RBC disorders 2
Anemia of diminished production

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- Iron deficiency anemia
- Anemia of chronic disease
- Megaloblastic anemia
- Others
  - anemia in liver disease
  - anemia in renal disease
  - aplastic anemia
  - myelophthisic anemia

1. All of the following can be found in iron deficiency anemia, except:
   A. Low ferritin
   B. Low serum iron
   C. Low TIBC
   D. Low transferrin saturation
   E. Low MCV

2. Anemia of chronic disease is caused by elevated levels of:

A. Hepcidin

B. Iron

C. Ferritin

D. B12

E. neutrophils

3. All of the following are true regarding megaloblastic anemia, except:

A. defective DNA synthesis, resulting in nuclear immaturity

B. macrocytic anemia

C. can be seen in the setting of pernicious anemia

D. most common cause is nutritional deficiency of B12

E. can be associated with neurological symptoms in the case of B12 deficiency.

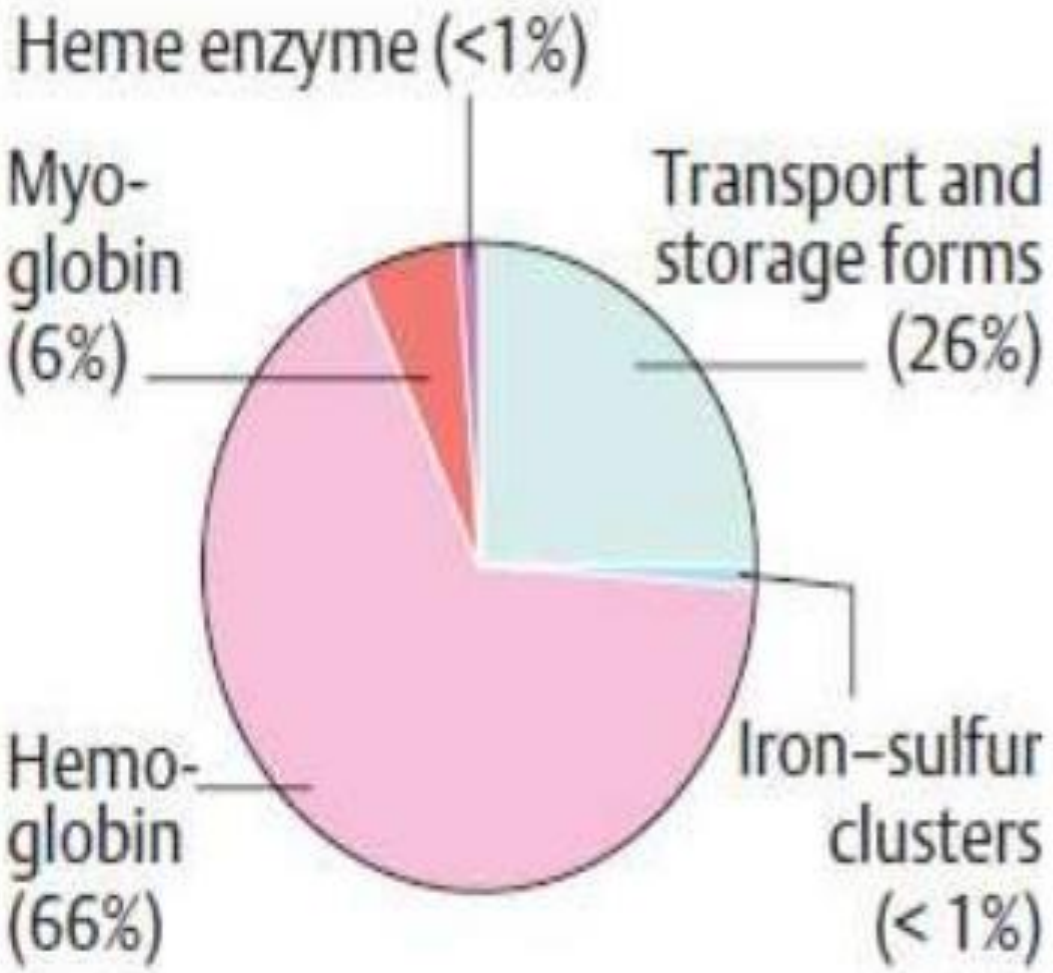
4. The most common cause of anemia in patients with liver disease is:

A. Iron deficiency
B. Hypersplenism
C. Therapy related hemolytic anemia
D. Therapy related suppression of EPO receptor
E. Alcoholic-cirrhosis-induced folate deficiency

5. One of the following can cause myelophthisic anemia:

A. Tuberculosis
B. B12 deficiency
C. Folate deficiency
D. Iron deficiency
E. Anemia of chronic disease.

Iron: Distribution

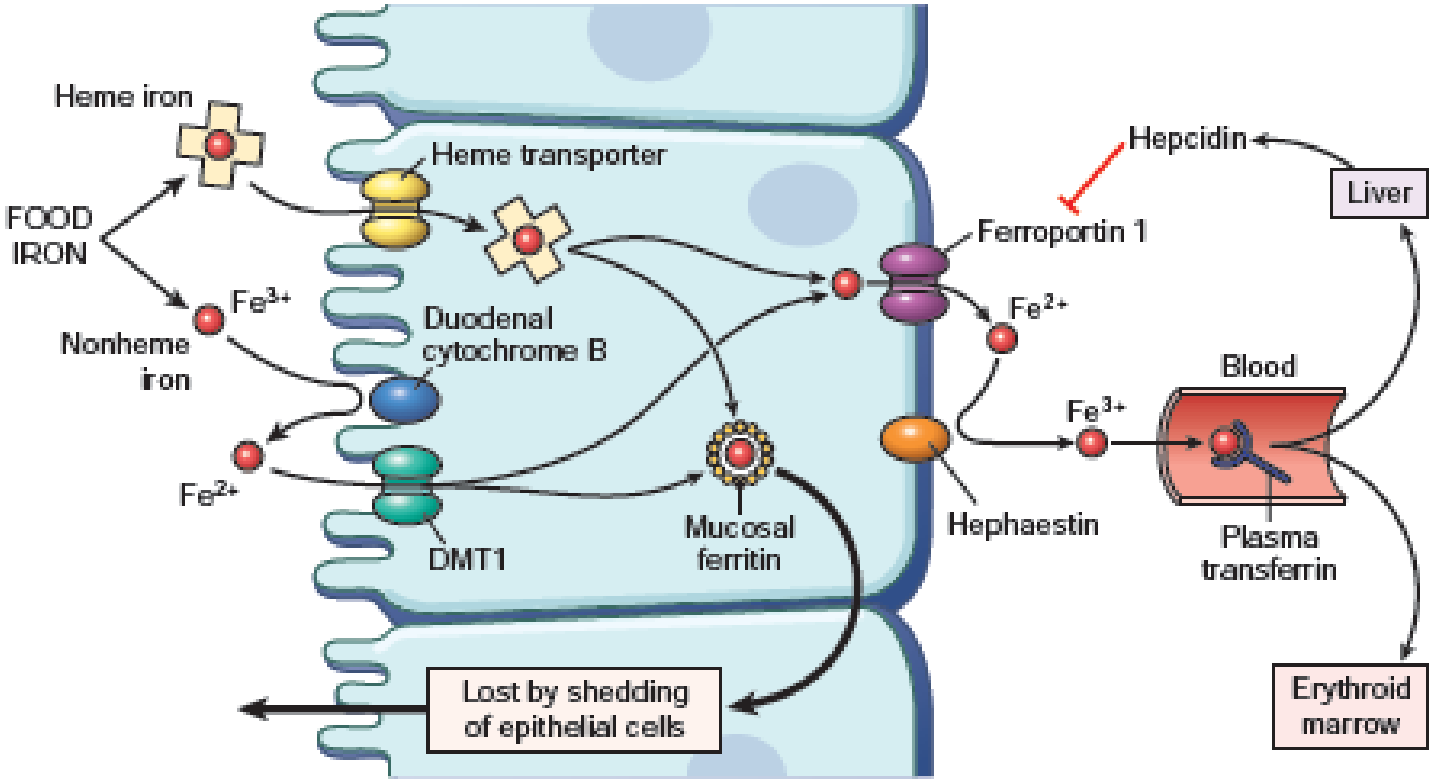


- human body: 4–5 g iron (protein-bound)
- **heme proteins (~72%)**
  - hemoglobin (2.5 g)
  - myoglobin (0.15 g)
- **transport and storage proteins (~26%)**
  - transferrin (1.0 g)
  - serum ferritin (0.0001 g)
- **iron–sulfur clusters (<1%)**
  - cofactors in the respiratory chain, other redox chains

- Transferrin is the major transport protein in plasma and is normally one third occupied.

