Red Blood Cell Disorders IV:

Impaired RBC production

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Impaired RBC production

I. Aplastic anemia
   A. Fanconi anemia
   B. Pure red cell aplasia

II. Macrocytic anemia
   A. Folate deficiency
   B. Vitamin B12 deficiency
      1. Pernicious anemia

III. Microcytic anemia
   A. Iron deficiency
   B. Anemia of chronic disease
   C. Sideroblastic anemia
      1. Lead toxicity

IV. Myelophthisic anemia

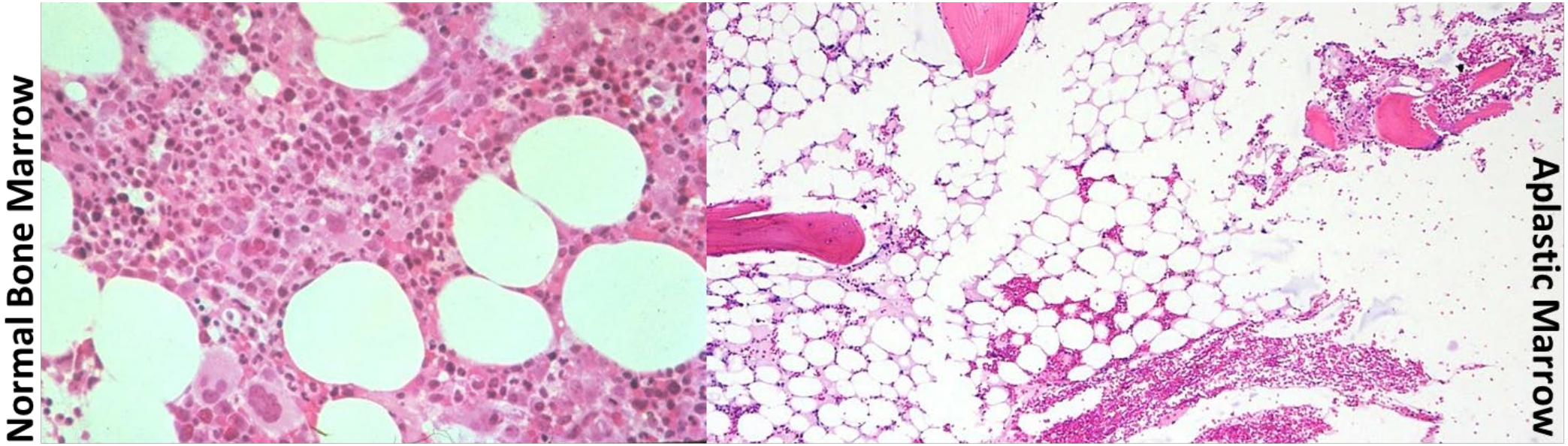
Impaired RBC production

- Disturbance of stem cell proliferation and differentiation

- Disturbance of proliferation/maturation of erythroid cells
  - Macrocytic anemia (high MCV)
  - Microcytic anemia (low MCV)

Aplastic anemia

- Failure of the stem cell to produce hematopoietic elements
- Peripheral blood: cytopenias
- Can evolve into acute leukemia



Aplastic anemia

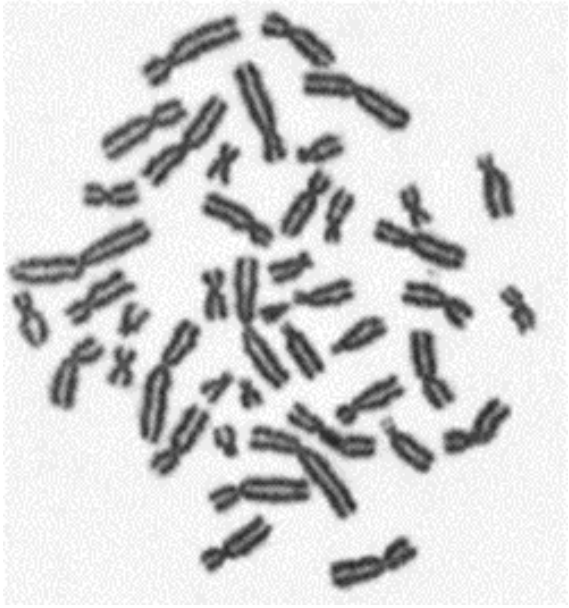
- Idiopathic
  - Primary stem cell defect
  - Immune mediated
- Toxic exposure
  - Drugs: antineoplastic drugs, chloramphenicol
  - Radiation
  - Chemicals: benzene
- Post-viral infection
  - Community acquired non-A,B,C hepatitis
- Inherited defects in DNA repair or telomerase
  - Fanconi anemia

- Treatment:
  - Remove offending agent
  - Supportive care: transfusions, G-CSF
  - Immunosuppression
  - Bone marrow transplant

