ANEMIA OF LOW PRODUCTION

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ANEMIA OF DECREASED PRODUCTION

General causes:

- Nutritional deficiency
- Chronic inflammation
- Bone marrow failure

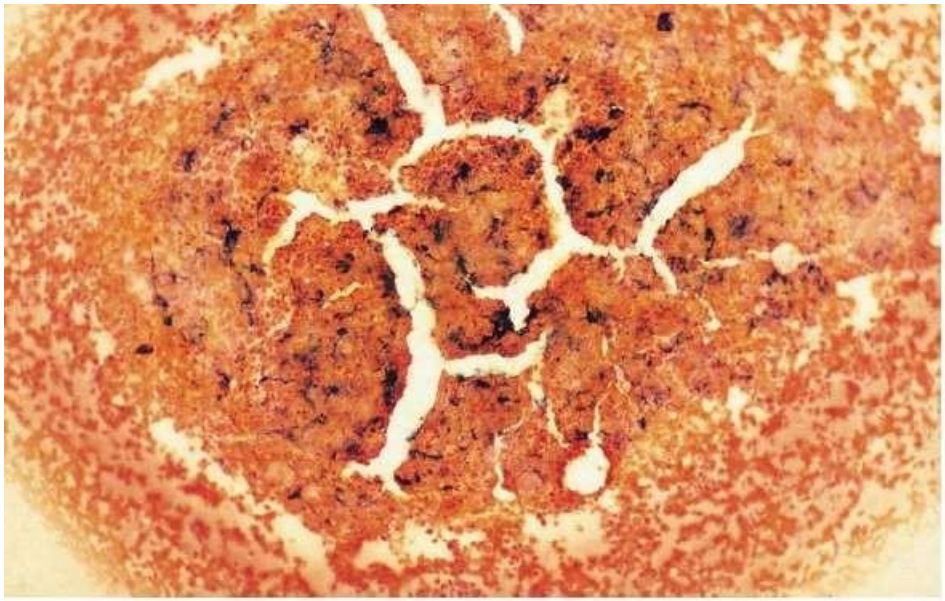
IRON DEFICIENCY ANEMIA

- Most common type of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries
- Iron storage pool: iron is stored in ferritin (soluble) and hemosiderin (insoluble) in bone marrow, liver and spleen, forming 15-20% of total iron
- Hemosiderin consists of large iron particles, granular in shape, intracellular, visible by light microscope
- Serum ferritin is derived from stored ferritin
- Serum iron is transported by transferrin, normally only one third of transferrin is saturated by iron

