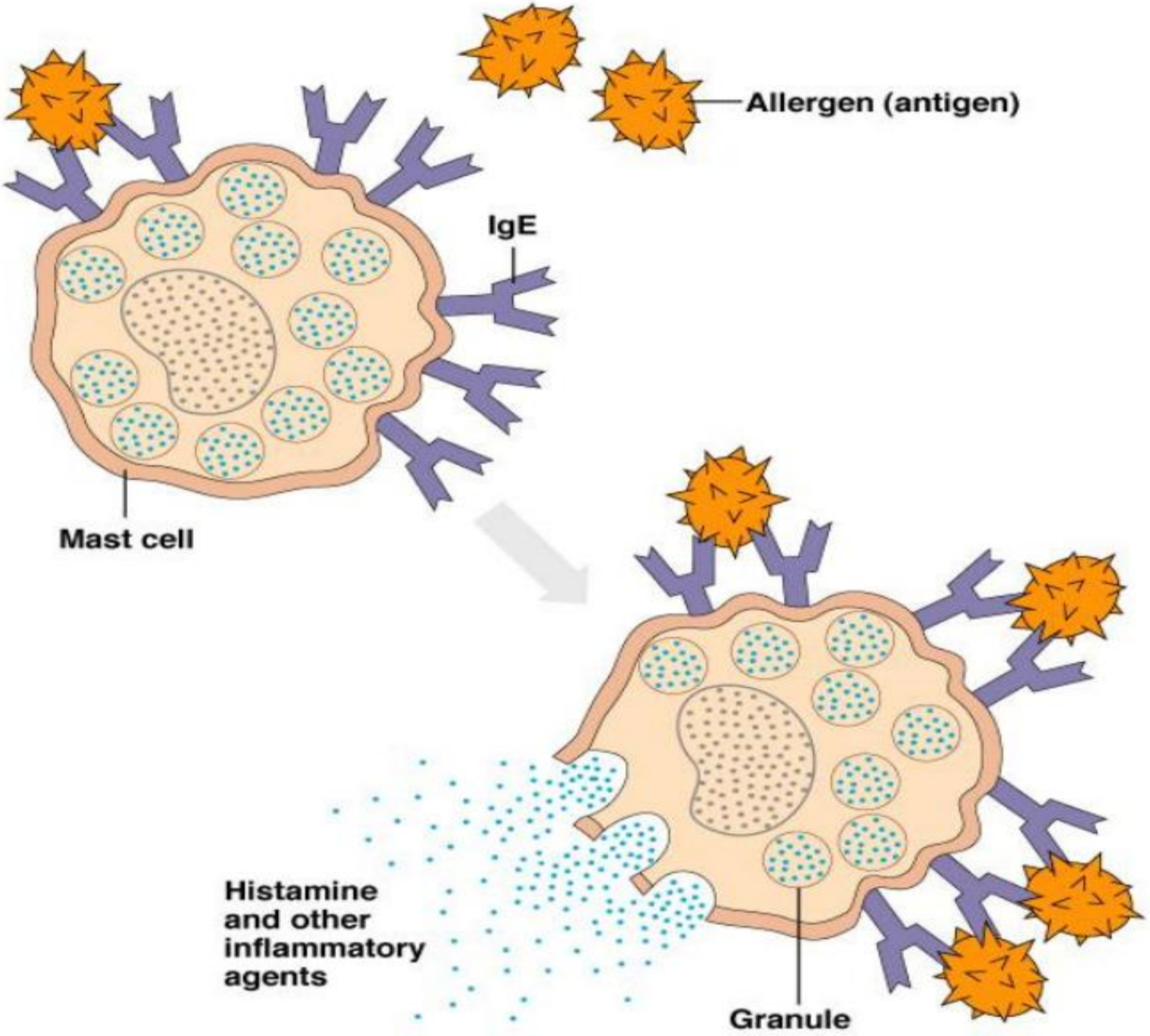
- **overreaction of the IS to antigens**
- Type I (Anaphylactic)
- Type II (Antibody-mediated)
- Type III (Immune complex-mediated)
- Type IV (Cytotoxic)
- Type V (Stimulation)

Type I (Anaphylactic)

- **immadiate reaction** - within minutes after exposure to antigen
- is an allergic reaction provoked by **reexposure** to a specific type of antigen (allergen)
- reaction of **IgE** + **antigen** → mastocytes & basophils
- degranulation of cells – **histamin**, leukotriens and prostaglandins
- **smooth muscle contraction** – bronchial spasmus
- **vascular dilation** – redness, blood pressure drop
- increase of endothelial permeabilty – secretion of mucus, mucous epithelium






Allergen (antigen)
IgE
Mast cell
Histamine
and other
inflammatory
agents
Granule

- **Local (atopic):**
  - Allergic asthma and rhinitis (hay fever)

- **Systemic: Anaphylaxis**
  - mild irritation to sudden death from anaphylactic shock

- Treatment:
  - antihistamines, corticosteroids

Type II (Ab mediated reaction)

- Binding of **IgG** or **IgM** on a cell surface antigen
- Activation of complement
- Lysis of the antigen presenting cells
- **Blood types**
  - ABO incompatibility