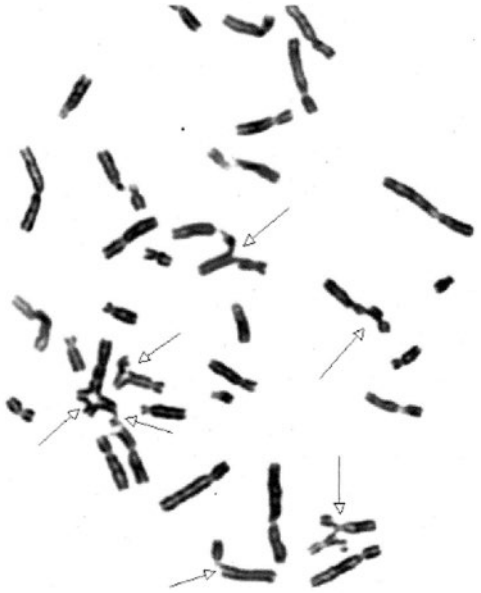
Fanconi Anemia

- Rare autosomal recessive disorder caused by defects in DNA repair
- Signs and symptoms:
  - Short stature
  - Skeletal anomalies
  - Endocrinopathy
  - Renal failure
  - Cutaneous café au lait spots
- Increased incidence:
  - Solid tumors
  - Leukemia (especially AML)
  - Bone marrow failure (aplastic anemia)
- Treatment:
  - Bone marrow transplant

- Testing:
  - Chromosome breakage test



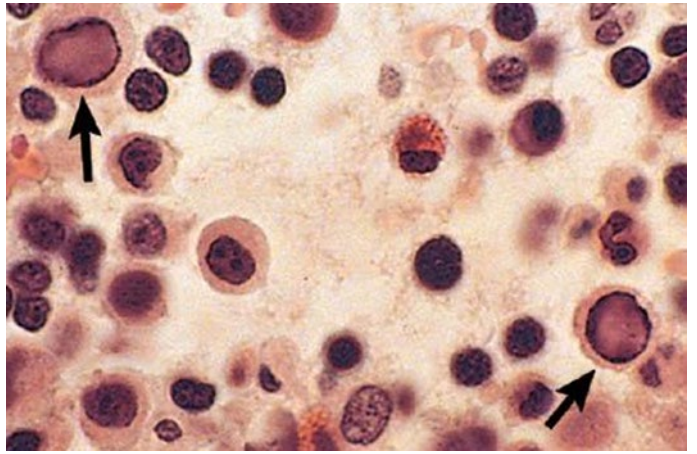
Normal



Abnormal

Pure red cell aplasia

- Subtype of aplastic anemia
- Only erythroid lineage is decreased
- Bone marrow shows decreased red blood cell precursors
- Many causes; examples:
  - Parvovirus B19 infection
    - Transient red cell aplasia
  - Diamond-Blackfan anemia (DBA)
    - Erythroid aplasia
    - Isolated anemia (normal platelets, white blood cells)
    - Presents in infancy



Parvovirus inclusions in nuclei of RBC precursors

Macrocytic anemias

Macrocytic anemia

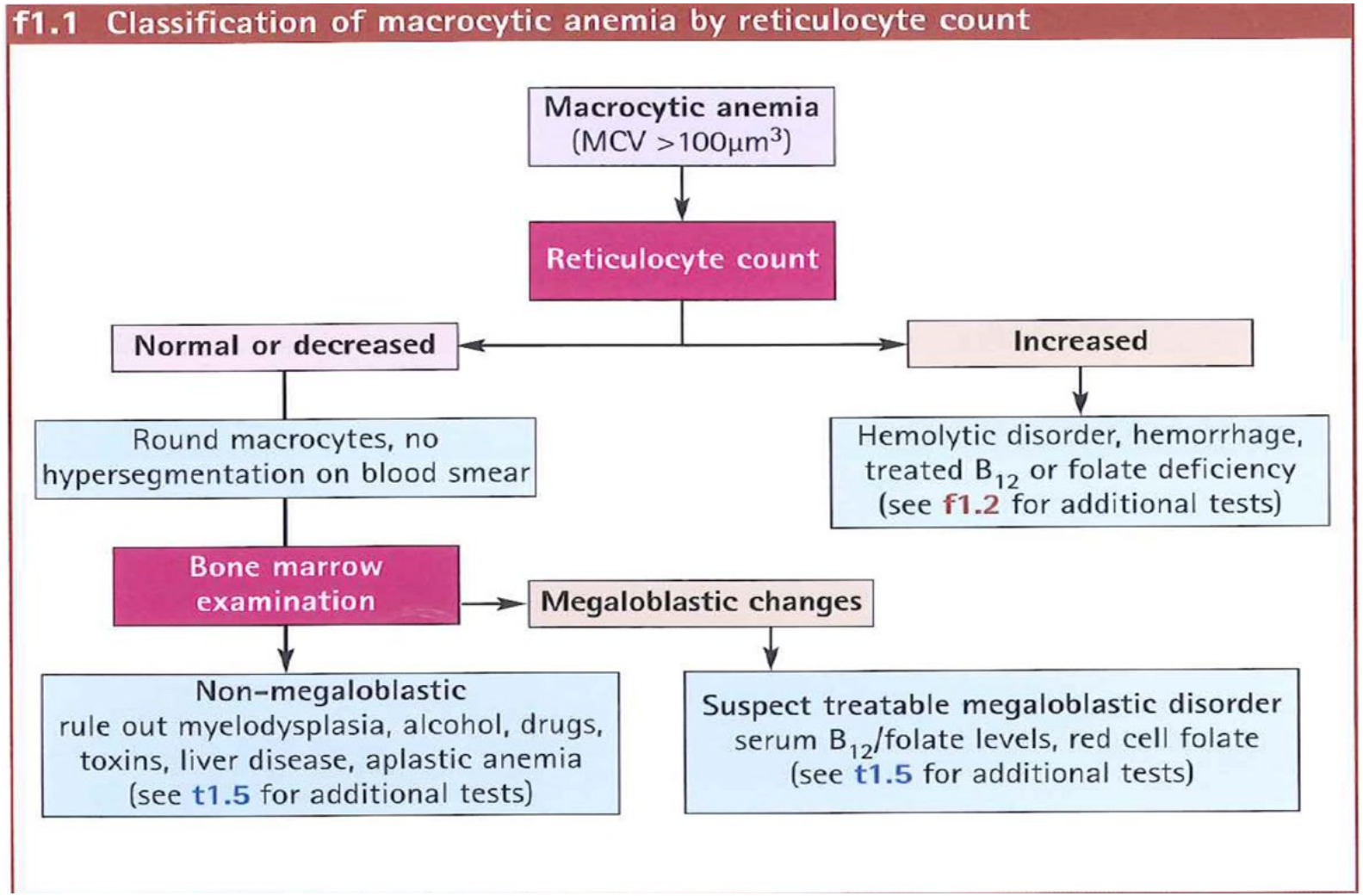
- Increased MCV (>100 fL)