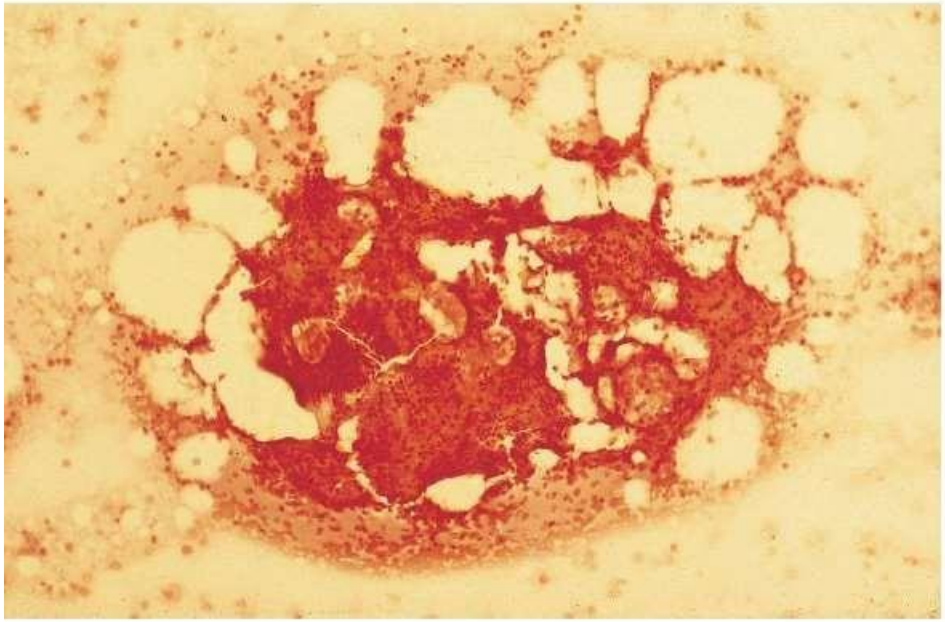
INDICATORS OF IRON STATUS

- Bone marrow aspirate: earliest changes, invasive procedure, Perl's Prussian blue stain (↓ in IDA)
- Serum ferritin level (↓ in IDA)*
- Serum iron level (↓ in IDA)
- Total iron binding capacity (↑ in IDA)
- Reticulocyte hemoglobin content (CHr): (↓ in IDA)
- Mean reticulocyte volume (MRV): (↓ in IDA)

* *Affected by inflammation (increased)*



Aspirate of normal bone marrow (BM): bluish-black iron (haemosiderin) in macrophages in a fragment. Perls' stain ×40.



Aspirate of normal BM: a fragment with no stainable iron. Perls' stain ×40.

IRON HOMEOSTASIS

- Normal loss of body iron: shedding skin and mucosal epithelium (no excretion)
- Dietary iron is either hem (red meat) or non-hem (inorganic, vegetarian)
- 20% of hem and 1% of non-hem iron are absorbed in duodenum

IRON HOMEOSTASIS

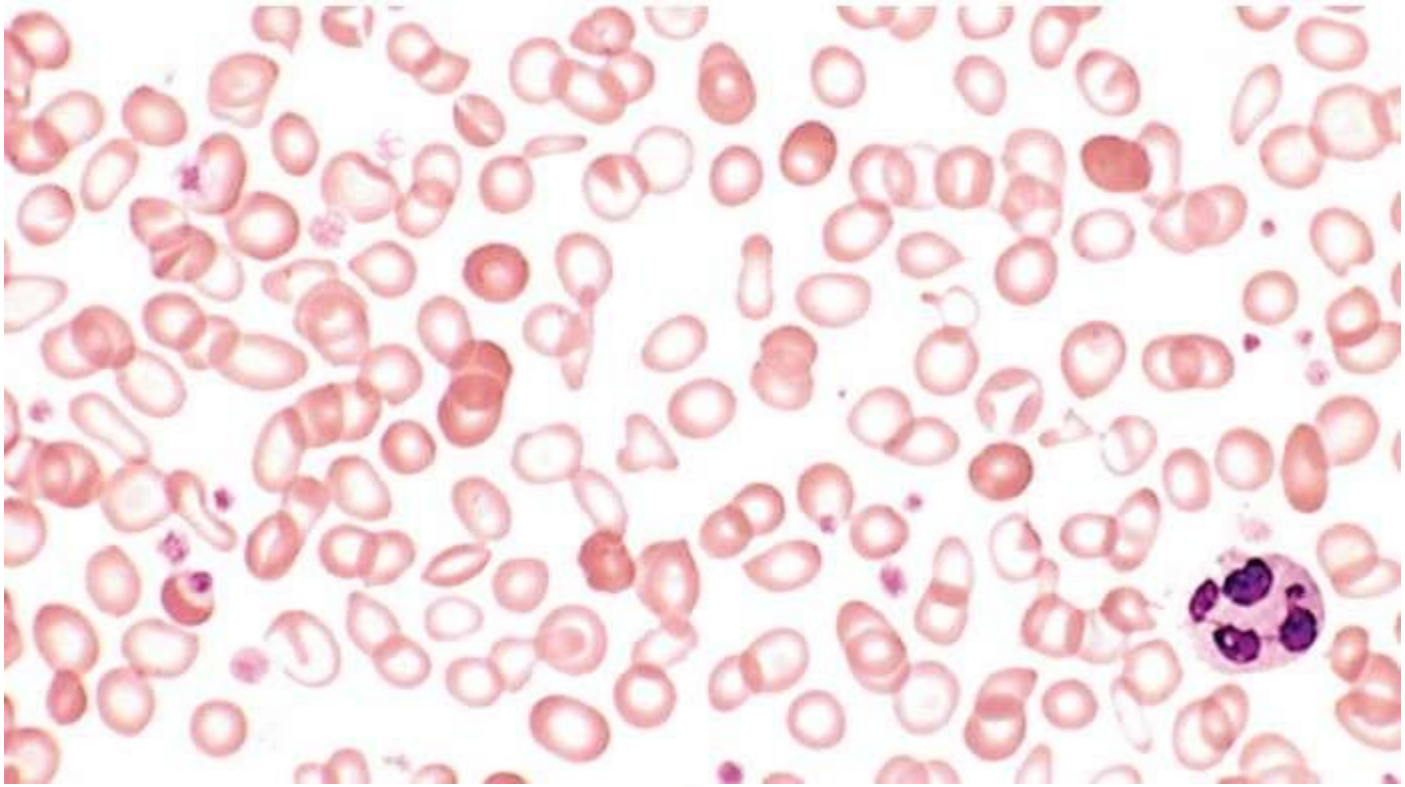
- Hepcidin: hormone secreted from liver, inhibits iron absorption (degradeferroportin on enterocytes)
- Hepcidin hormone is positively regulated by HFE protein on hepatocytes, which is activated when serum iron level rises
- Hepcidin hormone is also positively regulated by IL-6, which increases in inflammation
- Hepcidin is negatively regulated by erythroferrone, a hormone secreted by erythroblasts in bone marrow
- Low hepcidin: iron deficiency. Very low: thalassemia major (high erythroferrone), primary hemochromatosis (defective HFE)