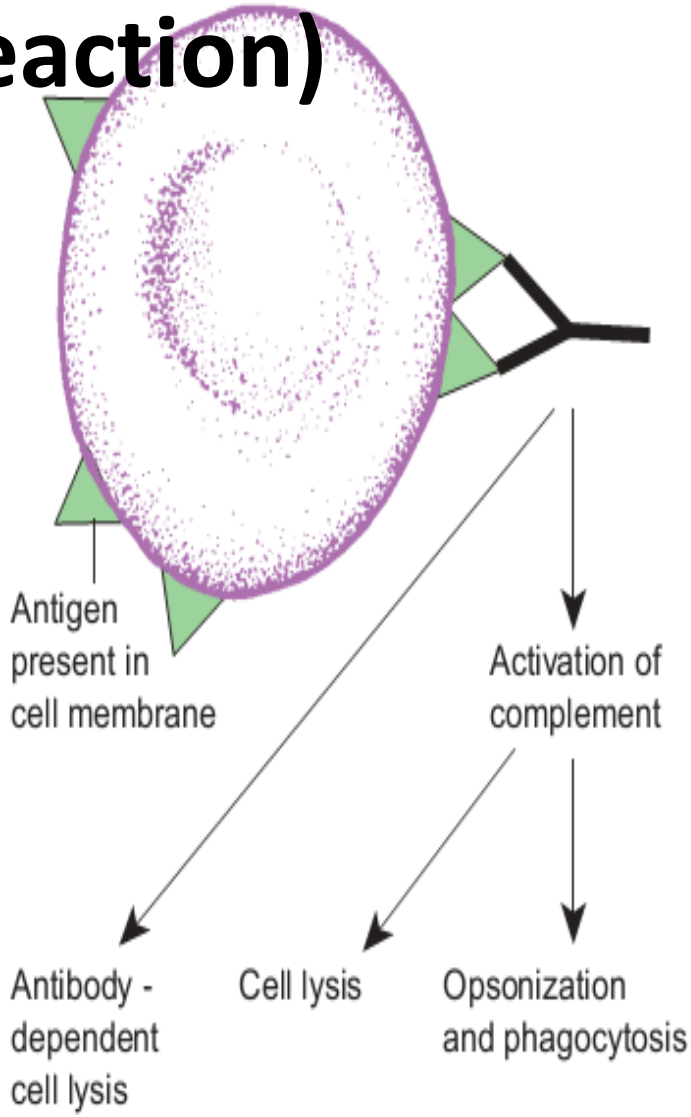
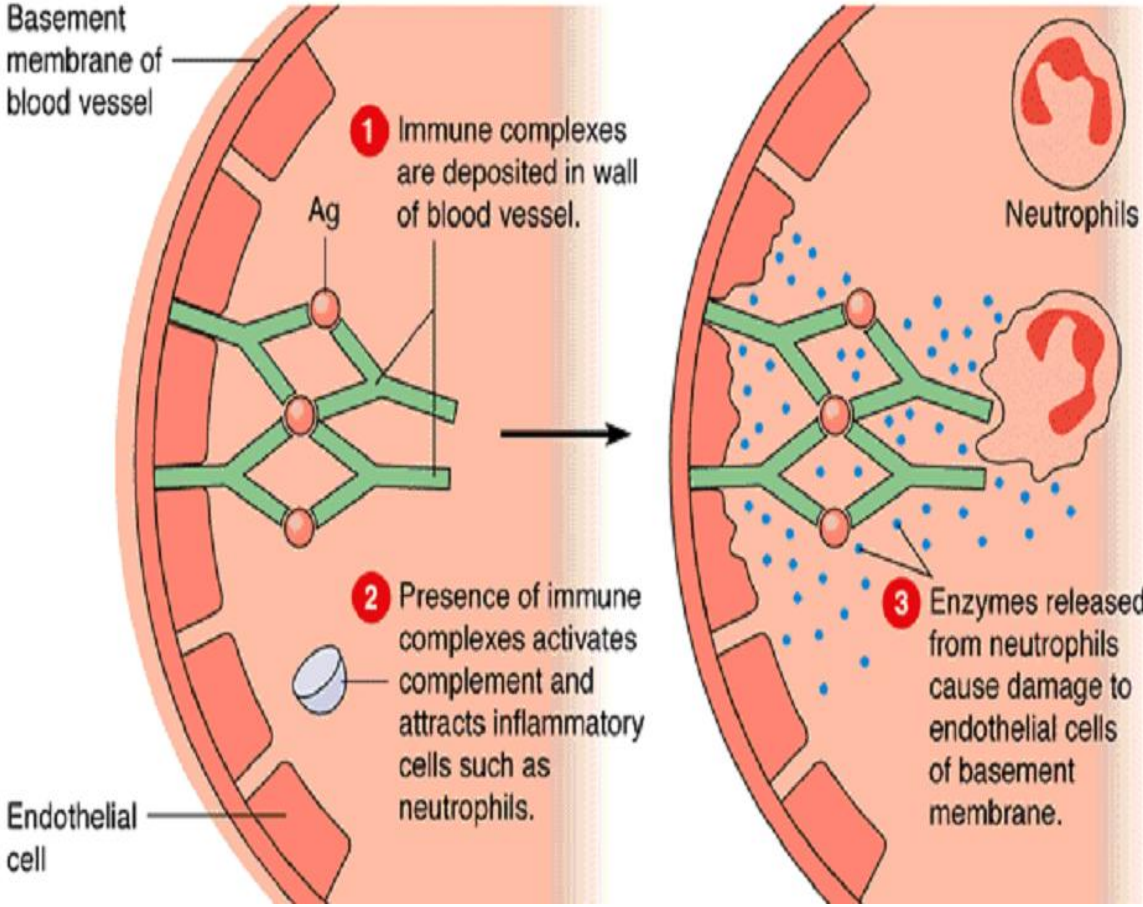


FIGURE 21-5 Type II, antibody-mediated reactions involve formation of immunoglobins (IgG and IgM) against cell surface antigens. The antigen-antibody response leads to (1) complement-mediated mechanisms of cell injury or to (2) antibody cytotoxicity that does not require the complement system.

Type III (Immune complex-mediated)

- **Immunocomplex – antigen + antibody**
- Reactions against soluble antigens including IgA
- Immunocomplexes - high amounts, deposit in the organs, activate the complement and **cause inflammation**
- **IgA glomerulonephritis**



Type IV (Cytotoxic)

- **delayed type hypersensitivity**
- **cell-mediated** response
- skin reactions – itching, edema, reddness, pain
- **TBC test**
- Allergies to metals (Ni)
- Allergies to latex