- Plasma ferritin is derived largely from the storage pool of body iron; its levels correlate well with body iron stores, if total iron is decreased ferritin will be low, and vice versa.

- Iron balance is maintained through absorption, excretion is limited to 1-2mg/day through shedding of mucosal cells.


Heme iron
FOOD IRON
Nonheme iron
Fe3+
Fe2+
Heme transporter
Duodenal cytochrome B
DMT1
Mucosal ferritin
Lost by shedding of epithelial cells
Hepcidin
Liver
Ferroportin 1
Fe2+
Fe3+
Hephaestin
Blood
Plasma transferrin
Erythroid marrow

Iron deficiency anemia

- Deficiency of iron is the most common nutritional disorder in the world and results in clinical signs and symptoms that are **mostly related to inadequate hemoglobin synthesis**.

- Iron deficiency can result from
  - (1) dietary
  - (2) impaired absorption,
  - (3) increased requirement,
  - (4) chronic blood loss.

Question time!!!

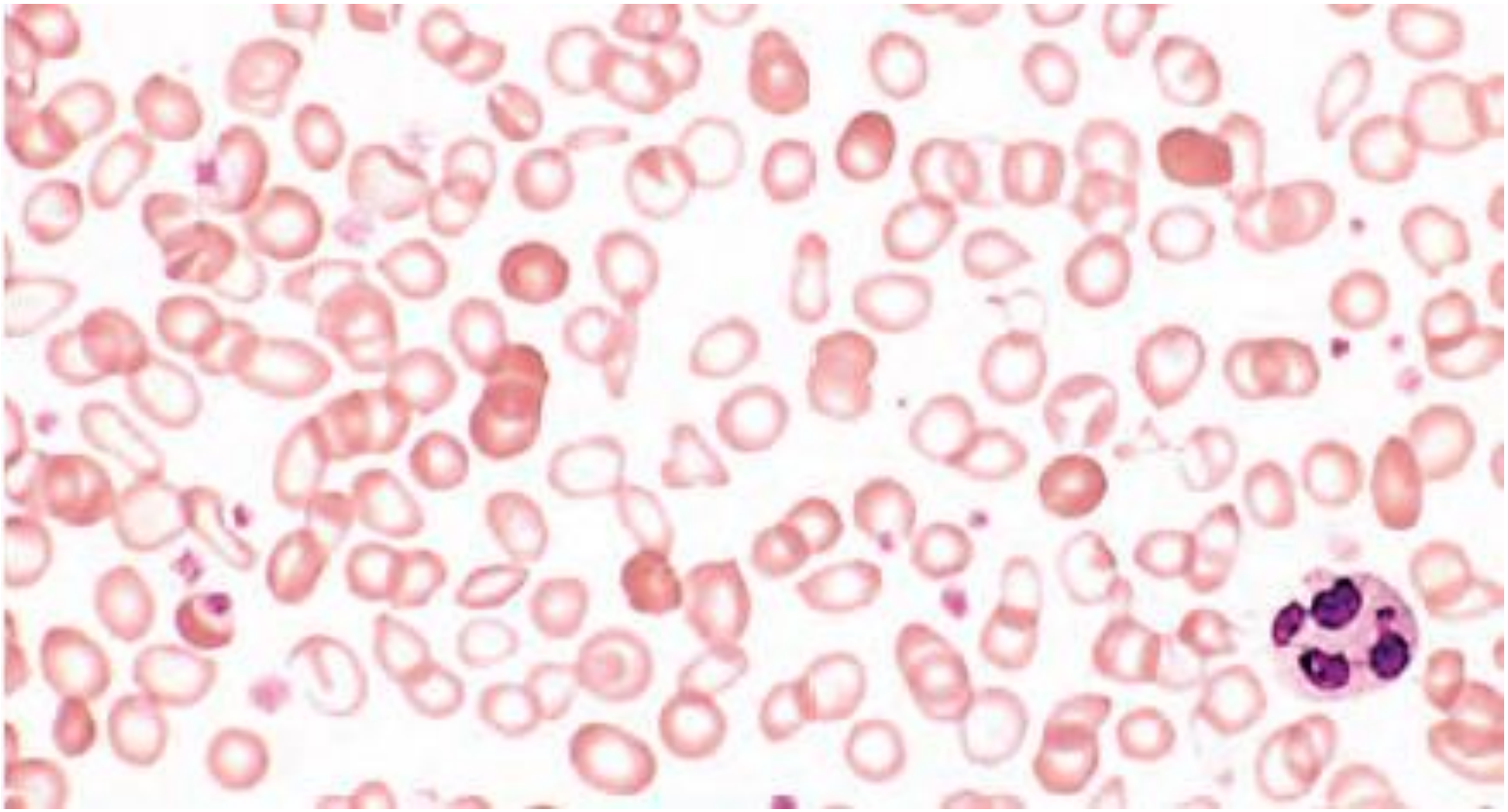
- Which clinical scenario is **more serious**
  - A 19 year old lady, with sever menorrhagia presenting with shortness of breath on exertion, fatigue, pallor and a hemoglobin of 7.6g/dl, low MCV
  - A 79 year old asymptomatic gentleman who, on routine check up, was found to have a hemoglobin of 11g/dl and low MCV

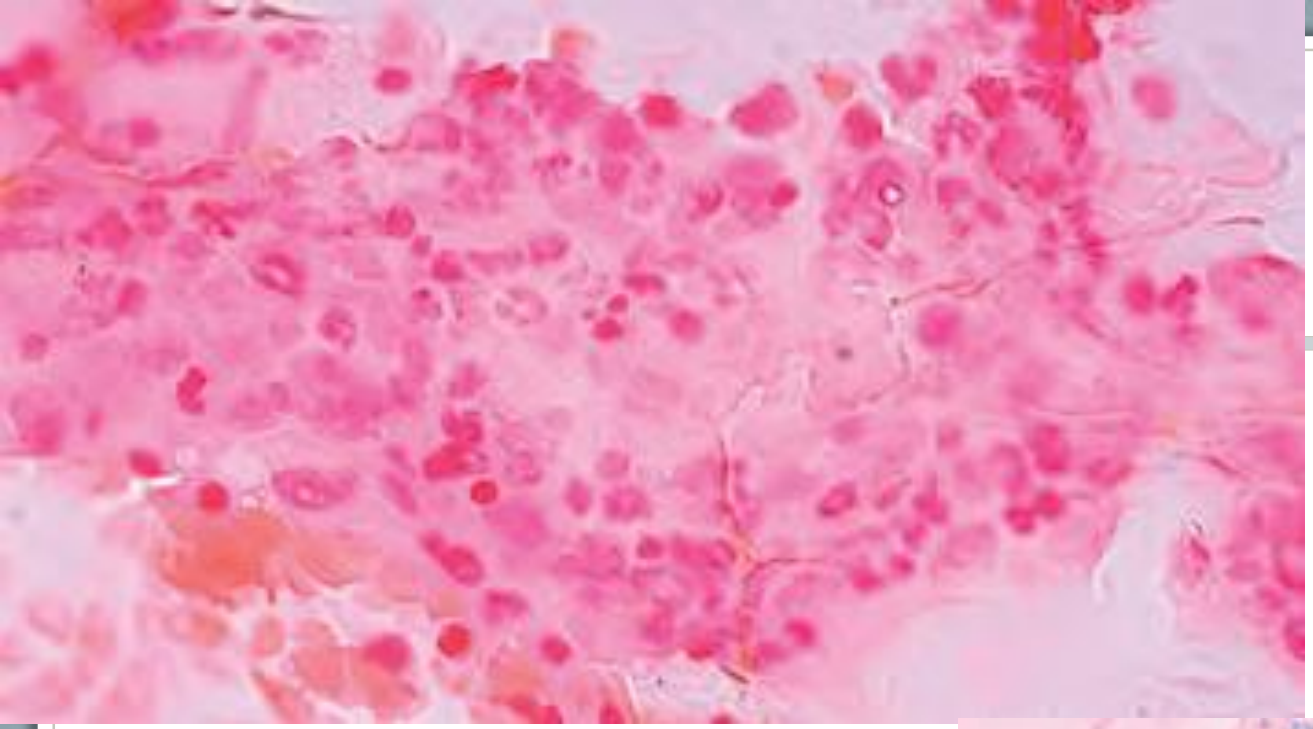
Think of anemia as you think of fever!!!