CAUSES OF IRON DEFICIENCY

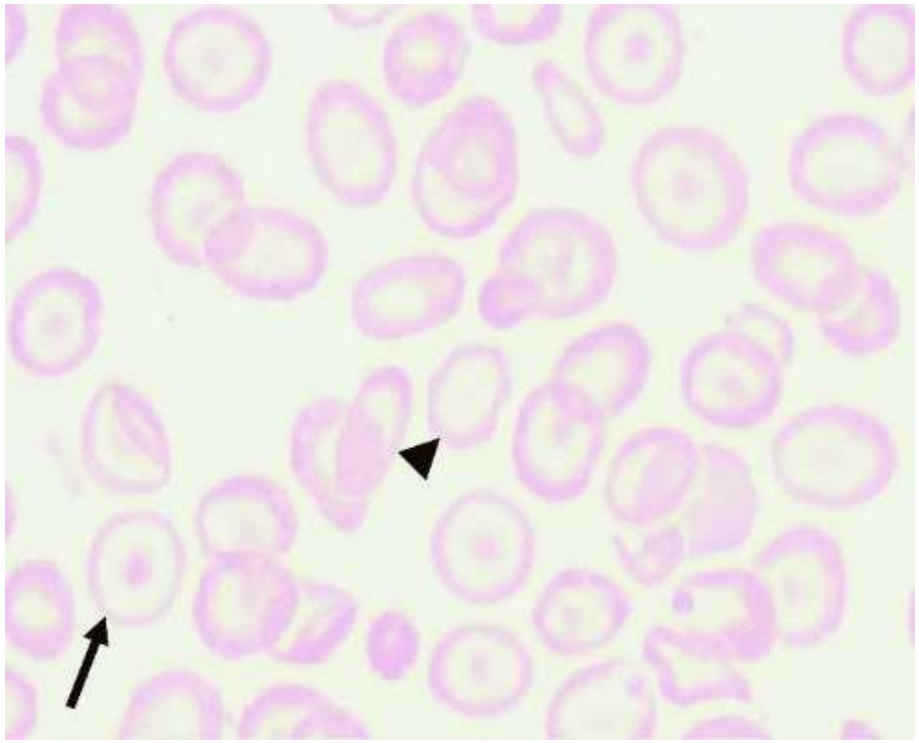
- Chronic blood loss
- Dietary: vegetarians, infants, teenagers
- Decreased absorption: gastrectomy, hypochlorhydria, intestinal diseases, elderly
- Increased demands: growing children, pregnancy, myeloproliferative neoplasms
- Hypotransferritinemia: decreased synthesis of transferritin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in urine (nephrotic syndrome)
- Enzymatic deficiency