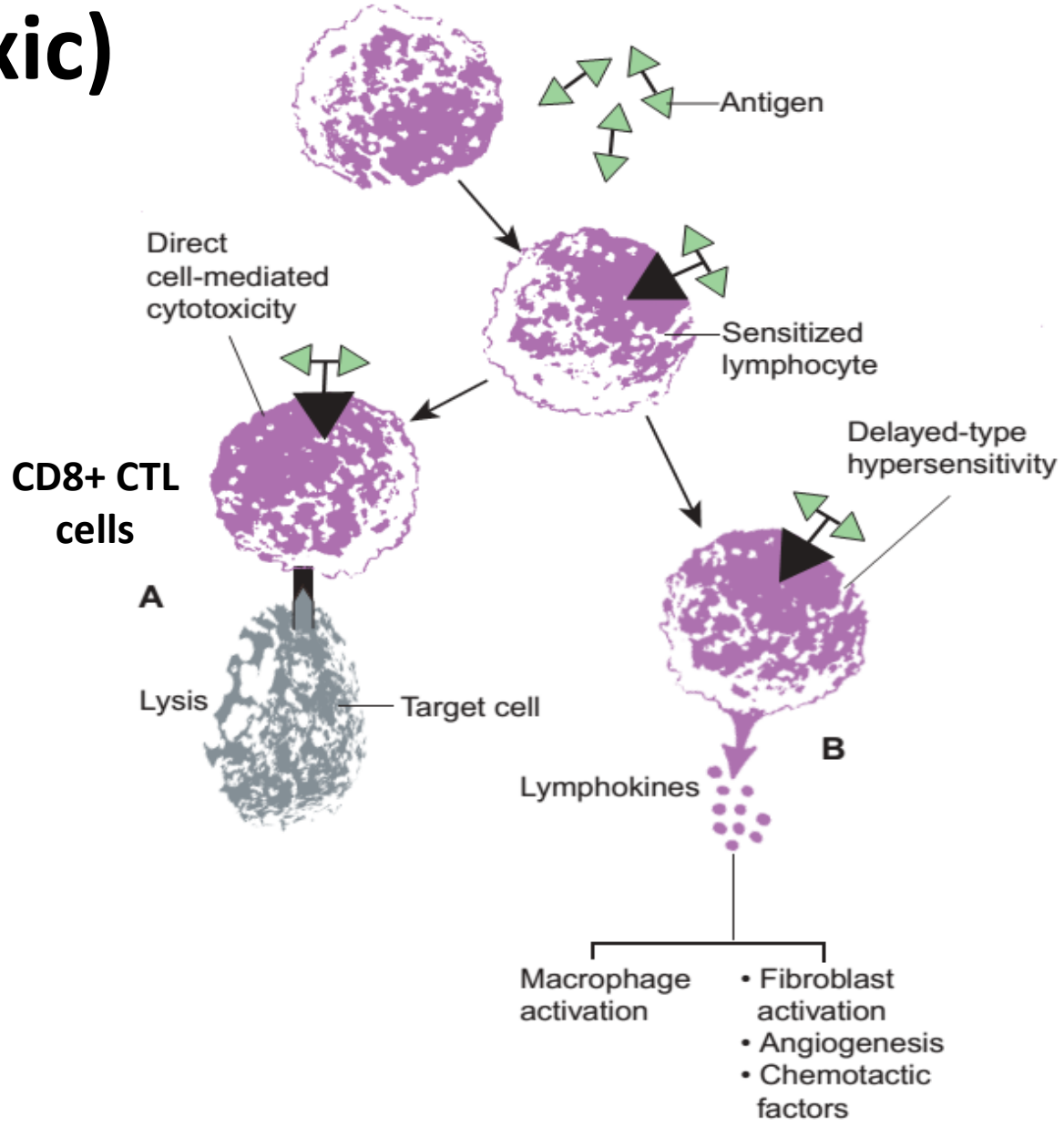
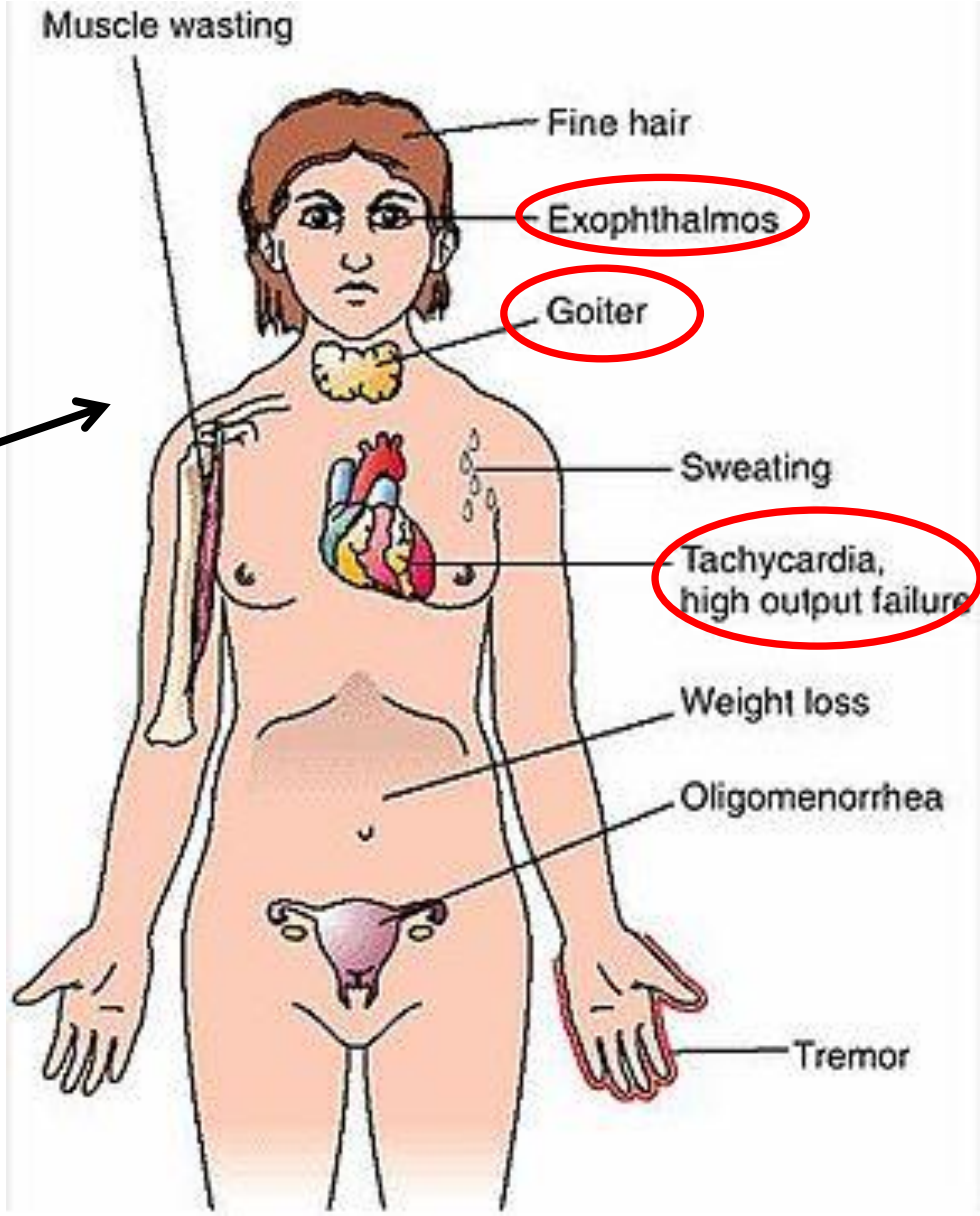


