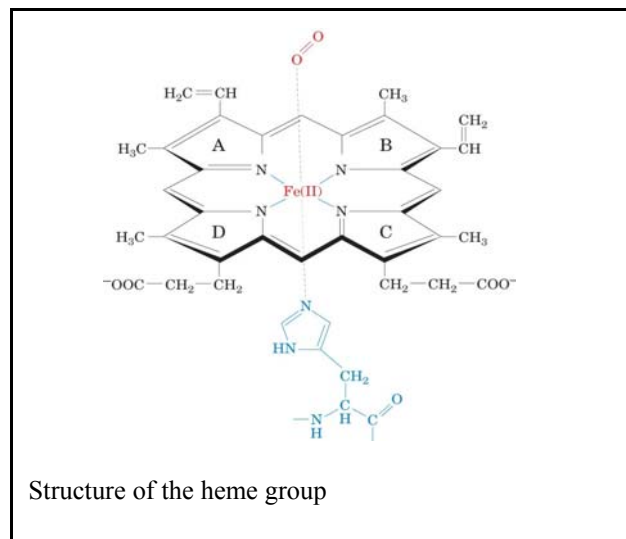
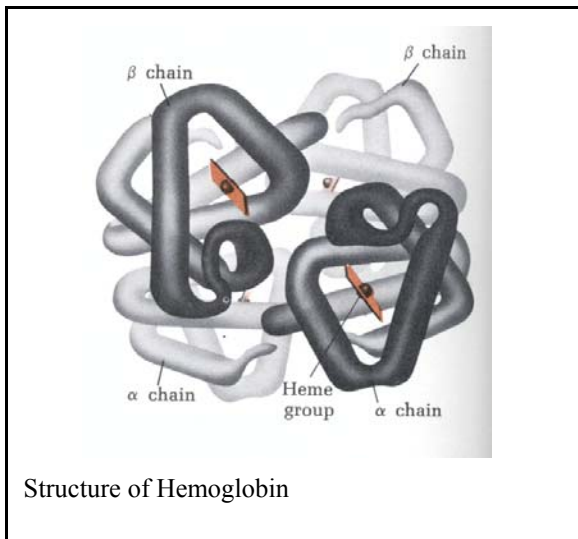


Category	Functional Defect	Common causes
Aplastic anemias	Disturbed stem cell	chemical, radiation, renal insufficiency, carcinomatosis, idiopathic
Megaloblastic anemias	Impaired DNA synthesis	vitamin B <sub>12</sub> /folate deficiency
Hypochromic anemias	Impaired hemoglobin synthesis	iron deficiency, anemia of chronic diseases, thalassemias, sideroblastic disorders



	Male (mg/kg of body weight)	Female
Essential iron		
Hemoglobin	31	28
Myoglobin and enzymes	6	5
Storage iron	13	4
Total	50	37

Ferritin: A large protein (~ 450 kDa) for iron storage.

Hemosiderin: Aggregated ferritin

Predominant site of iron storage:  
 hepatocytes  
 reticuloendothelial system  
 (minor site: muscle)

Iron is absorbed through duodenum and jejunum.

Transferrin: A plasma protein of ~76 kDa for the transport of iron from plasma to various tissues. There are 2 iron binding sites/molecule.