- Megaloblastic
  - DNA replication disorders
  - Hypoproliferative anemia (decreased reticulocyte production)
  - Causes:
    - B12 deficiency
    - Folate deficiency

    ⌐ necessary for production of DNA

- Non-megaloblastic
  - Hypoproliferative (decreased reticulocyte production):
    - Excess alcohol use
    - Liver disease
    - Lipid disorders
    - Hypothyroidism
    - Myelodysplasia
  - Hyperproliferative (increased reticulocyte production):
    - Hemorrhage
    - Hemolysis

Macrocytic anemia

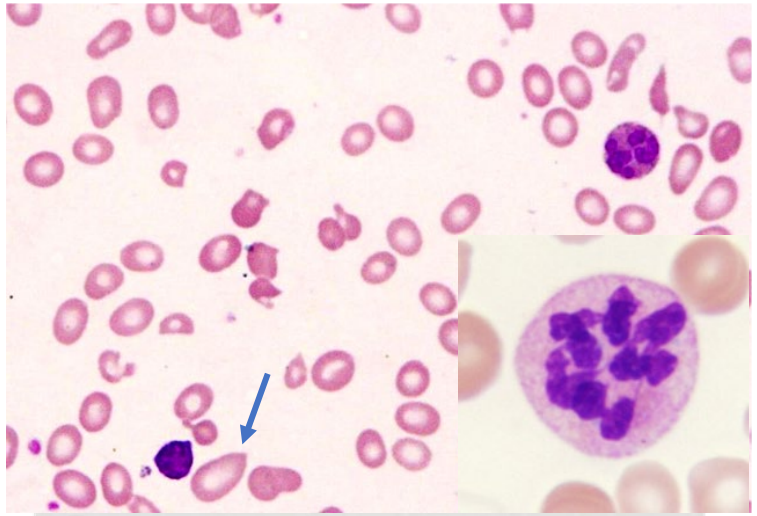


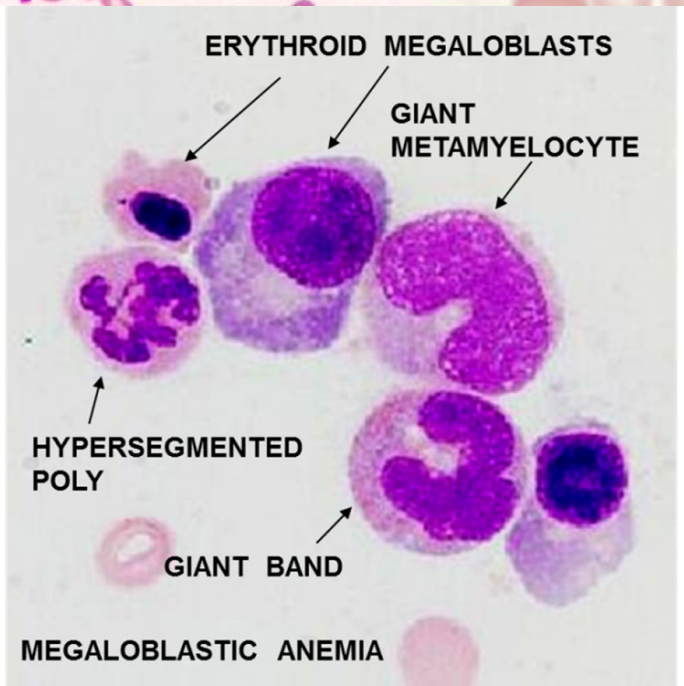
Megaloblastic anemia

- Clinical findings
  - Symptoms of anemia: fatigue, weakness, pallor, tachycardia
  - B12 deficiency: neurologic impairment
    - Decreased vibratory sensation in lower extremities
    - Demyelination of posterior and lateral columns
- CBC
  - Decreased hemoglobin, hematocrit, RBC count
  - High MCV
  - +/- decreased WBC, platelets
- Diagnostic tests
  - Serum B12, folate levels
  - B12 deficiency – consider pernicious anemia
    - Anti-intrinsic factor antibodies
    - Anti-parietal antibodies