FIGURE 21-7 Type IV, direct cell-mediated cytotoxicity (**A**) or delayed-type hypersensitivity (**B**) reactions involve sensitization of T lymphocytes with the subsequent formation of cytotoxic T cells that lyse target cells or T cells that release cell-damaging lymphokines.

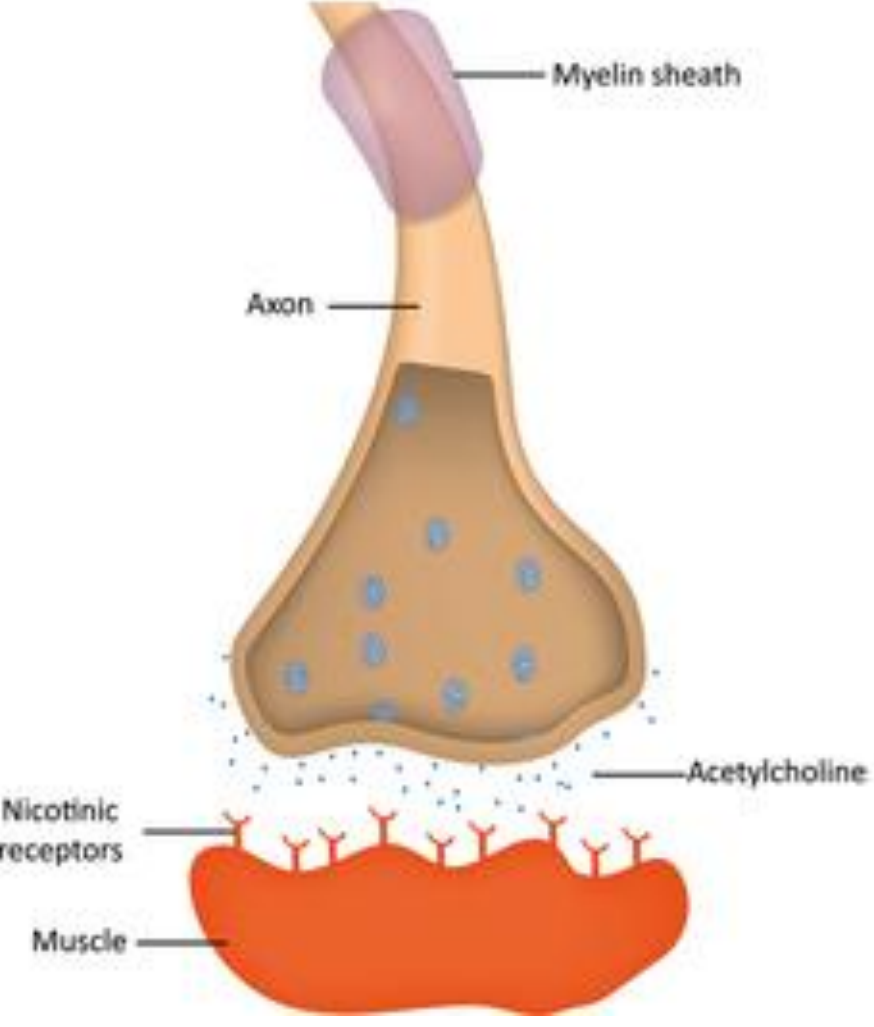
Type V (Stimulation)

- Interaction of autoantibodies with cell receptors
- **Antibody activates receptor as a ligand**
- **Grave´s disease**
- Autoantibodies against TSH receptor activate the TSH receptor in the thyroid gland