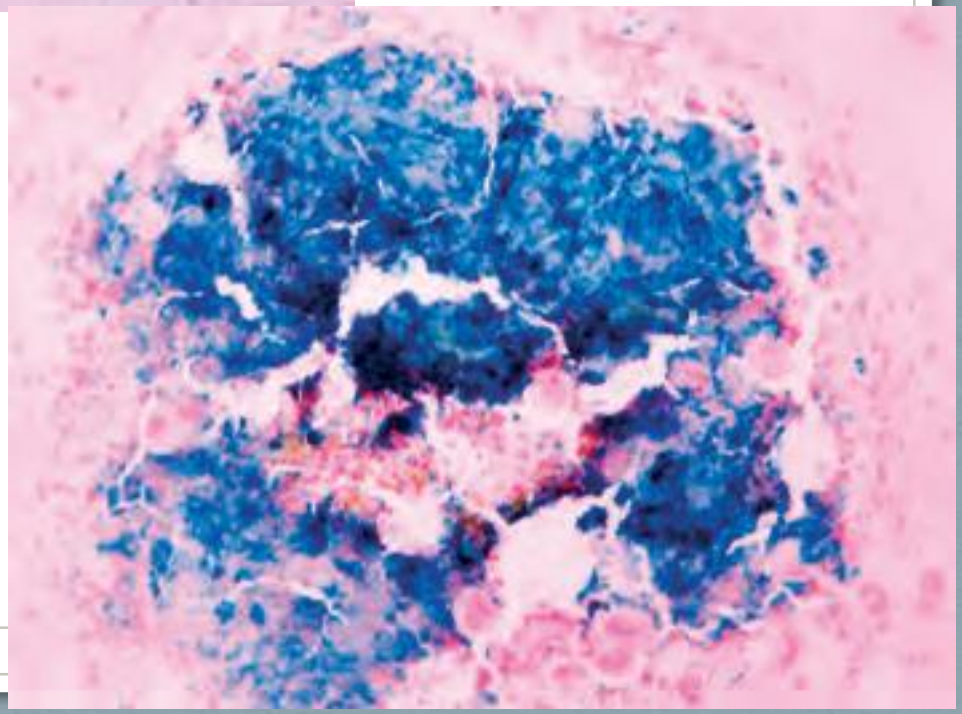
pathogenesis

- Negative iron balance due to any reason
- Compensation by storage iron
- Progressive deficiency until complete depletion
- Anemia develops accompanied by low ferritin and low transferrin saturation