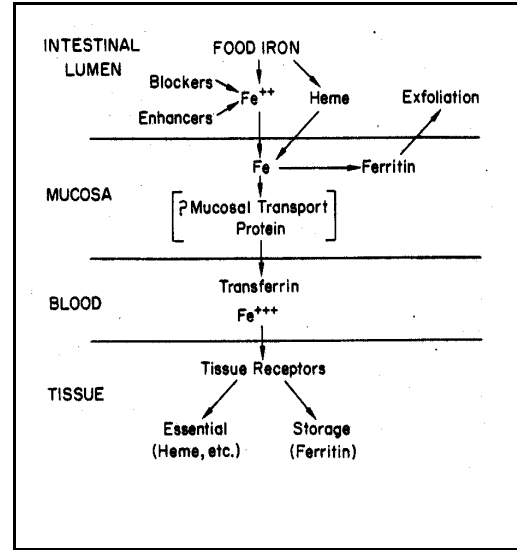


Table 3. DAILY IRON INTAKE AND ABSORPTION

SUBJECT	IRON REQUIREMENT ( $\mu\text{g}/\text{kg}$ )	AVAILABLE IRON IN POOR DIET-GOOD DIET ( $\mu\text{g}/\text{kg}$ )	SAFETY FACTOR (Available Iron/ Requirement)
Infant	67	33-66	0.5-1
Child	22	48-96	2-4
Adolescent (male)	21	30-60	1.5-3
Adolescent (female)	20	30-60	1.5-3
Adult (male)	13	26-52	2-4
Adult (female)	21	18-36	1-2
Mid-to-late pregnancy	80	18-36	0.22-0.45

Iron deficiency caused by:

- 1). Dietary intake of iron inadequate to meet normal requirement;
- 2). Conditions producing an increased requirements of iron because of iron loss;
- 3). Interference of iron absorption.

Treatment of iron deficiency:

- 1). Oral therapy

Drug of choice: ferrous sulfate (not recommended to use in combination with vitamin B<sub>12</sub> and folate unless the patient is also deficient in these compounds).  
 \*\*administered when fasting.

Side effects: heartburn, nausea, upper gastric discomfort, constipation, diarrhea

Antidote: deferoxamine

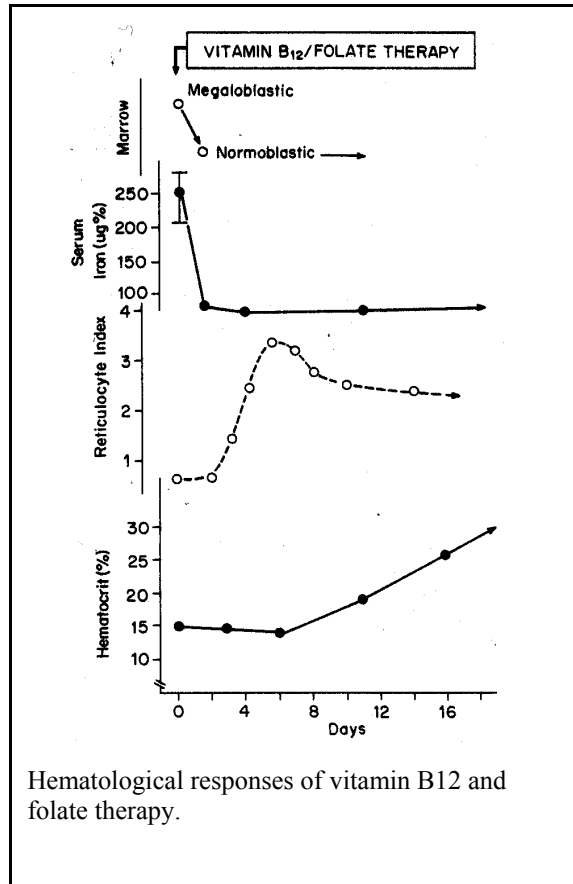
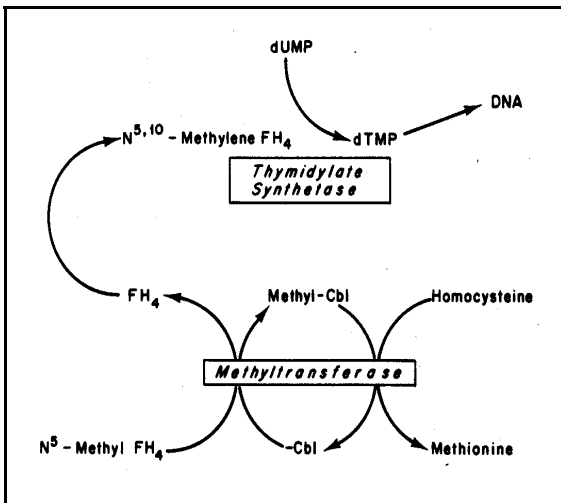
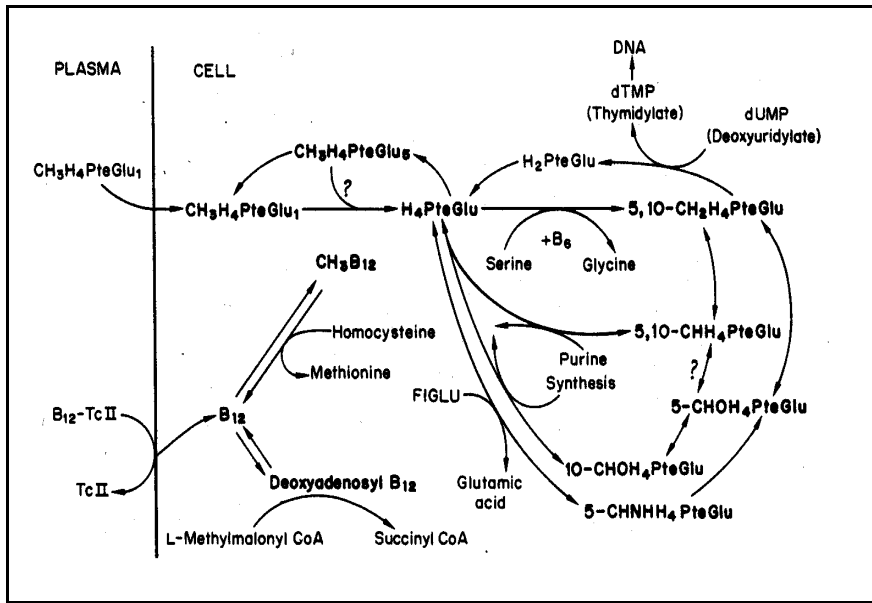
- 2). Parenteral therapy