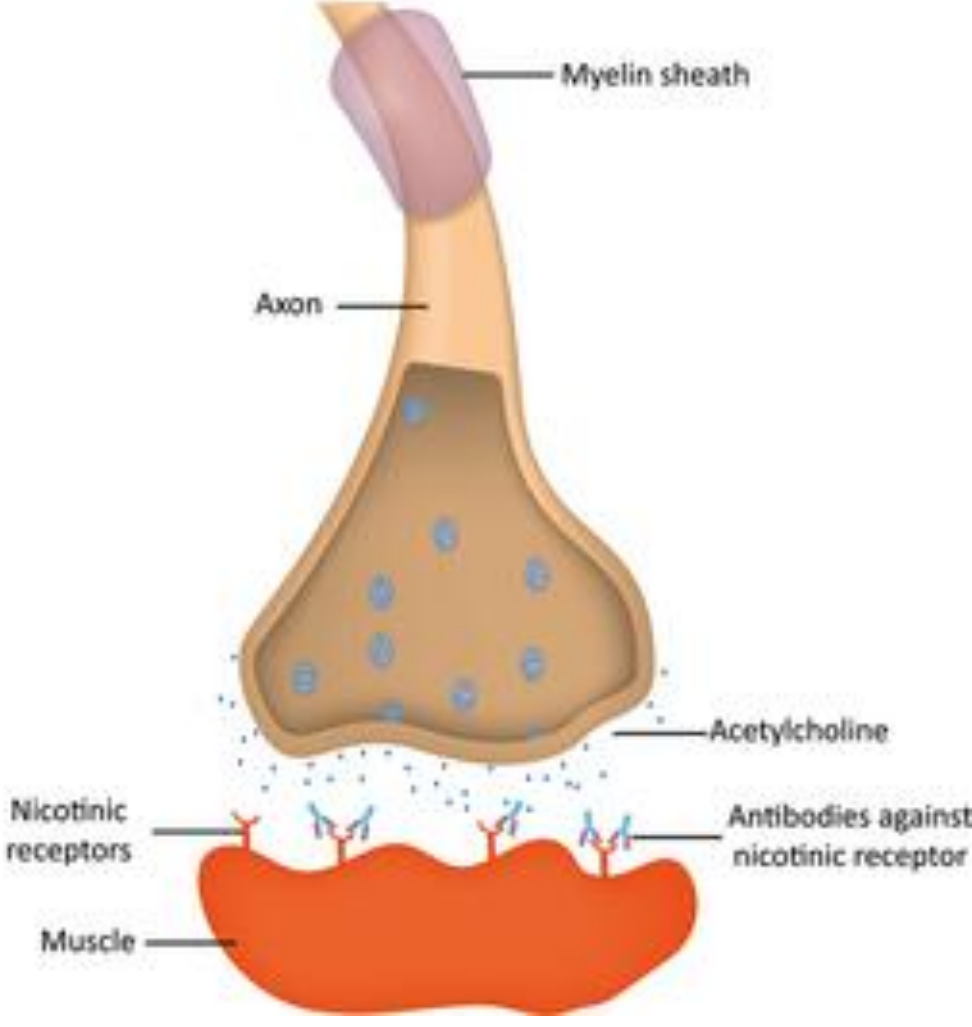


Myasthenia Gravis

Normal Neuromuscular Junction



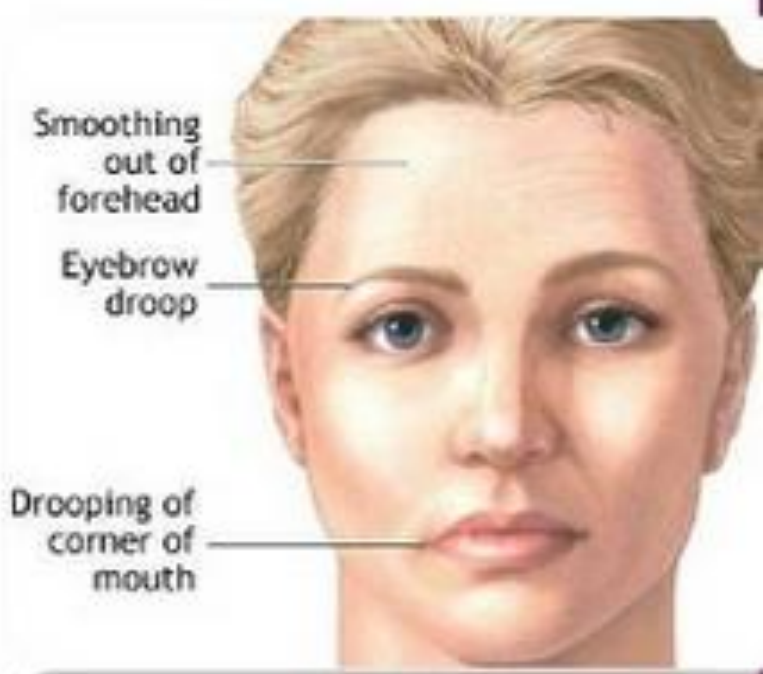
Myasthenia Gravis



Myasthenia Gravis

SYMPTOMS

- **Eye muscles**
- Drooping of one or both eyelids (ptosis).
- Double vision (diplopia)
- **Face and throat muscles**
- Altered speaking(dyasarthria)
- Difficulty swallowing(dysphagia)
- Problems chewing
- Limited facial expressions
- **Neck and limb muscles**
- Weakness in arms, legs, neck, fingers etc.