morphology

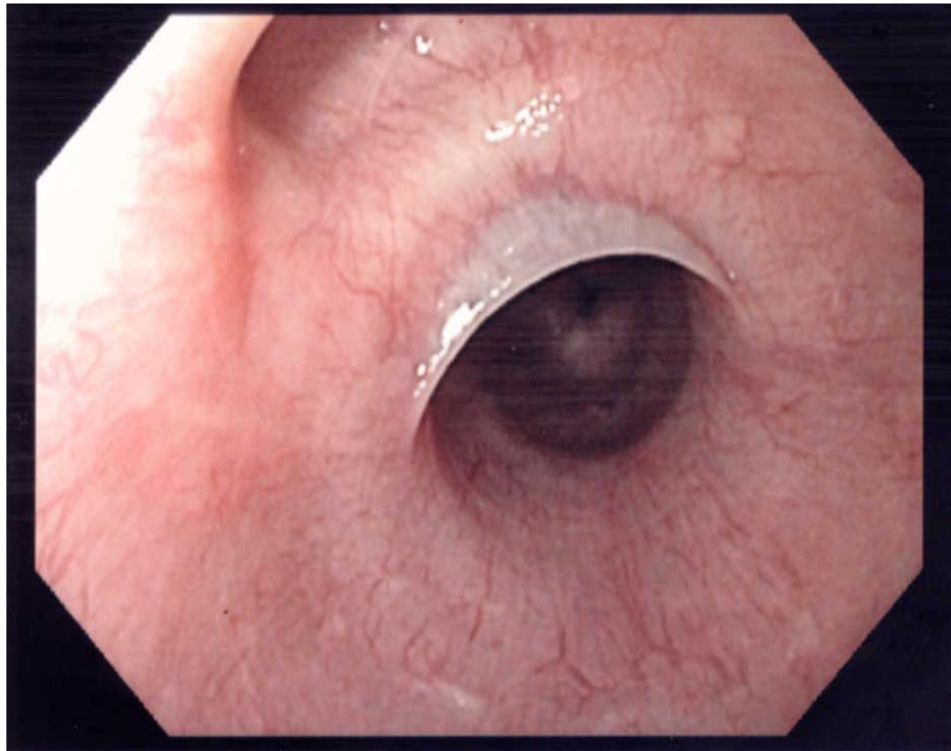






Clinical presentation

Symptoms and signs of anemia



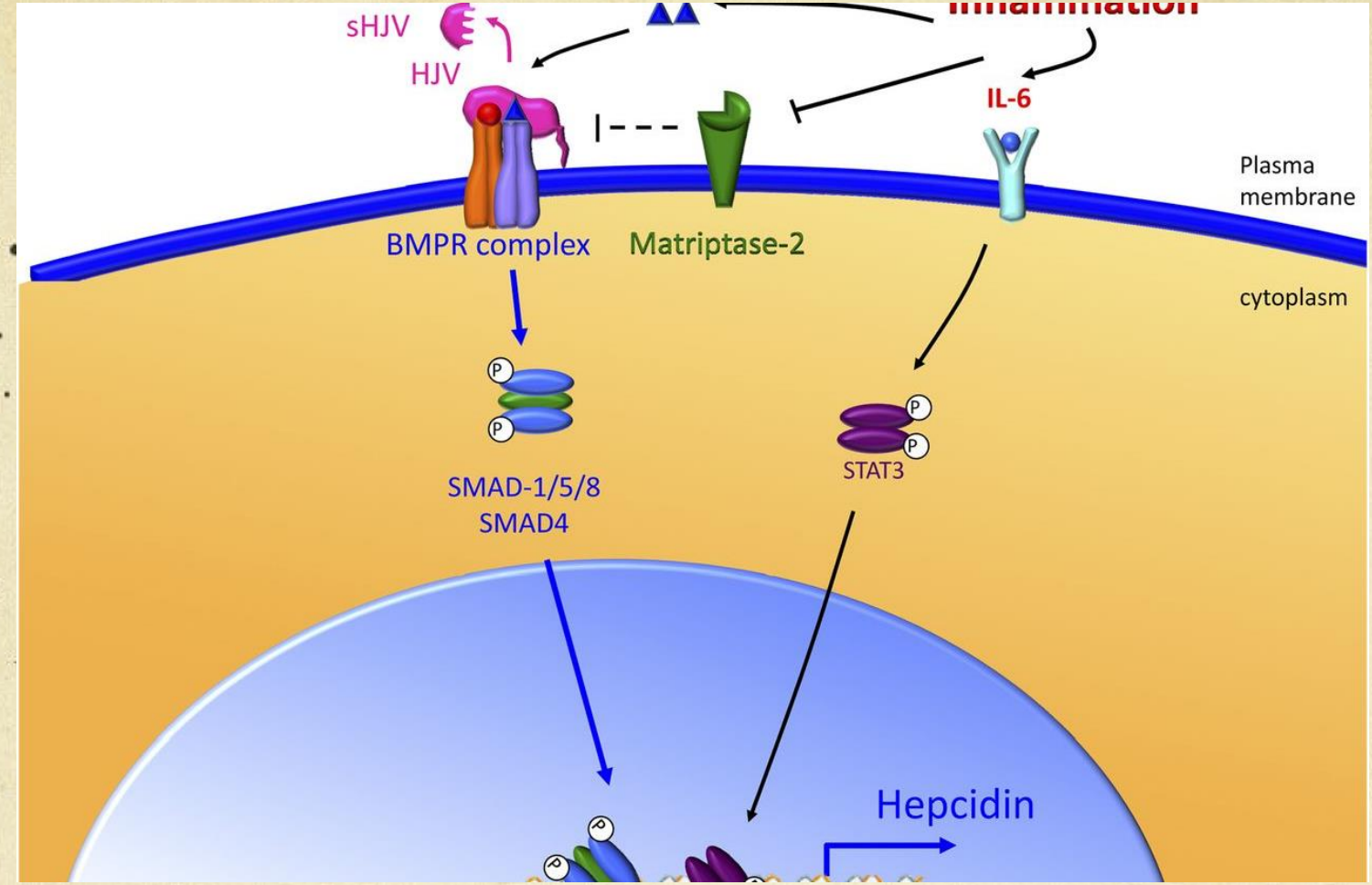
Lab findings

- Low hemoglobin and hematocrit
- Low MCV
- Low MCH
- Low iron levels
- Low ferritin
- **High TIBC**
- **High RDW**
- Low hepcidin
- Low transferrin saturation

- Treat by iron supplementation and treating the underlying cause.

Anemia of chronic disease

- Anemia of chronic disease is impaired red cell production associated with **chronic diseases that produce systemic inflammation**
- The most common cause of **anemia among hospitalized** patients
- Examples include chronic microbial inflammation, autoimmune inflammation, and malignancy.



IL6 results in increased hepcidin

- Starves the EP cells of iron.
- Inhibits erythropoietin and subsequently decreases EP proliferation
    - Possible immunologic role for hepcidin

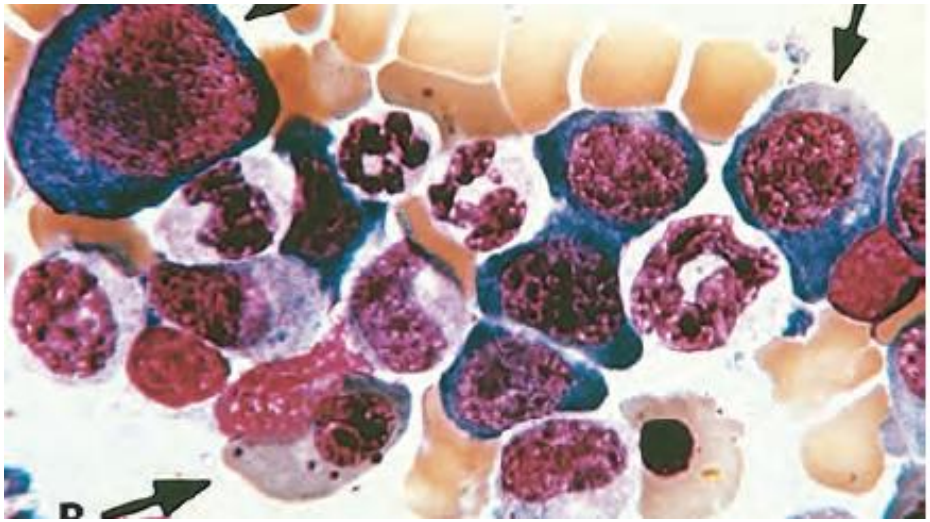
Clinical presentation

- Mild anemia
- Signs and symptoms of underlying disease

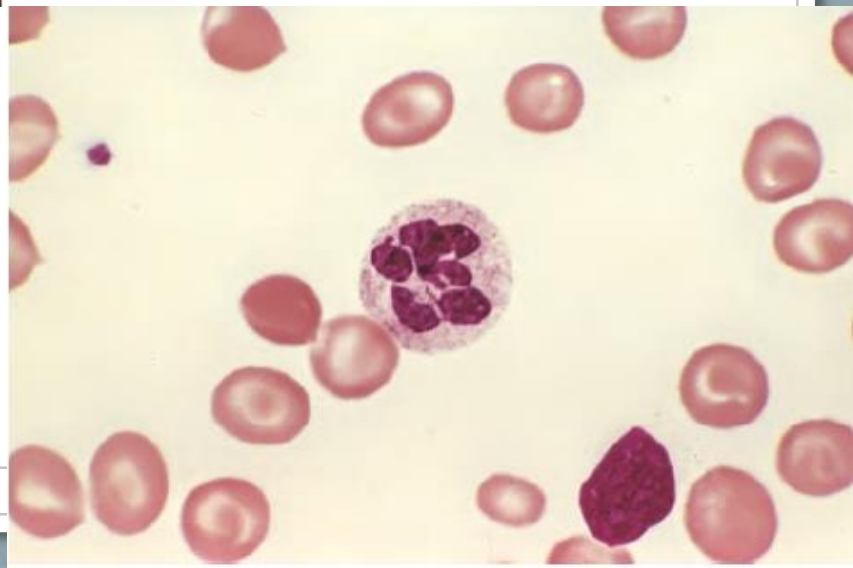
Lab findings

- Low HB and Hct
- Can be hypochromic microcytic or normochromic normocytic.
- High ferritin and low TIBC (exactly opposite to iron deficiency anemia)