Megaloblastic anemia

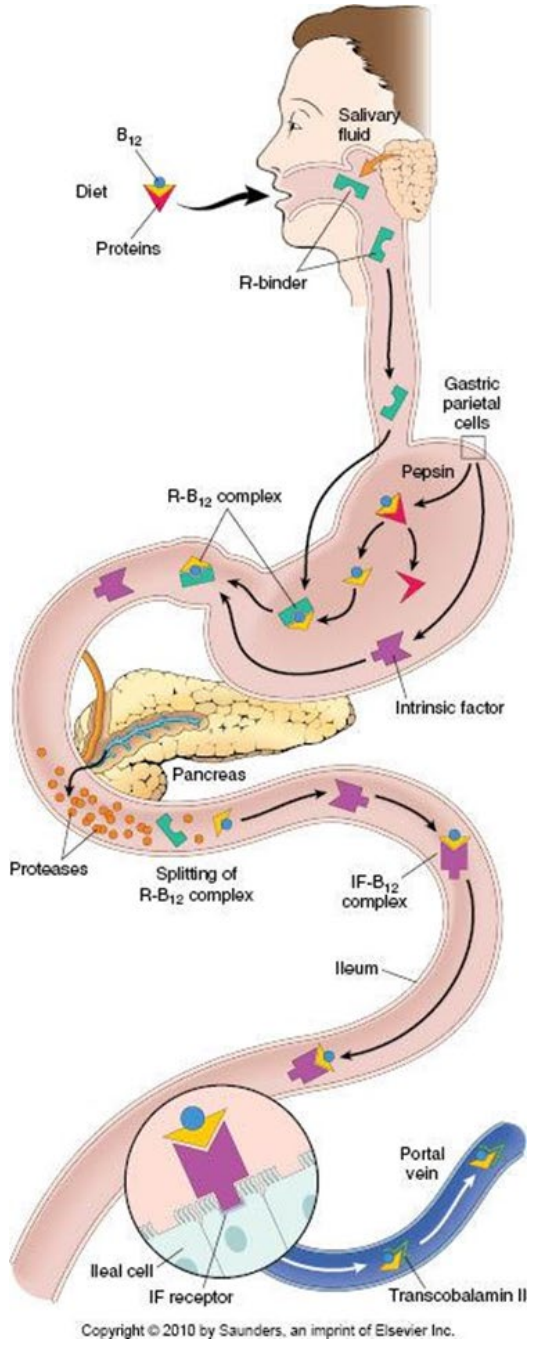
- Peripheral blood smear
  - Oval, teardrop macrocytes
  - Anisopoikilocytosis
  - Large platelets
  - Nucleated RBCs
  - Large neutrophils
  - Hypersegmented neutrophils
- Bone marrow
  - Dysplastic changes
    - Abnormally large RBC/WBC precursors





Vitamin B12 (cobalamin)

- Human intake dependent on dietary intake
  - Animal products
  - Excess stored in liver
- Absorption:
  - Vitamin B12 is freed from food by pepsin
  - Haptocorrin protects B12 from degradation
  - Pancreatic proteases split haptocorrin from B12
  - Intrinsic factor (IF) binds B12
  - IF bound with B12 endocytosed by ileal cells
  - Inside ileal cells, B12 binds to transcobalamin II and is secreted into plasma
  - B12 is delivered to liver and other areas that need it