MORPHOLOGY

- RBCs appear small and empty (hypochromic microcytic)
- Different shapes of RBCs appear (poikelocytosis)
- Target cells
- Low reticulocytes (Erythropoietin is high, but ineffective)
- Thrombocytosis is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid)



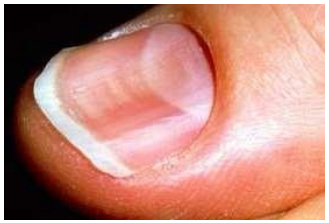
- IDA: note the hypochromia and poikelocytosis



- IDA: note the target cells (arrow)

SYMPTOMS

- IDA is a chronic anemia
- General symptoms of anemia
- Pica
- Glossitis, stomatitis
- Spooning of fingernails
- Restless leg syndrome
- Hair loss
- Blue sclera
- Weakened immunity
- Cognitive impairment



ANEMIA OF CHRONIC INFLAMMATION

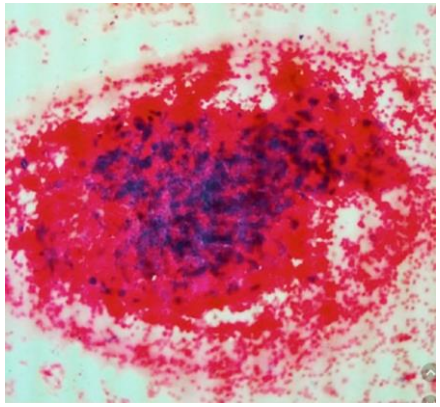
- Also called anemia of chronic disease
- Seen in chronic infections, cancer, chronic immune diseases
- Common in hospitalized patients
- High IL-6 → high hepcidin → blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages). Also suppress erythropoietin secretion from kidneys

LABORATORY FINDINGS

- Similar to IDA: serum iron is low
- RBCs: normal morphology, then hypochromic microcytic
- Reticulocytes ↓

In contrast:

- Bone marrow iron stores ↑
- Serum ferritin ↑



MEGALOBLASTIC ANEMIA

- Caused by deficiency in vitamin B12 or folate
- Both are required for synthesis of thymidine, thus DNA replication is impaired
- Abnormalities occur in all rapidly dividing cells, but hematopoietic cells are most severely affected
- Maturation of RBC progenitors is deranged, many undergo apoptosis inside bone marrow (ineffective erythropoiesis, mild hemolysis)
- Viable nucleated RBCs take a longer time to mature, resulting in typical morphology (megaloblastoid)

FOLATE DEFICIENCY

- Normally, minimal amount of folate is stored in human body
- Folate is vastly present in food (green leaves), but it is destroyed by cooking

Causes of deficiency:

- Decreased dietary intake
- Increased demands (pregnancy, chronic hemolytic anemia)
- Intestinal diseases
- Beans, legume, alcohol, phenytoin (inhibit absorption)
- Methotrexate: inhibits folate metabolism and cellular usage

VITAMIN B12

- Mainly present in animal products
- Resistant to cooking
- Synthesized by bacteria in bowel
- Enormous stores in the liver
- Dietary deficiency occurs most commonly in vegetarians
- More commonly: deficiency results from defective absorption

PERNICIOUS ANEMIA

- Autoimmune gastritis
- Autoreactive T-lymphocytes, causing injury to parietal cells
- Activates B-lymphocytes and plasma cells to synthesize and secrete auto antibodies that further damage parietal cells, and blocks binding of vitamin B12 to intrinsic factors