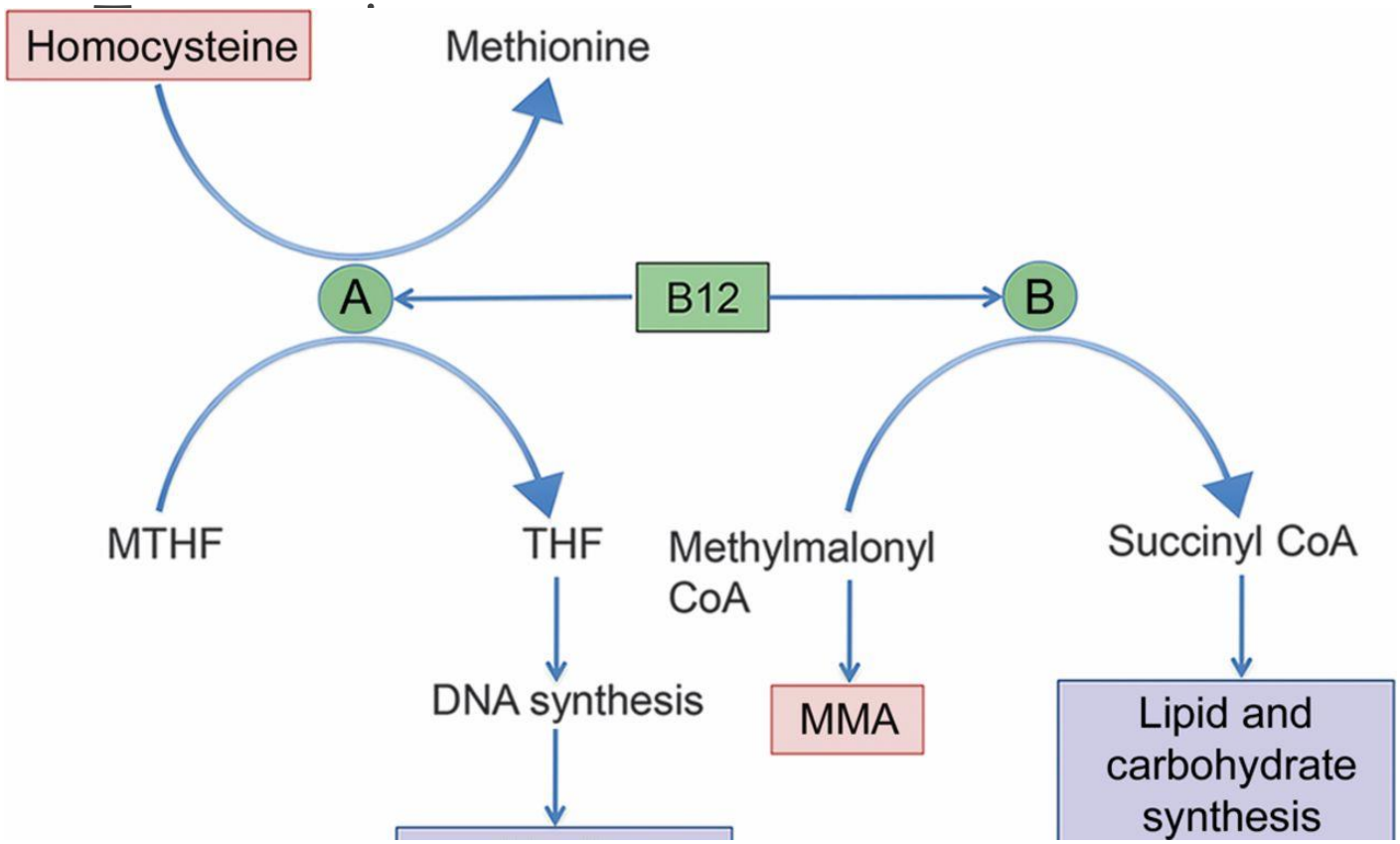
Megaloblastic anemia

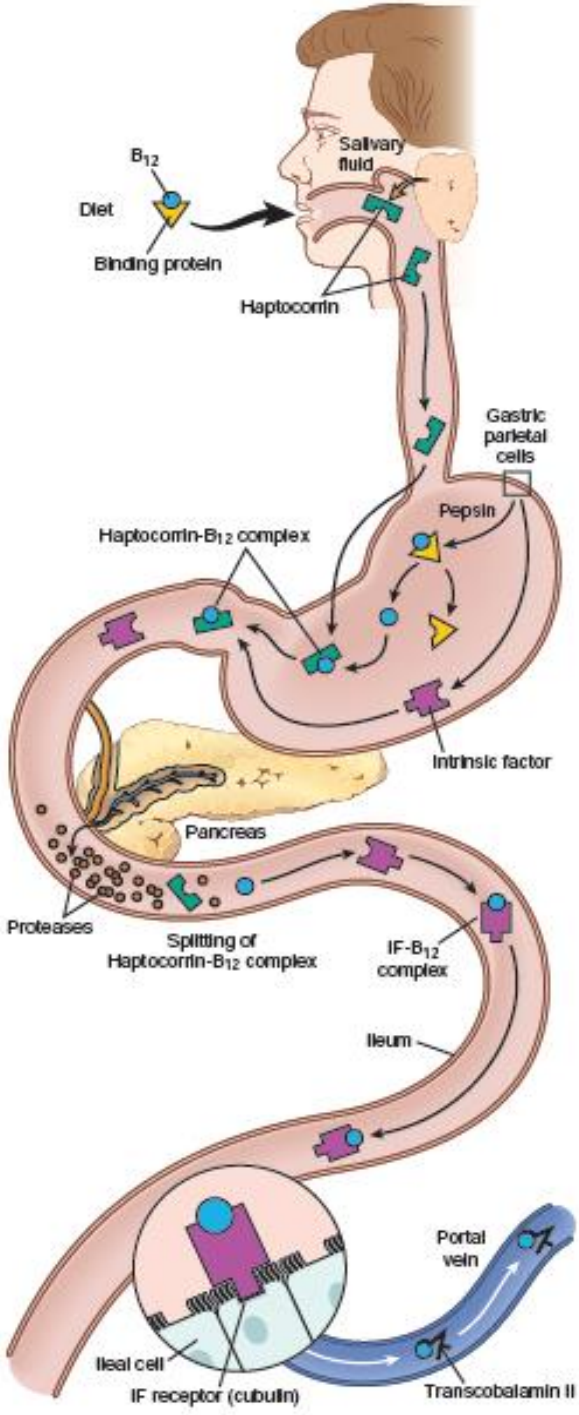


Vitamin B12 or folate deficiency



Biochemical role of B12




B_{12}
Diet
Binding protein
Salivary fluid
Haptocorrin
Gastric parietal cells
Pepsin
Haptocorrin-B_{12} complex
Intrinsic factor
Pancreas
Proteases
Splitting of Haptocorrin-B_{12} complex
IF-B_{12} complex
Ileum
Portal vein
Ileal cell
IF receptor (cubulin)
Transcobalamin II

Vitamin B_{12} Deficiency

Decreased Intake

Inadequate diet, vegetarianism

Impaired Absorption

Intrinsic factor deficiency
- Pernicious anemia
- Gastrectomy

Malabsorption states

Diffuse intestinal disease (e.g., lymphoma, systemic sclerosis)

Ileal resection, ileitis
- Competitive parasitic uptake
- Fish tapeworm infestation

Bacterial overgrowth in blind loops and diverticula of bowel

Pernicious anemia

Autoimmune attack on gastric mucosa.

three types of antibodies

1-parietal canalicular antibodies

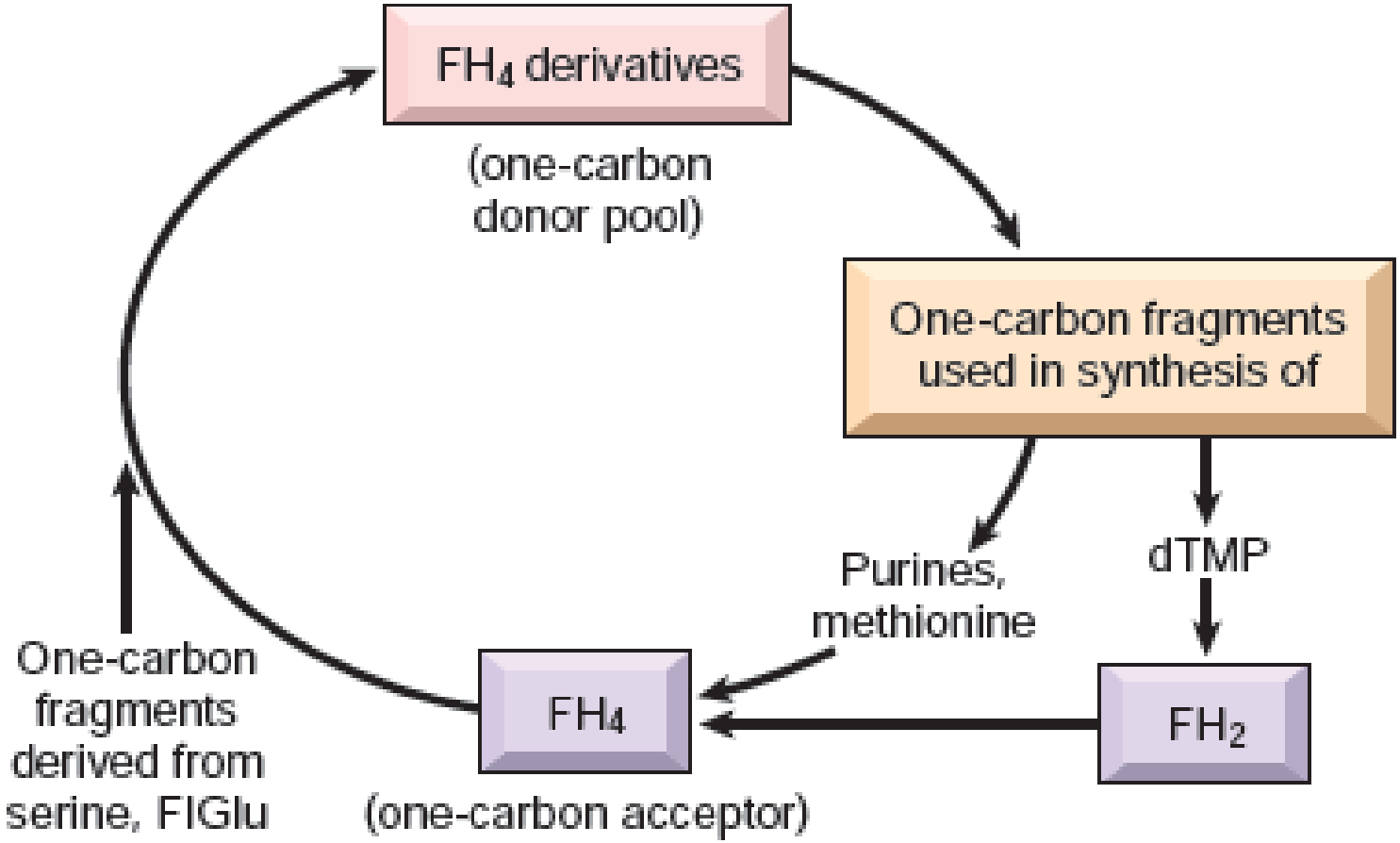
2-blocking antibodies

3-intrinsic factor–B12 complex antibodies

Clinical manifestations

- Related to anemia similar to those found in folate deficiency
- Additionally, leukopenia with hypersemented neutrophils can be seen
- Neurological symptoms:
  - Numbness
  - Unsteady gate
  - Loss of position sense
- Increase risk of malignancy in patient with pernicious anemia