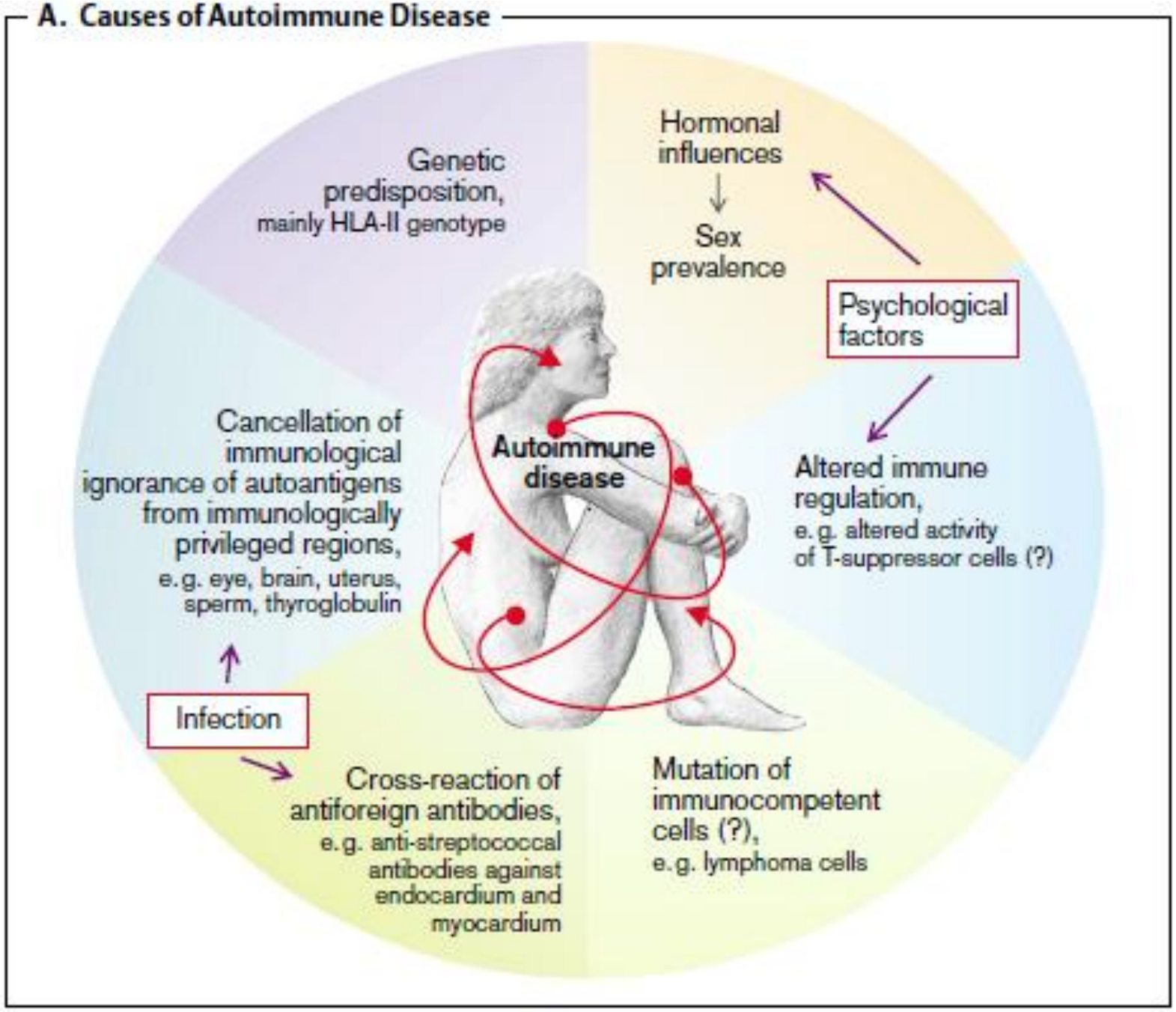


Autoimmune diseases

- **impaired ability of the immune system to differentiate between self and nonself antigens**

- can affect almost any cell or tissue in the body

- continuous production autoantibodies or activation of T cells against endogenous antigens – damage to tissue or organs (autoimmune disease)

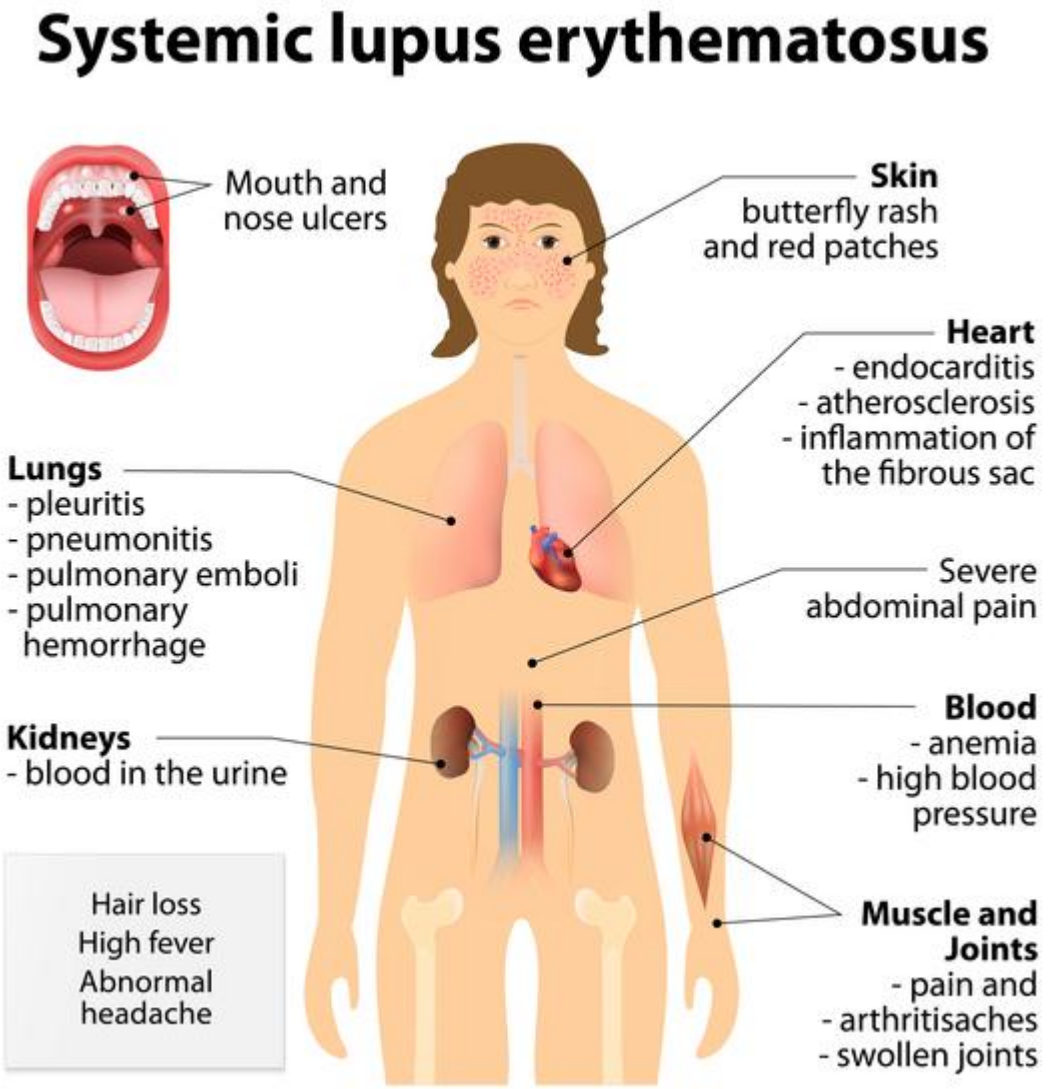

A. Causes of Autoimmune Disease
Genetic predisposition, mainly HLA-II genotype
Hormonal influences
Sex prevalence
Psychological factors
Altered immune regulation, e.g. altered activity of T-suppressor cells (?)
Mutation of immunocompetent cells (?), e.g. lymphoma cells
Cross-reaction of antiforeign antibodies, e.g. anti-streptococcal antibodies against endocardium and myocardium
Infection
Cancellation of immunological ignorance of autoantigens from immunologically privileged regions, e.g. eye, brain, uterus, sperm, thyroglobulin
Autoimmune disease