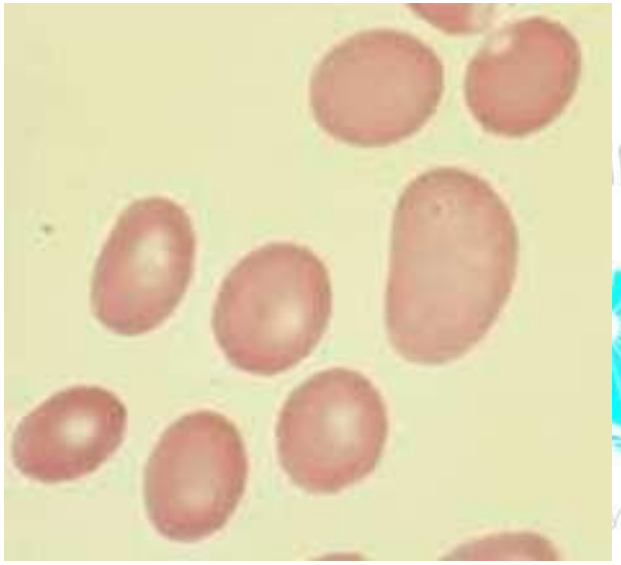
OTHER CAUSES OF VITAMIN B12 DEFICIENCY

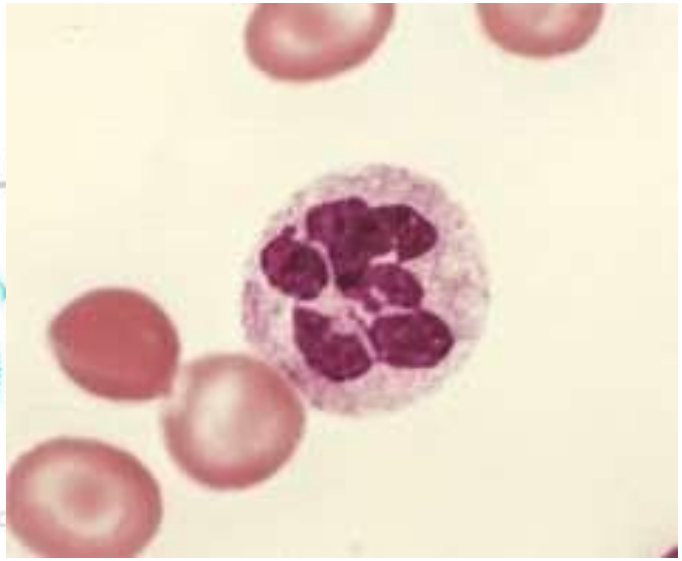
- Gastrectomy
- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- Metformin (inhibits absorption)

OTHER FUNCTIONS OF VITAMIN B12

- Recycling of tetrahydrofolate
- Synthesis of myelin sheath
- Synthesis of neurotransmitters (dopamine, serotonin)
- Metabolism of homocysteine (toxic to neurons)
- Degree of neuronal damage does not correlate with the degree of anemia

MORPHOLOGY OR MEGALOBLASTIC ANEMIA





- Macroovalocyte: characteristic of megaloblastic anemia

SYMPTOMS

- Chronic, general symptoms of anemia
- Glossitis (beefy tongue)
- Mild jaundice
- In severe cases: pancytopenia

<u>In vitamin B12 deficiency:</u>

- Posterior and lateral columns degeneration of spinal cord (paresthesia, loss of proprioception)
- Peripheral neuropathy
- Neuropsychotic symptoms

Aplastic Anemia

- Damage to multipotent stem cell in bone marrow
- Bone marrow becomes depleted of hematopoietic cells
- Peripheral blood pancytopenia
- Low reticulocytes
- Affects all age groups
- Patients develop life-threatening infections, bleeding and symptoms of anemia