Folate


FH_4 derivatives
(one-carbon donor pool)
One-carbon fragments used in synthesis of
Purines, methionine
dTMP
FH_2
FH_4
(one-carbon acceptor)
One-carbon fragments derived from serine, FIGlu

Folic Acid Deficiency
Decreased Intake
Inadequate diet, alcoholism, infancy
Impaired Absorption
Malabsorption states
Intrinsic intestinal disease
Anticonvulsants, oral contraceptives
Increased Loss
Hemodialysis
Increased Requirement
Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
Impaired Utilization
Folic acid antagonists
Unresponsive to Vitamin B_{12} or Folic Acid Therapy
Metabolic Inhibitors of DNA Synthesis and/or Folate Metabolism (e.g., Methotrexate)

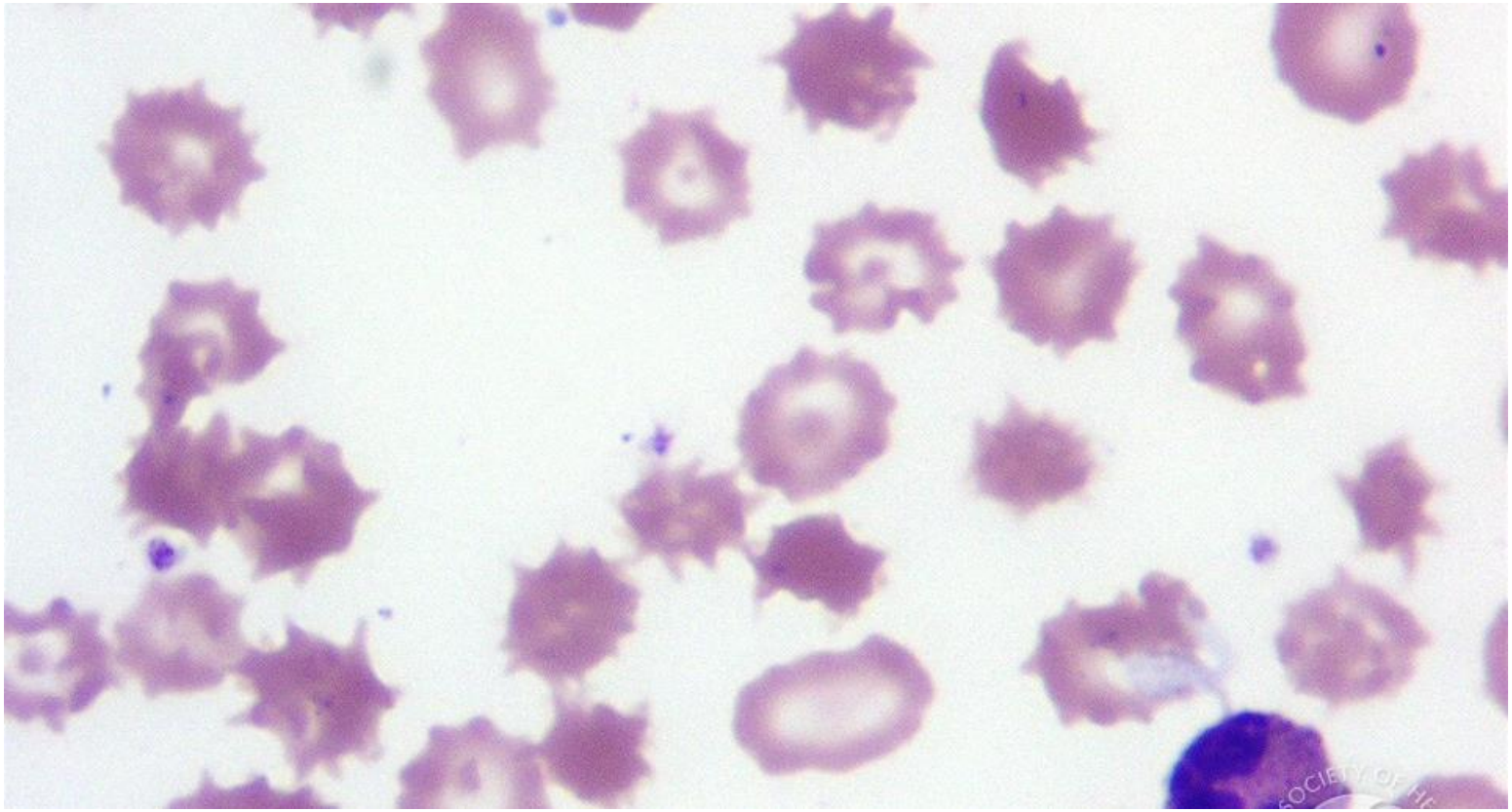
Clinical manifestations

- Nonspecific symptoms of anemia, weakness, fatigue…etc
- GI symptoms due to the effect on GI epithelial lining cells.
- NO neurological symptoms
- Diagnose by serum and RBC folate levels.

Anemia in liver disease

- Multiple etiologies:
  - Iron deficiency is the most common
  - Hypersplenism
  - Therapy related hemolytic anemia and suppression of EPO receptor
  - Alcoholic-cirrhosis-induced folate deficiency