Autoimmune diseases

1. Myastenia gravis (Typ V)

2. Systemic lupus erythematosus (Typ III)

- Antibodies against DNA, RBC etc.
- Deposition of immune complexes (joints, kidneys)
- Redness of face, arthritis, nephritis



Autoimmune diseases

3. Rheumatoid arthritis (Typ III)

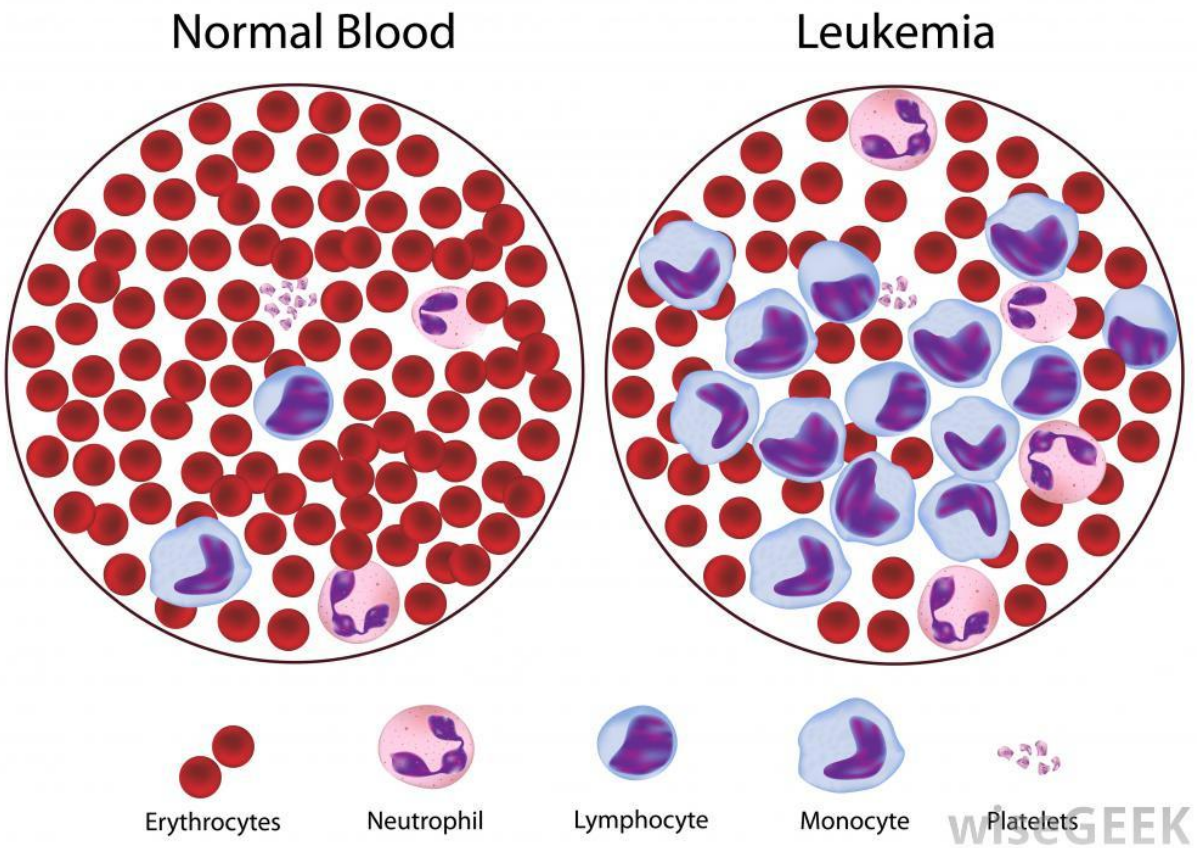
- Depositions of immune complexes in joints

4. **Diabetes mellitus I (Typ IV)**

- Cytotoxic T lymphocytes destroy pancreatic β-cells

5. Morbus Basedow (Typ V)

Leukemias



- Malignant neoplasms of cells originally derived from hematopoietic cells
- Diffuse replacement of bone marrow with unregulated, proliferating, immature neoplastic cells
- Leukemic cells spill out to blood in large numbers
- Solid organ infliltration
- **Lymphocytic** vs **myelogenic** vs **biphenotypic**
- **Acute** vs **chronic**

Leukemias

- **Acute lymphocytic** leukemia (ALL)
- **Chronic lymphocytic** leukemia (CLL)

➢ immature lymphocytes and their progenitors from BM

but infiltrate the spleen, lymph nodes and CNS and other tissues

- **Acute myelogenic** leukemia (AML)
- **Chronic myelogenic** leukemia (CML)