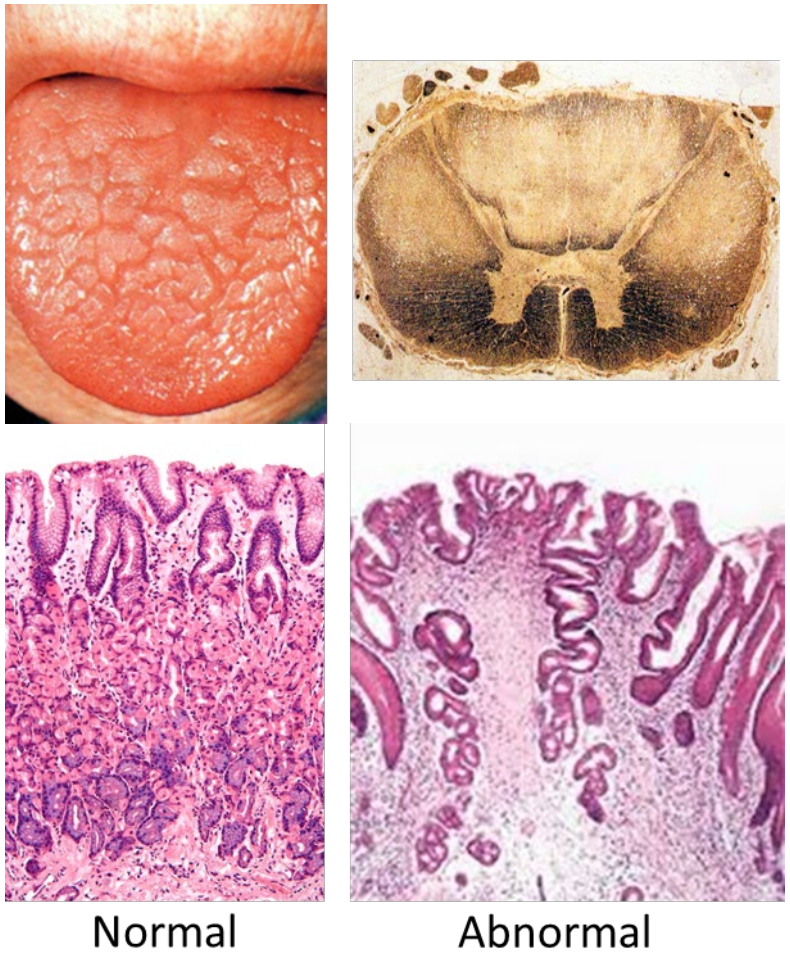


Vitamin B12 deficiency

- Decreased intake
  - Inadequate diet
  - Vegetarian/vegan
- Impaired Absorption
  - Intrinsic factor deficiency
    - Pernicious anemia, gastrectomy, gastritis
  - Malabsorptive states
  - Diffuse intestinal disease (Crohn's disease)
  - Bacterial overgrowth, parasites
  - Pancreatic insufficiency
  - Agents that block absorption: proton pump inhibitors, inherited transcobalamin II deficiency
- Increased requirement
  - Pregnancy
  - Hyperthyroidism
  - Cancer

Tapeworm

Pernicious anemia



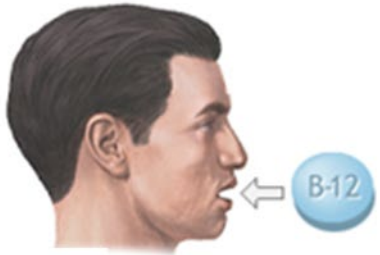
Normal Abnormal

- Lack of intrinsic factor
  - Likely due to autoimmune attack of gastric mucosa
- Signs and symptoms
  - Pancytopenia
  - Neuropathy (peripheral and central)
  - Papillary atrophy of tongue
  - pH elevation in stomach
  - Psychosis
- Diagnostic tests
  - Antibodies:
    - Anti-parietal cell (sensitive, less specific)
    - Anti-IF antibodies (specific, less sensitive)
  - Schilling test
- Treatment
  - Supplemental intrinsic factor

Pernicious anemia: Schilling test

- Part 1:
  - Patient is given oral radioactive B12 + intramuscular B12 injection
    - Intramuscular B12 saturates liver receptors
  - If B12 is absorbed by the GI, the radiolabeled B12 should pass into the urine
  - The urine is tested for radioactive B12
    - Normal = ↑ amount of the labeled B12 in urine
    - Abnormal = ↓ labeled B12 in urine (remained in bowel, passed into feces)

- Part 2: (performed only if part one yields abnormal result)
  - Repeat steps of part one + supplemental intrinsic factor
  - Normal (↑ labeled B12 in urine) = diagnostic of pernicious anemia (body was missing IF)
  - Abnormal (↓ labeled B12 in urine) = indicates malabsorption



Radioactive B12 ingested


Injection of nonradioactive vitamin B12 given


Urine samples are collected

Folate (folic acid/pteroglutamate)

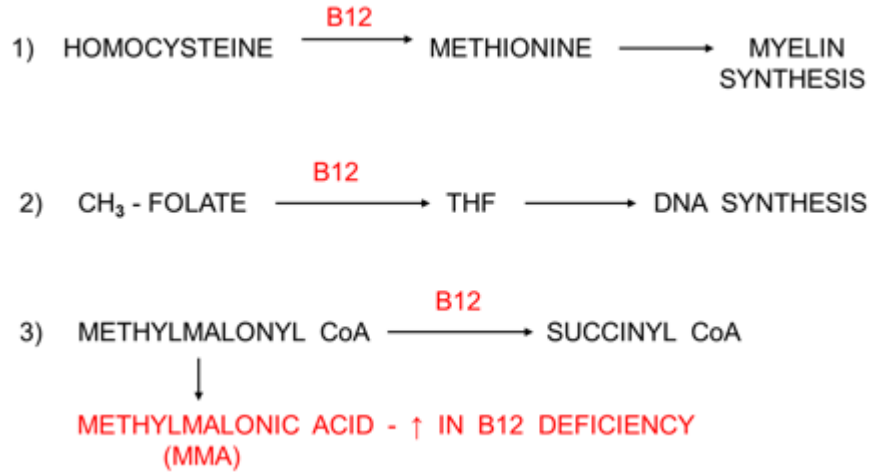
- Human intake dependent on dietary intake
  - Green veggies, fruits, fortified cereals, dairy products, liver
  - Heat labile
- Absorbed in duodenum, jejunum
- Stored in liver (stores last 3-4 months)
- Function:
  - Transfers carbon units in many biochemical reactions
    - Purine synthesis → DNA synthesis

Folate deficiency

- Decreased intake
  - Poor diet
- Decreased absorption
  - Celiac disease, inflammatory bowel disease, short bowel syndrome
- Increased requirement
  - Pregnancy, lactation, chronic hemolytic anemia, exfoliative dermatitis, infancy, disseminated cancer
- Impaired utilization
  - Drugs acting as folic acid antagonists: methotrexate, phenytoin, oral contraceptives, trimethoprim

B12 vs. folate deficiency

- CBC and peripheral blood findings similar in both
- Measure B12 and RBC folate levels
  - If ambiguous results, measure homocysteine and methylmalonic acid
- Folate given when B12 is deficient:
  - Anemia may be reversed
  - Neurologic problems will persist