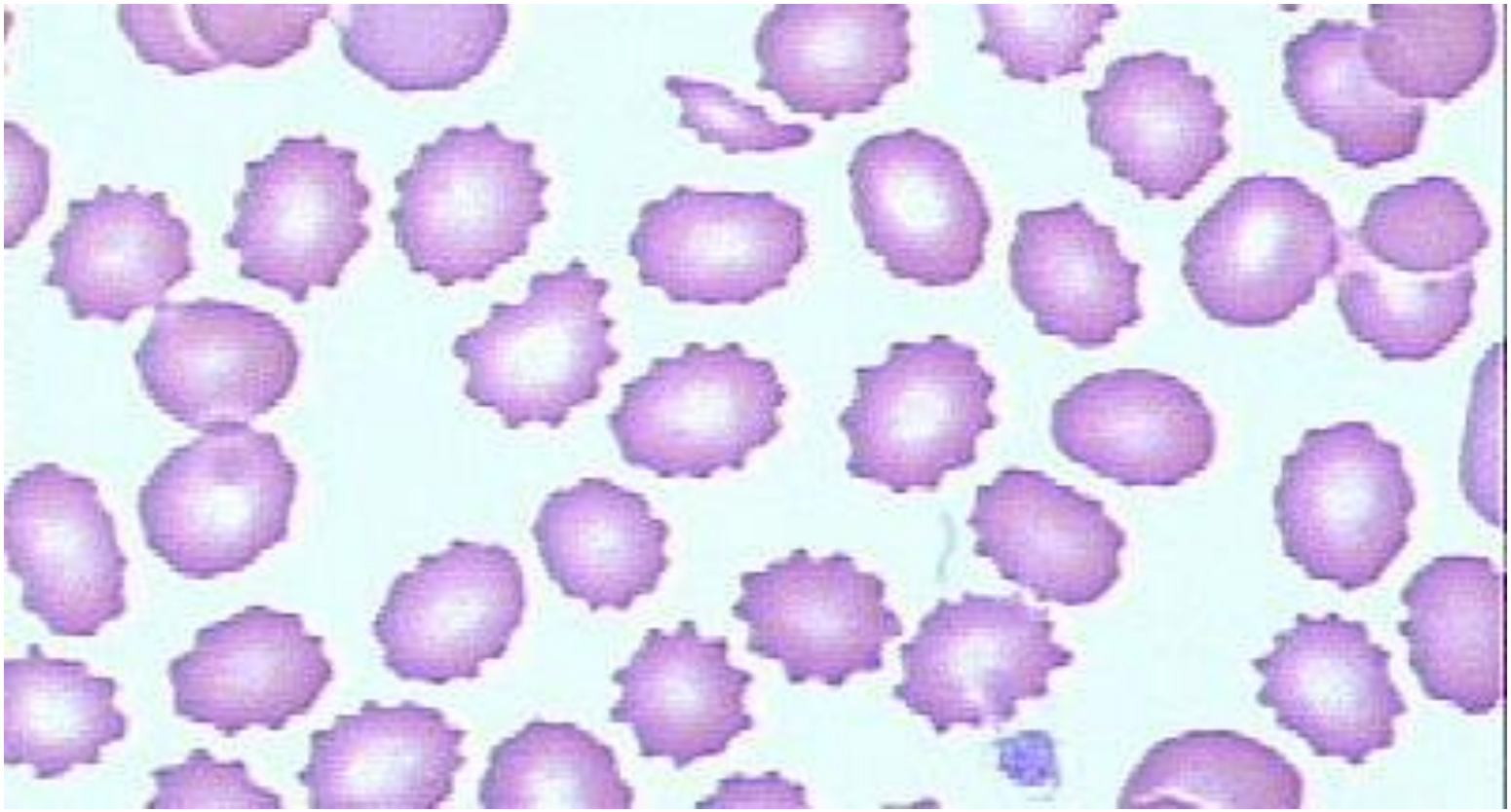
Spur cells



Anemia of renal disease

- Related to decrease EPO production by the damaged kidney.
- High levels of inflammatory cytokines
- Hemolysis
- Chronic bleeding
- Folate deficiency in patients on dialysis.

ecchinocytes



Aplastic anemia

*Aplastic anemia refers to a syndrome of chronic primary **hematopoietic failure** and attendant **pancytopenia** (anemia, neutropenia, and thrombocytopenia)*

Acquired

Idiopathic
Acquired stem cell defects
Immune mediated

Chemical Agents

Dose related
- Alkylating agents
- Antimetabolites
- Benzene
- Chloramphenicol
- Inorganic arsenicals

Idiosyncratic
- Chloramphenicol
- Phenylbutazone
- Organic arsenicals
- Methylphenylethylhydantoin
- Carbamazepine
- Penicillamine
- Gold salts

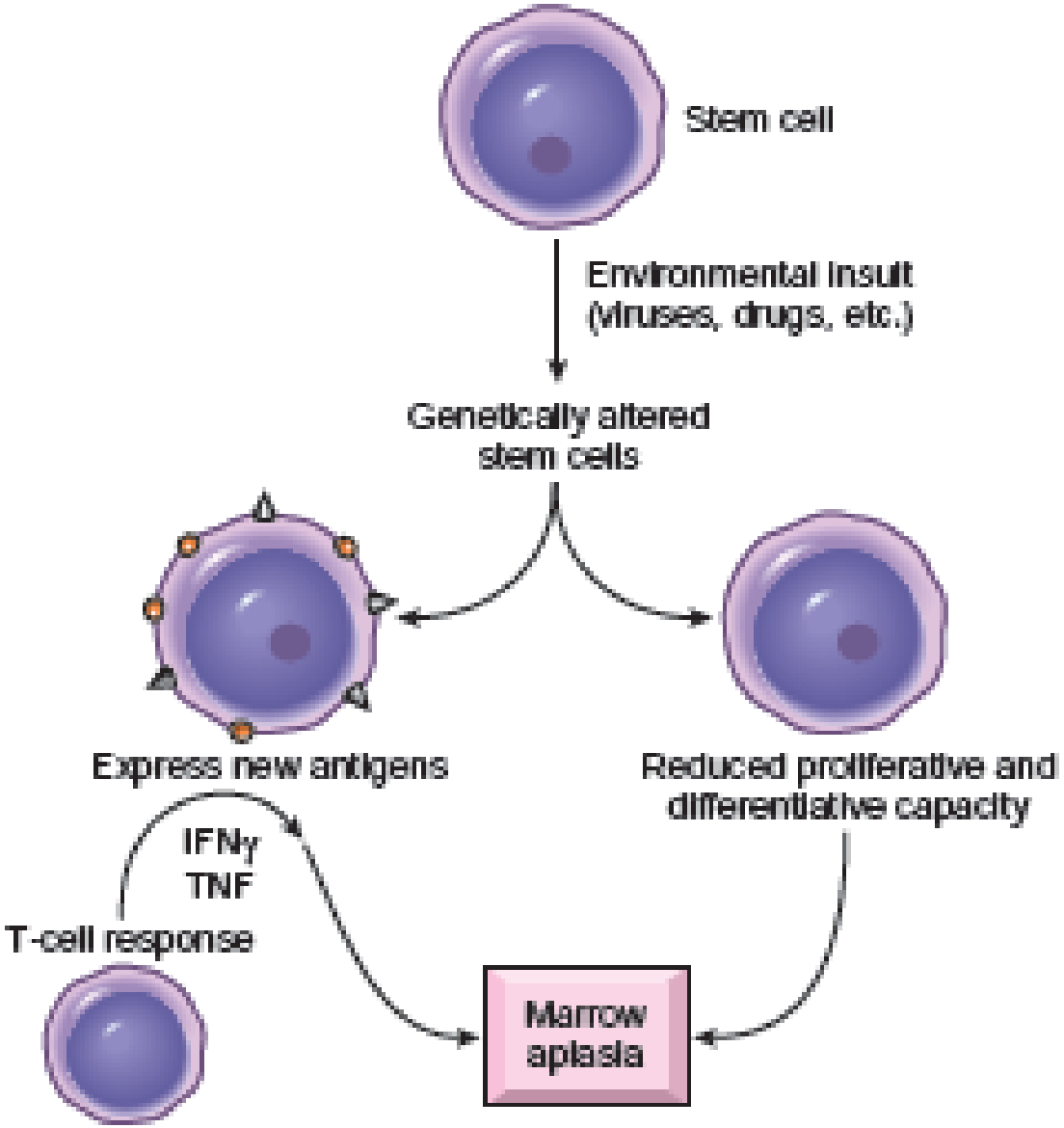
Physical Agents

Whole-body irradiation
Viral Infections
Hepatitis (unknown virus)
Cytomegalovirus infections
Epstein-Barr virus infections
Herpes zoster (varicella zoster)