Drug: iron dextran injection (IMFERON); given im or iv

Side effects: Intramuscular: long term discomfort, local discoloration of skin, malignant changes at injection sites

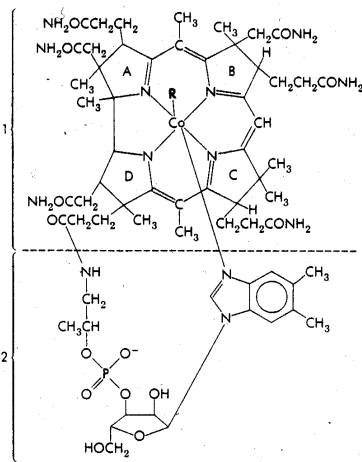
Intravenous: serious anaphylactic reactions.

Interrelationship of vitamin B<sub>12</sub> and folate metabolism



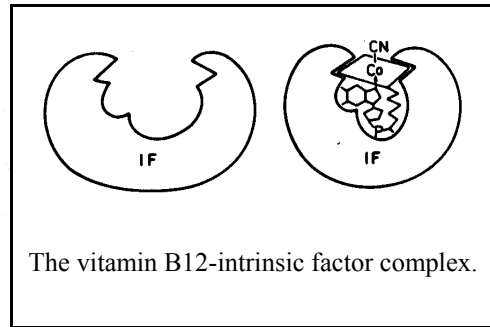
Hematological responses of vitamin B12 and folate therapy.