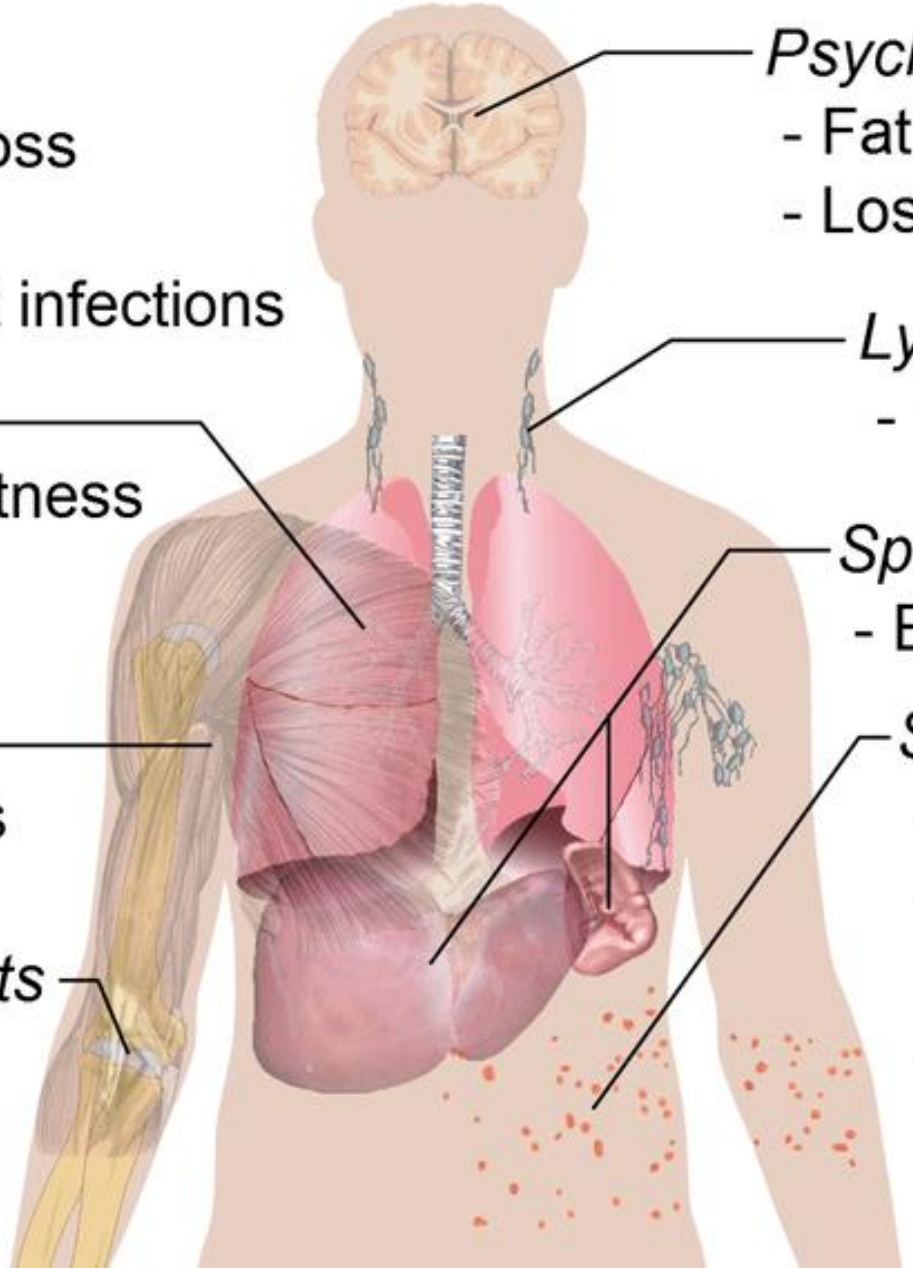
➢ pluripotent myeloid stem cells in BM, interfere with the maturarion of all blood cells (granulocytes, ERY, thrombocytes)

Etiology

- Not fully understood
- Antitumor drugs
- Genetic predisposition
- Smoking
- Ionizing radiation
- Previous chemotherapy

Common symptoms of

Leukemia



Systemic
- Weight loss
- Fever
- Frequent infections

Psychological
- Fatigue
- Loss of appetite

Lymph nodes
- Swelling

Lungs
- Easy shortness of breath

Spleen and/or liver
- Enlargement

Muscular
- Weakness

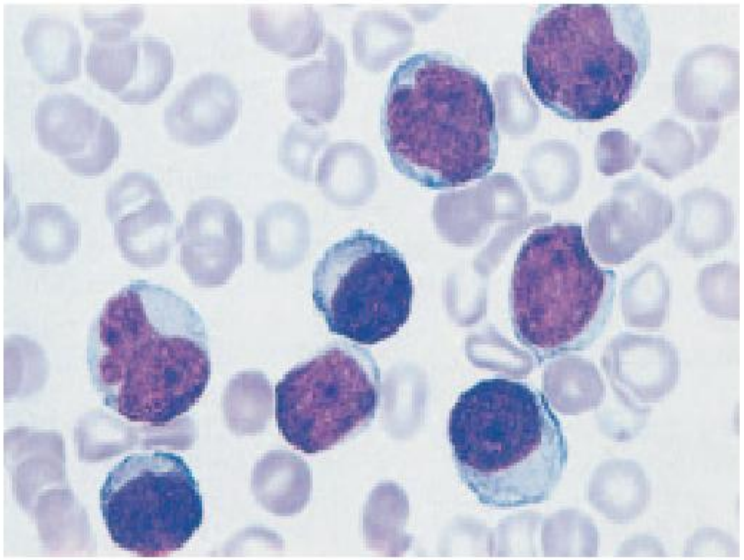
Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots

Bones or joints
- Pain or tenderness

Acute leukemias

- Sudden onset
- Acute lymphoblastic leukemia (immature precursors of T & B cells) – children
- Acute myelogenous leukemia (heterogenous) – toxins – adults

ALL



Acute leukemias - manifestations

- **Both ALL & AML have similar clinical features:**

- Fatigue
- Pallor
- Low grade fever
- Night sweats
- Weight loss (due to rapid proliferation and hypermetabolism of leucemic cells)
- Repeated infections
- Easy bruising (↓ thrombocytes)
- Nosebleeds and other types of hemorrhage
- Splenomegaly, hepatomegaly
- Nausea, vomiting, occasional seizures and coma (CNS)
- Leukostasis (100,000 cells/µL)

Chronic leukemias

- **Chronic lymphocytic leukemia – age > 55**
- lymphoproliferative – lymphocytosis, lymphadenopathy & splenomegaly
- 95% - malignant transformation of B-cells which are immunologically incompetent - hypogammaglobulinemia

- **Chronic myelogenous leukemia – age 30 – 50**
- myeloproliferative - malignant transformation of pluripotent hematopoietic stem cells
- Philadelphia chromosome (95%)

Chronic leukemias - manifestations

- **Chronic lymphocytic** leukemia
- slow and indolent course
- progressive infiltration of neoplastic lymphocytes in BM
- fatigue, lymphatic swelling, splenomegaly later

- **Chronic myelogenous** leukemia
- Triphasic course: **a) chronic** – variable length **b) short accelerated phase c) terminal blast crisis**
- A) leukocytosis, fatigue, anemia, weakness, weight loss
- B) splenomegaly and progressive symptoms, low-grade fever, night sweats, bone pain, weight loss, bleeding and bruising may occur
- C) ↑ myeloid precursors mainly blast cells, splenomegaly, infiltration of lymph nodes

Animal models