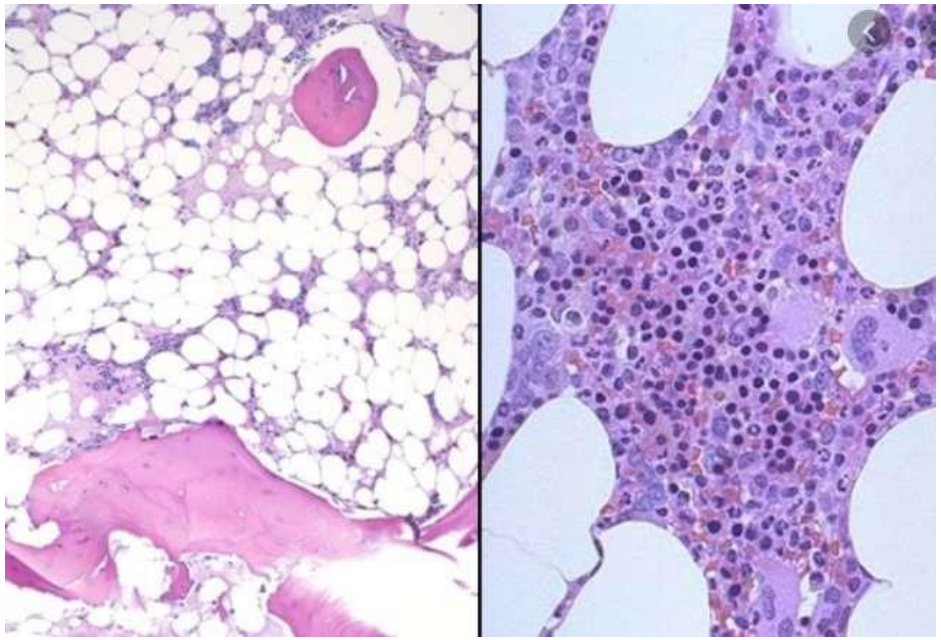
Pathogenesis

- **Extrinsic factor**
- Antigen cross reactivity with stem cells (drug, virus, environmental factor)
- Activated T-lymphocytes destroys stem cells
- Evidence: immunesuppressive drug restores bone marrow in 70% of cases
- Most cases are idiopathic
- Associated factors: chloramphenicol, gold injections, NSAID, pregnancy, some hepatitis viruses

- **Intrinsic factor**
- 10% of aplastic anemia patients have inherited defects in telomerase (stability of chromosomes)
- Stem cells die early
- These genetically altered stem cells might express abnormal antigen?? Attracting T-cells

Laboratory Findings

- Peripheral blood: pancytopenia, anemia is normochromic or macrocytic
- Bone marrow: decreased hematopoietic cells and predominance of fat



Special types of bone marrow failure

- Fanconi anemia: rare, inherited form of AA, defect in DNA repair proteins, patients develop AA and acute leukemia in early life

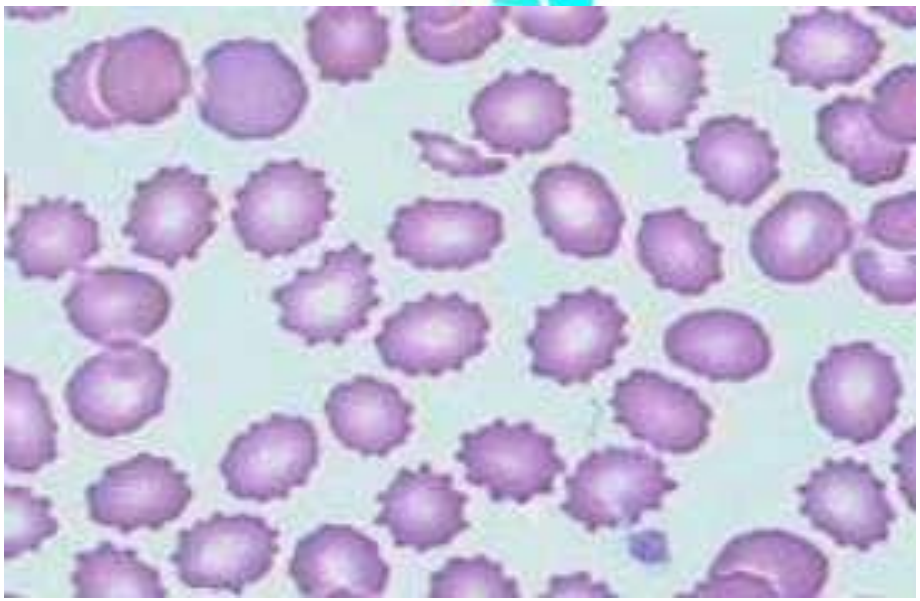
- Pure red cell aplasia: only erythroid cells are absent in bone marrow, can be congenital (Diamond-Blackfan anemia) or acquired (autoimmune, Parvovirus B19 infection)