## Vitamin B<sub>12</sub> (Cobalamin)



**VITAMIN B<sub>12</sub> CONGENERS**

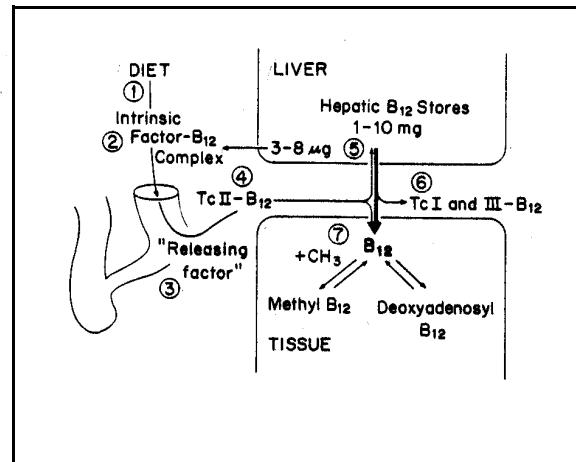
Permissible Name	R Group
Cyanocobalamin (Vitamin B <sub>12</sub> )	—CN
Hydroxocobalamin	—OH
Methylcobalamin	—CH <sub>3</sub>
5'-Deoxyadenosylcobalamin	—5'-Deoxyadenosyl



### Vitamin B<sub>12</sub> absorption:

- release from food
- binds to Intrinsic Factor (IF)
- absorbed through ileum
- binds to transcobalamin II in blood
- target tissue

Addisonian pernicious anemia - IF deficiency



### Vitamin B<sub>12</sub> deficiency:

- 1). The combination of gastric achlorhydria and decreased secretion of intrinsic factor due to gastric atrophy or gastric surgery.
- 2). Pancreatic disorders since pancreatic proteases are required for the release of vitamin B<sub>12</sub> from proteins.
- 3). Antibodies to intrinsic factor and intrinsic factor-vitamin B<sub>12</sub> complex.
- 4). Bacterial overgrowth and certain intestinal parasites prevent adequate vitamin B<sub>12</sub> from reaching the ileum.
- 5). Damaged to the ileal mucosal cells by diseases or surgical procedures.
- 6). Congenital absence of transcobalamin II (very rare).

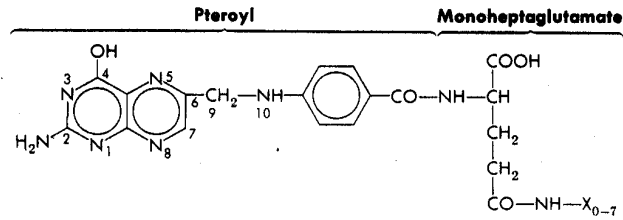
### Treatments:

Oral preparations - only used to supplement deficient diet and to prevent vitamin B<sub>12</sub> deficiency in situations of increased utilization.

Cyanocobalamin injection (REDISOL, RUBRAMIN RC, others) -

Given by intramuscular and subcutaneous routes, but NOT intravenously.

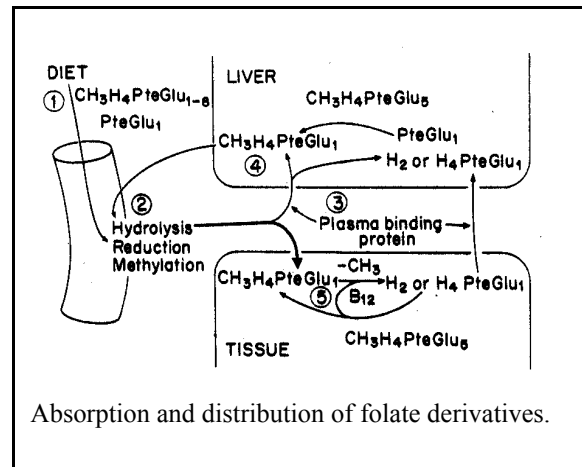
## Folate (pteroylglutamic acid)



Position	Radical	Congener	
N <sup>5</sup>	—CH <sub>3</sub>	CH <sub>3</sub> H <sub>4</sub> PteGlu	Methyltetrahydrofolate
N <sup>5</sup>	—CHO	5-CHOH <sub>4</sub> PteGlu	Folinic acid (Citrovorum Factor)
N <sup>10</sup>	—CHO	10-CHOH <sub>4</sub> PteGlu	10-Formyltetrahydrofolate
N <sup>5-10</sup>	—CH—	5,10-CHH <sub>4</sub> PteGlu	5,10-Methenyltetrahydrofolate
N <sup>5-10</sup>	—CH <sub>2</sub> —	5,10-CH <sub>2</sub> H <sub>4</sub> PteGlu	5,10-Methylenetetrahydrofolate
N <sup>5</sup>	—CHNH	CHNHH <sub>4</sub> PteGlu	Formiminotetrahydrofolate
N <sup>10</sup>	—CH <sub>2</sub> OH	CH <sub>2</sub> OHH <sub>4</sub> PteGlu	Hydroxymethyltetrahydrofolate