	B12 Deficiency	Folate Deficiency
Folate	Normal	↓
B12	↓	Normal
Homocysteine	↑	↑
Methylmalonate	↑	Normal
Neurologic Defects	Yes	No

Microcytic anemia

Microcytic anemia (low MCV)

- Disorders of iron metabolism
  - Iron deficiency
    - Poor intake/increased requirement
    - Malabsorption
  - Chronic infection/inflammation
  - Neoplasia

} Anemia of chronic disease

- Sideroblastic anemias
- Lead toxicity
- Thalassemias

Iron deficiency anemia

- Anemia due to insufficient iron

- Signs and symptoms:
  - Pica
  - Koilonychia
  - Angular chelitis
  - Smooth tongue/glossitis

Iron deficiency anemia: Causes

- Low dietary intake
  - Most common in developing world
  - Breast milk low in iron
- Malabsorption
  - Celiac disease
  - Post-gastrectomy
- Increased demand
  - Pregnancy
  - Infancy
- Chronic blood loss - most common in US
  - GI tract (peptic ulcers, colon cancer, hemorrhoids)
  - Female genital tract (menorrhagia, cancer)

Laboratory evaluation of iron

- Serum Iron
  - Amount of iron in blood
  - Normal 60-170 µg/dL
- Total Iron Binding Capacity (TIBC)
  - Amount of transferrin available for binding iron
  - Normal 250-370 µg/dL
- % Saturation
  - Amount of transferrin bound to iron
  - Normal 20-50%
- Ferritin
  - Indirect indication of iron stores
  - Normal 20-200 µg/dL

Laboratory diagnosis of iron deficiency anemia

- CBC
  - ↓ hemoglobin and hematocrit
  - ↓ MCV
  - ↓ MCH
  - ↓ MCHC
- Peripheral blood smear
  - Anisopoikilocytosis
  - Microcytic RBCs
  - Hypochromic RBCs
- Serum iron studies
  - ↓ iron
  - ↓ ferritin
  - ↓ % iron saturation
  - ↑ total iron binding capacity (TIBC)

Stages of iron deficiency anemia

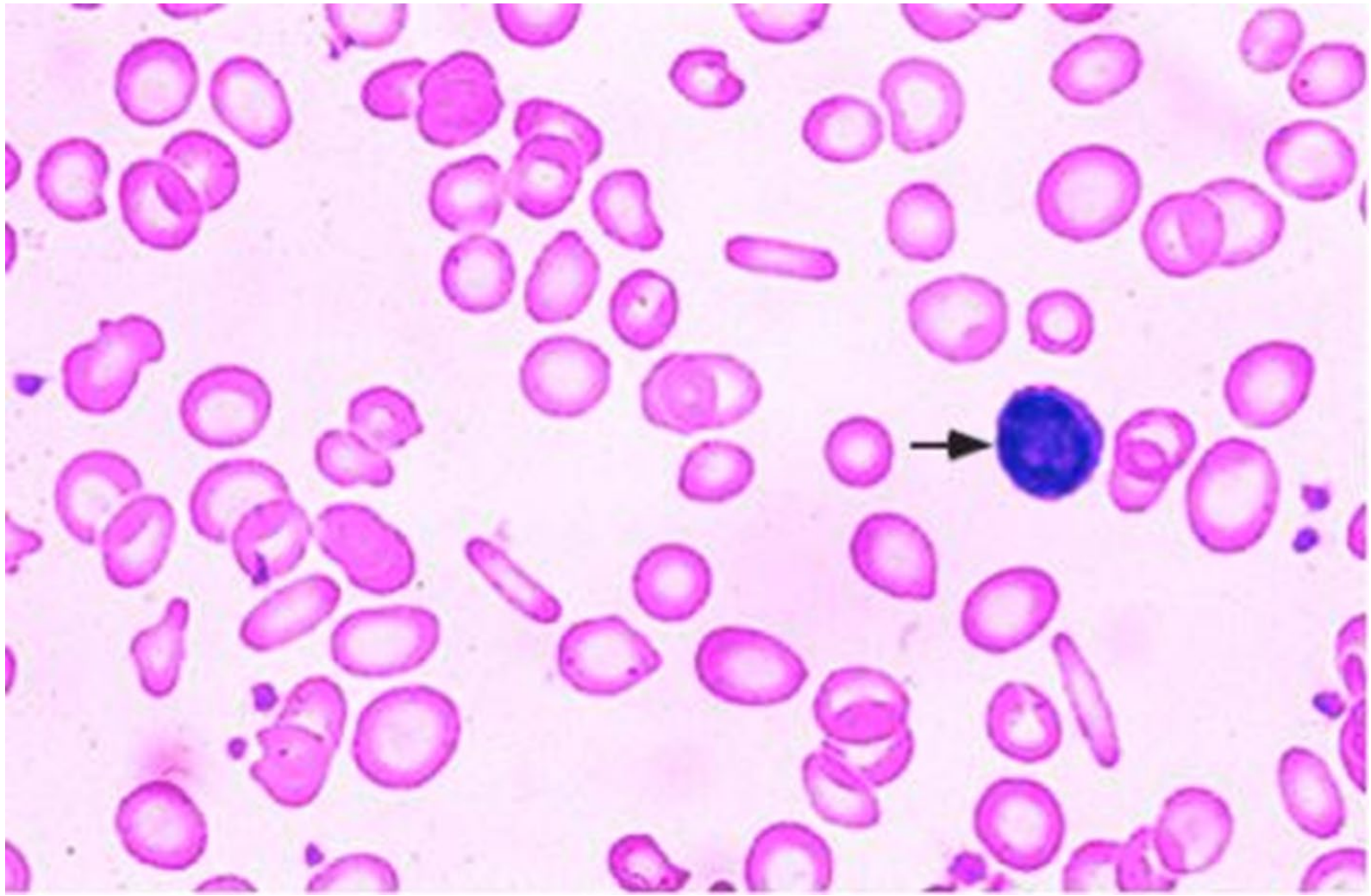
1. Depletion of storage iron
   - Low ferritin
   - High TIBC