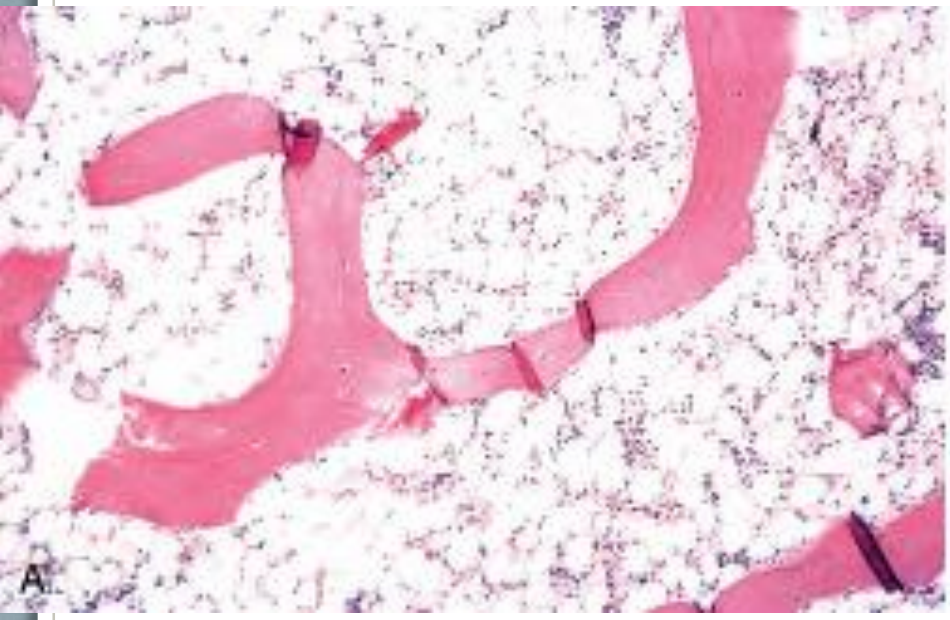
Inherited

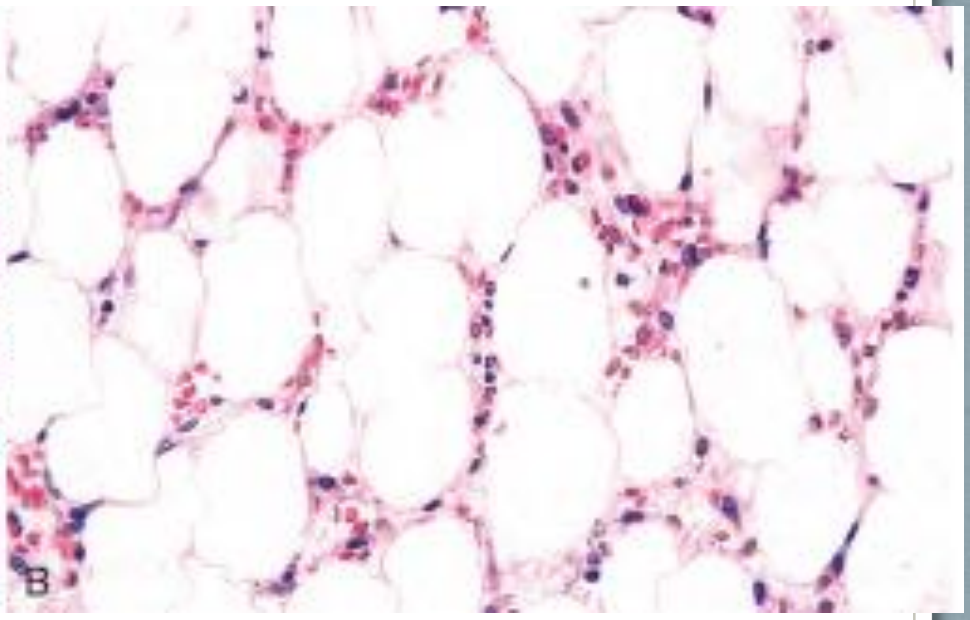
Fanconi anemia
Telomerase defects

Pathogenesis of aplastic anemia



Morphology





Clinical features

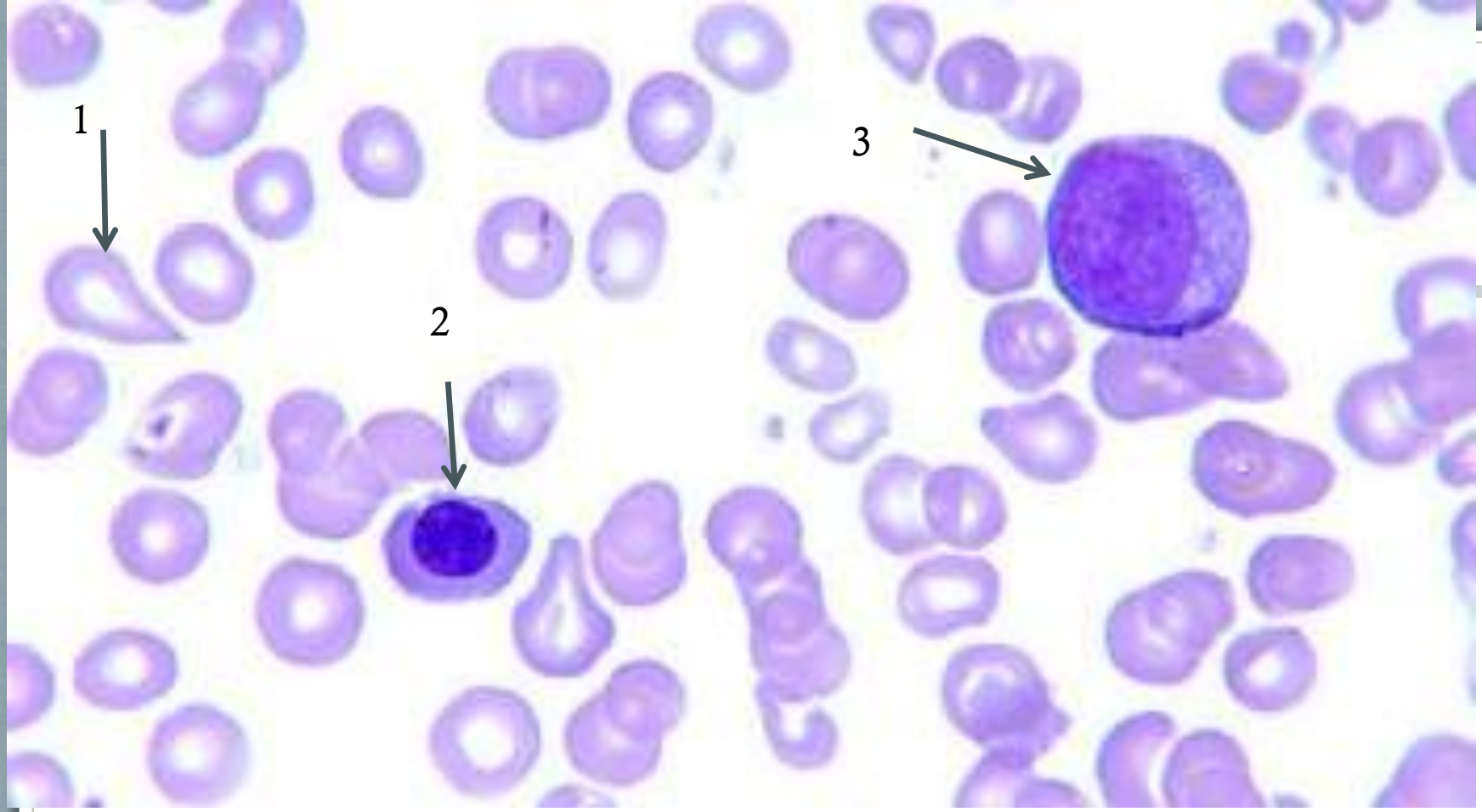
- Any age with no gender predilection
- Stigmata of pancytopenia
- Normocytic and occasionally macrocytic anemia.
- No splenomegaly
- No increased reticulocyte count
- Bone marrow exam is a must for diagnosis
- Respond well to immunosuppressive therapy, BM transplantation is the treatment of choice with 5 year survival of more than 75%.

Myelophthisic anemia

Extensive infiltration of the marrow by tumors or other lesions.

- Metastatic cancer (lung, breast, prostate)
- Tuberculosis
- Lipid storage disorders
- Osteoscelrosis

- Leukoerythroblastic reaction on peripheral blood.



1-tear drop RBC
2-immature erythroid precursor cell
3-immture myeloid cell

- Patients present with anemia and thrombocytopenia
- WBC are usually less affected.

- **Treatment is directed at the underlying etiology.**

1. All of the following can be found in iron deficiency anemia, except:
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   B. Low serum iron
   C. Low TIBC
   D. Low transferrin saturation
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2. Anemia of chronic disease is caused by elevated levels of:
   A. Hepcidin
   B. Iron
   C. Ferritin
   D. B12
   E. Neutrophils

3. All of the following are true regarding megaloblastic anemia, except:

A. defective DNA synthesis, resulting in nuclear immaturity

B. macrocytic anemia

C. can be seen in the setting of pernicious anemia

D. most common cause is nutritional deficiency of B12

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4. The most common cause of anemia in patients with liver disease is:

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D. Therapy related suppression of EPO receptor
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5. One of the following can cause myelophthisic anemia:

A. Tuberculosis
B. B12 deficiency
C. Folate deficiency
D. Iron deficiency
E. Anemia of chronic disease.

THANK YOU