### Folate Absorption:

- hydrolyzed, reduced and methylated
- duodenum, jejunum
- transport by folate binding protein in blood
- target tissues
- liver to bile for reabsorption (enterohepatic cycle)



### Folate deficiency:

- 1). Malnutrition resulting from inadequate supply to meet requirements, especially in acute and chronic alcoholism.
- 2). Defect of flow of folate into the bile for reabsorption (the folate enterohepatic cycle)
- 3). Small intestinal diseases.
- 4). Deficiency of folate binding protein in plasma.
- 5). Deficiency of vitamin B<sub>12</sub>.

### Treatments:

Oral preparations: folic acid (FOLVITE) is the drug of choice.  
Folic acid injection.

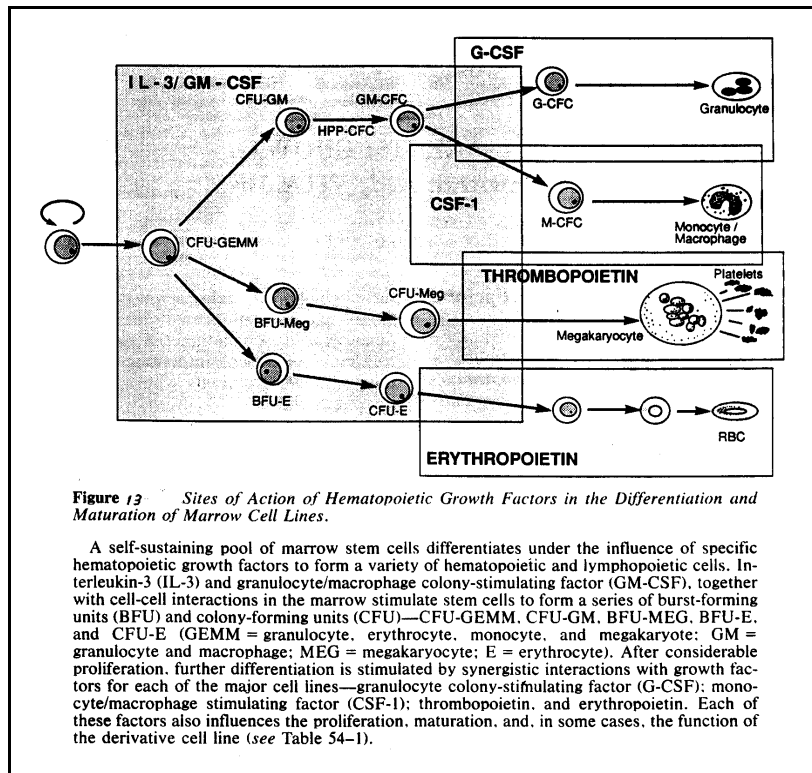
\*\*\* Do not use folic acid for treatment of vitamin B<sub>12</sub> deficiency because the latter is associated with neurological disorders.

### Hematopoietic Growth Factors

Hematopoiesis: formation and development of blood cells and their liberation into the circulation.

Marrow multipotential stem cells:

- progenitor of all blood cells.
- differentiate into both hematopoietic and lymphopoietic cell lines.
- through the combined action of hematopoietic growth factors, cell-cell and cell-extracellular matrix interaction, the pluripotential hematopoietic cells differentiate to committed hematopoietic cell lines from which red blood cells, platelets, granulocytes, monocytes and macrophages are derived.
- pancytopenia: defect in the pluripotential GEMM cells.