2. Depletion of serum iron
   - Low iron
   - Low % saturation

3. Normocytic anemia

4. Microcytic, hypochromic anemia

Iron deficiency anemia: peripheral blood smear



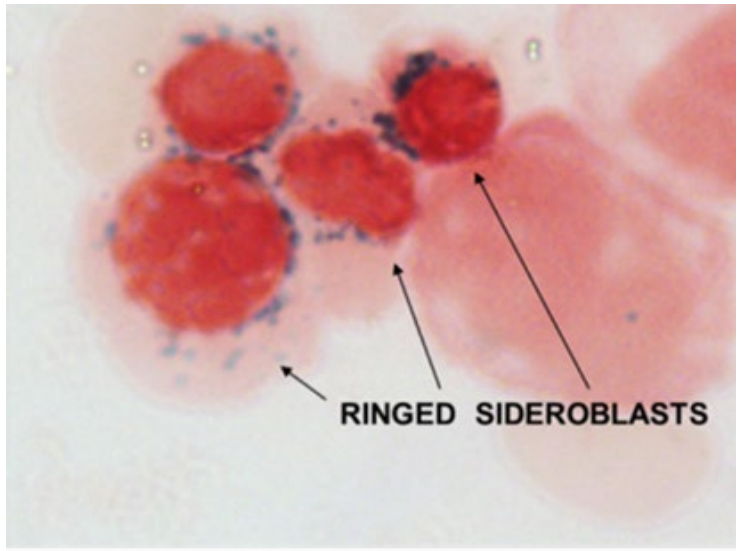
Anemia of chronic disease

- Most common anemia in hospitalized patients
- CBC
  - Moderate anemia
  - Normocytic or microcytic
  - Normochromic or hypochromic
- Associated conditions
  - Chronic infections
  - Chronic immune disorders
  - Neoplasms
- Iron studies
  - Decreased iron
  - Decreased TIBC
  - Increased ferritin

- Physiologic mechanisms:
  - Improper iron transfer
    - Iron trapped in bone marrow macrophages
    - Increased bone marrow storage iron
    - Decreased access of iron for use in hemoglobin synthesis
  - Inhibition/suppression of erythropoiesis by cytokines (hepcidin)

Sideroblastic anemia

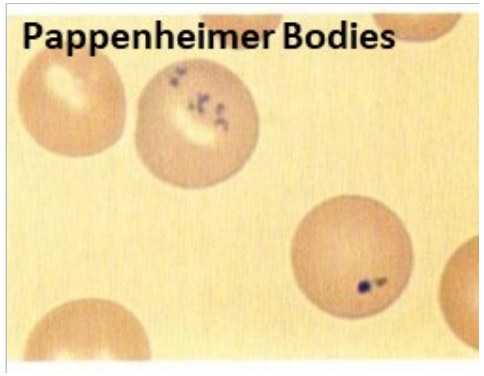
- Defective protoporphyrin synthesis
  - ↓protoporphyrin → ↓heme → ↓hgb → anemia
- Causes:
  - Inherited
  - Myelodysplastic syndrome
  - Alcohol abuse
  - Drugs
  - Toxic exposure
    - Lead
    - Zinc
    - Arsenic
  - Vitamin B6 deficiency
- Iron studies
  - Increased iron
  - Increased ferritin
  - Increased % saturation
  - Decreased TIBC

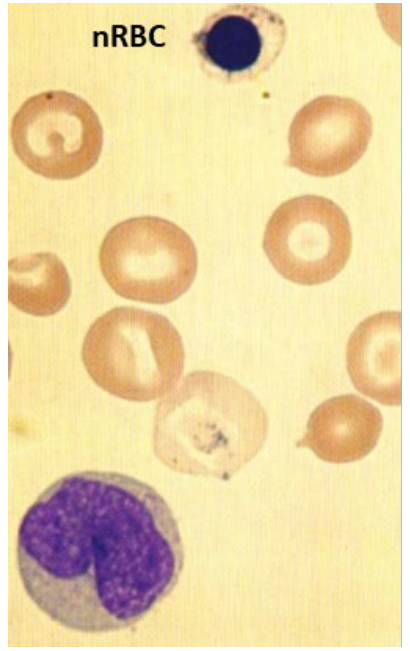


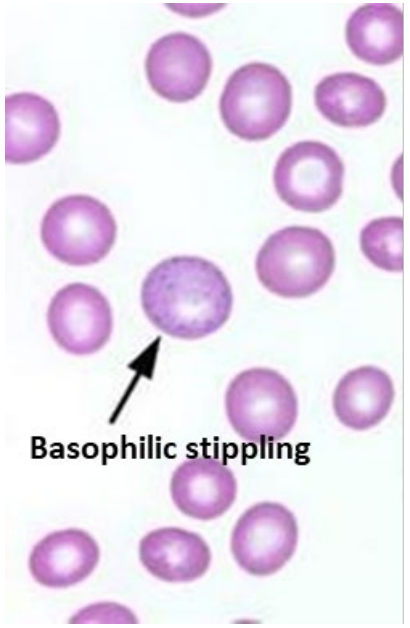
Sideroblastic anemia

- Peripheral blood smear
  - Dimorphic RBC population
    - Increased RDW
  - Hypochromic or normochromic
  - Microcytic or normocytic
  - Pappenheimer bodies (iron)
  - Basophilic stippling
  - +/- nucleated RBCs (nRBC)