Myelophthisic Anemia

- Infiltration of bone marrow causing physical damage to hematopoietic cells
- Cancer: most commonly in acute leukemia, advanced lymphoma, metastatic cancer
- Granulomatous disease: TB
- Storage diseases: Gaucher
- Immature granulocytic and erythroid precursors commonly appear in peripheral blood

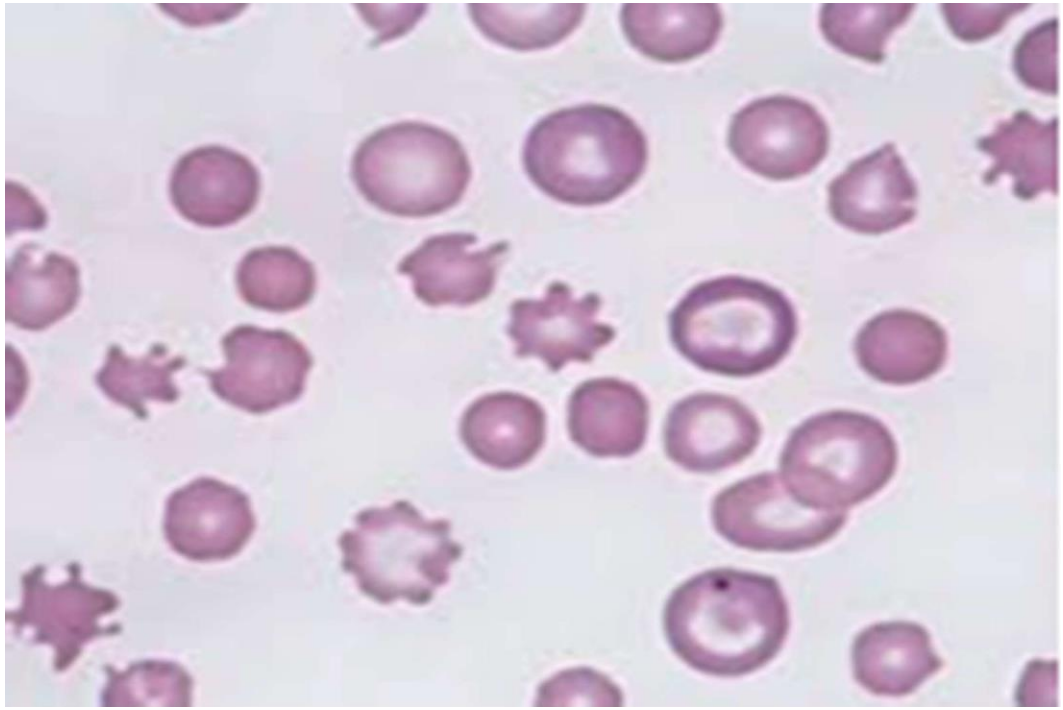
Anemia of renal disease

- Mainly results from decreased erythropoietin production from kidneys
- Does not correlate well with kidney function (serum creatinine)
- Decreased RBC production (low retic count)
- Patients with uremia develop abnormal platelets function (bleeding), echinocytes (Burr cells) appear



Anemia of liver disease

- Multiple factors causing anemia
- Decreased synthesis of clotting factors (bleeding)
- Bleeding from varices
- Decreased synthesis of transferrin
- Acanthocyte (spur cell) appears



Anemia of hypothyroidism

- Thyroid hormones stimulate erythropoiesis
- Also stimulates erythropoietin production
- Anemia is most commonly normocytic, but can be marcocytic

Myelodysplastic syndrome

- Acquired neoplastic disease of bone marrow
- Primarily disease of old age
- Mutations in BM stem cell, results in prolonged survival and defective maturation
- Mature blood cells do not exist bone marrow like in the normal way
- Patients commonly develop neutropenia and thrombocytopenia as well
- Anemia is refractory to treatment
- RBCs are macrocytes