### Hematopoietic and Lymphopoietic Growth Factors

- glycoproteins produced by marrow cells and peripheral tissues.
- active at very low concentrations on more than one committed cell linages.
- show synergistic interactions with other growth factors.
- show “networking” effect wherein stimulation of one growth factor induces the production of additional growth factors.
- exert actions at several points during cell proliferation and differentiation.

## Erythropoietin

- Stimulates proliferation, maturation, and hemoglobin formation by committed erythroid progenitors (CFU-E).
- Stimulates early release of reticulocytes from marrow into the circulation.
- Acts synergistically with interleukin (IL-3) and granulocyte/macrophage colony-stimulating factor (GM-CSF) to expand the BFU-E compartment.
- A glycoprotein of 34 kDa. Glycosylation is important for prolonging its lifetime in circulation but not for biological activity. It binds to a receptor on the surface of erythroid precursor cells and activates the cells to differentiate through signal transduction processes.
- Produced primarily by the kidney. A small amount is also produced by the liver. Lack of erythropoietin is a serious problem in anephric patients.
- With anemia and hypoxemia, renal synthesis and secretion of erythropoietin increase by 100-fold or more. The kidneys contain a sensor system which receive signals from hypoxic tissues and transmit them to the erythropoietin producing cells.

### Erythropoietin therapy

- Recombinant erythropoietin is available as epoetin alpha (EPOGEN, EPREX).
- Administered parenterally. Its half-life when administered intravenously is ~10 hours. Following subcutaneous injection, peak concentrations in plasma occur within 5-24 hours.
- Recommended doses: 50-100 units/kg; 3 times a week in patients with chronic renal failure.
- Titrate the dose to avoid an excessive rapid increase in the hematocrit early in the treatment. The hematocrit must be determined at least once a week to measure the initial response. Once the hematocrit exceeds 30%, the weekly dosage should be reduced.
- No significant allergic reactions have been associated with intravenous and subcutaneous administration. Adverse effects may include increased clotting of dialyzer, hypertension, seizures, increases of peripheral vascular resistance and blood pressure. Lower doses if these problems are encountered.
- If hematocrit does not increase by 5% after 2 month of therapy, increase dosage and check for iron and vitamin B<sub>12</sub>/folate deficiency.

## Myeloid Growth Factors

- The myeloid growth factors or colony-stimulating factors are glycoproteins that stimulate the proliferation of one or more myeloid cell lines (see Figure).
- Recombinant forms of several myeloid growth factors are available:
  - GM-CSF: granulocyte/macrophage colony-stimulating factor
  - G-CSF: granulocyte colony-stimulating factor
  - IL-3: interleukin-3
  - M-CSF or CSF-1: monocyte/macrophage colony-stimulating factor
  - SCF: stem cell factor
  - thrombopoietin
- GM-CSF, *sargramostim* (LEUKINE) : treatment of patients with relative or absolute neutropenia secondary to neoplasia, congenital cyclic neutropenia, aplastic anemia, myelodysplasia, and AIDS.  
Administered by subcutaneous injection or slow intravenous infusion.  
Half-life: 2-3 hours.  
A transient decrease in absolute leukocyte count followed by a biphasic increase.  
Adverse effects: high doses are associated with pronounced side effects including bone pain, malaise, flu-like symptoms, fever, diarrhea, dyspnea and rash. Some patients may be extremely sensitive to GM-CSF and demonstrate flushing, hypertension, nausea, vomiting, and dyspnea. With prolonged use, a few patients develop a capillary leak syndrome.
- G-CSF, *filgrastim* (NEUPOGEN): effective in the treatment of severe neutropenia following autologous bone marrow transplantation and high-dose chemotherapy.  
Administered by subcutaneous injection or slow intravenous infusion.  
Half-life: 3.5 hours.  
Adverse effects: mild to moderate bone pain in patients receiving high doses over a protracted period; local skin reactions following subcutaneous injection, and rarely, a cutaneous necrotizing vasculitis. Patients on long-term therapy may experience mild to moderate splenomegaly.