- Bone marrow biopsy
  - Ringed sideroblasts

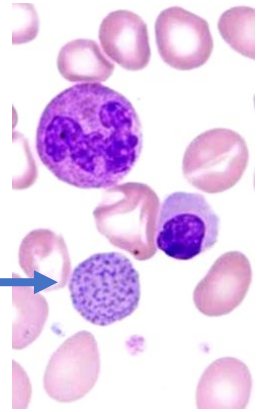






Lead toxicity

- Interferes with heme production
- Peripheral blood smear
  - Hypochromic RBC's
  - Normal RDW
  - Basophilic stippling



- Other lab tests
  - Increased lead level
  - Increased aminolevulinic acid
  - Increased free erythrocyte protoporphyrin (FEP)

- Signs and symptoms
  - Neurologic changes
  - GI upset
  - Gingival "lead line"

Microcytic anemias: iron studies

	Iron Deficiency	Anemia of Chronic Disease	Sideroblastic Anemia
Serum Iron	↓	↓	↑
TIBC	↑	↓	↓
% Saturation	↓	↓	↑
Serum Ferritin	↓	↑	↑

Microcytic anemias: CBC findings

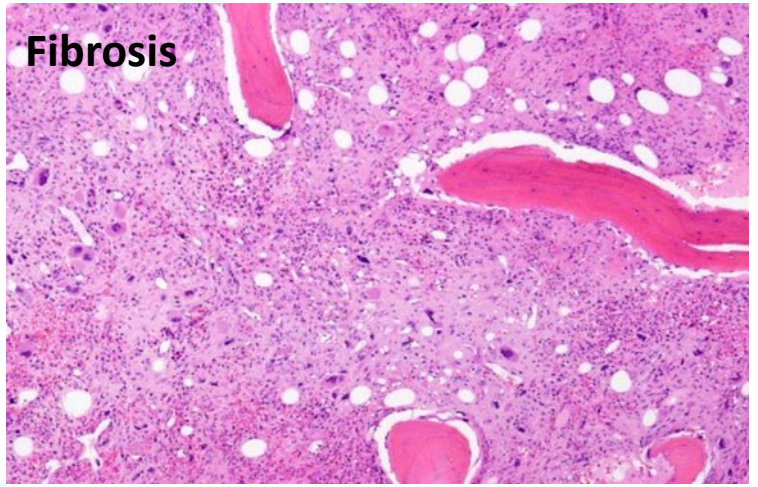
Cause	RBC #	RDW	Anisopoikilo-cytosis	Basophilic Stippling
Iron Deficiency	↓	↑	Yes	No
Thalassemia	Normal/↑	Normal	No	Yes
Sideroblastic	↓	↑	Yes	Yes
Chronic Disease	↓	Varied	Varied	No

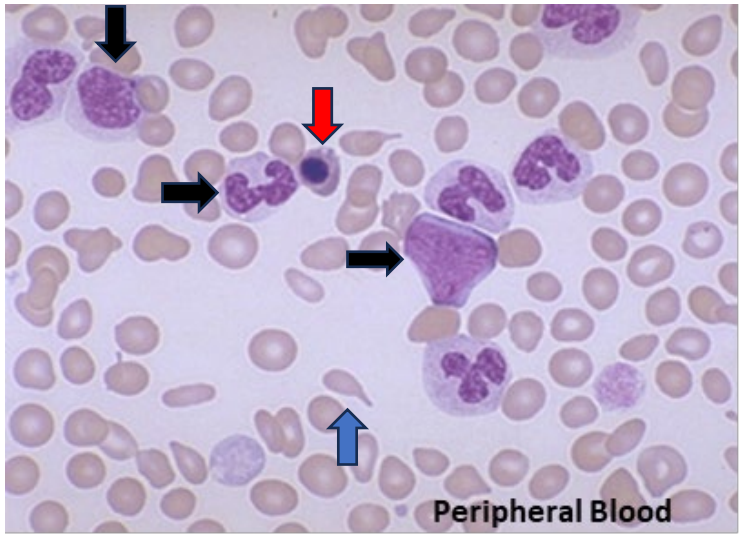
Myelophthisic anemia

- Bone marrow is replaced by non-hematopoietic elements
  - Fibrosis
  - Metastatic cancer
  - Granulomatous infection

- Peripheral blood smear
  - Leukoerythroblastosis
    - **Immature/left shifted granulocytes**
    - **Nucleated RBCs**
    - **Teardrop shaped RBCs/dacryocytes**

- Splenomegaly +/- hepatomegaly
  - Extramedullary hematopoiesis





Questions?