Anemia: the decrease ability of the RBCs to carry adequate oxygen to different tissues
→ nutritional anemia = iron/vitamin deficiency anemia

Hypochromic microcytic anemia: iron deficiency anemia
- Most common form of anemia
- Iron levels are too low to make Hb

Megaloblastic anemia: vitamin deficiency anemia
- Anemia due to folic acid deficiency → folate deficiency
- Anemia due to vitamin B12 deficiency --> pernicious anemia

Hematopoiesis: production from undifferentiated stem cells of circulating erythrocytes, platelets & leukocytes
→ requires a constant supply of these 3 essential nutrients (iron, vitamin B12, folic acid)

Iron: forms the nucleus of the iron-porphyrin heme ring; found mainly in Hb (major protein in erythrocytes)

Requirements:
- 7-27 mg/day of elemental iron (10% in heme form)
  - → Heme iron contributes an avg. dietary iron bioavailability of 18%
- Vegetarians/vegans: RDA increased by 1.8x (to substitute for heme iron)

Tolerable upper intake level (UL):
45 mg/day for adults based on the occurrence of GI SEs (doesn't apply to those being treated for iron deficiency)
→ iron overdose in children = poisoning

Transport:
1. Plasma-bound to transferrin (β-globulin that can bind 2 molecules of ferric iron)
2. Transferrin receptors (membrane glycoproteins) on proliferating erythroid cells bind & internalize the transferrin-iron complex (endocytosis → clathrin-coated vesicle)
3. In endosomes, ferric iron is released, reduced to ferrous iron, and transported by DMT1 into cytoplasm
4. Ferrous iron is funnelled into Hb synthesis or stored as ferritin

Elimination: no mechanism for excretion
- Small amounts lost (1mg/day): feces by exfoliation of intestinal mucosal cells; excreted in bile, urine & sweat
- Serum ferritin: in equilibrium w/ storage ferritin in reticuloendothelial tissues (estimates total body iron stores)

Absorption: 5-10% (0.5 – 1 mg daily)
- Increases in response to low iron stores
  - → 3-4 mg/day in pregnant women
- Iron is abundant in meat (efficiently absorbed)
  - → Intact heme iron in meat taken up by GI epithelial cells
- Iron in vegetables & grains are less available for absorption
  - → Bound to organic compounds – phytates, tannins
  - → Absorption enhanced by enhancers (ascorbic acid)

Factors favoring absorption	Factors reducing absorption
Heme iron*	Inorganic iron
Ferrous form (Fe^{2+})	Ferric form (Fe^{3+})
Organic acids & enhancers	Alkalis, antacids, phytates
Reduced serum hepcidin	Increased serum hepicidin
Increased/ineffective erythropoiesis	Decreased erythropoiesis
Pregnancy	Inflammation
Hereditary hematochromatosis	

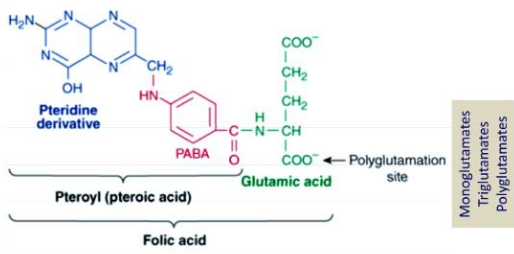
* Heme iron absorption can increase from 10-15 → 35-40% when stores depleted

1. Fe^{3+} (dietary non-heme iron) → Fe^{2+} reduction by DCYTB (ferri-reductase) for transport across apical brush border
2. DMT1 mediates proton-dependent Fe^{2+} import (GIT → cell)
3. HCP1 transports dietary heme iron (GIT → cell)
4. Heme oxygenase releases iron from protoporphyrin, allowing it to enter the same pool as non-heme iron
5. Some iron is used or stored within the enterocyte in ferritin → later lost when intestinal mucosa is sloughed
6. Ferroportin exports some iron, where it is oxidized to Fe^{3+} (by ferroxidase aka hephaestin) for incorporation into serum transferrin
7. Transferrin bind iron in plasma (to transport around body)

Storage: intestinal mucosal cells; macrophages in liver, spleen, bone; parenchymal liver cells
→ Hepcidin controls mobilization of stored iron
- Low hepcidin → iron release from storage sites
- High hepicidin → inhibits iron release

Folic acid: required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines, and DNA

→ Folate deficiency is relatively common → anemia & implicated in congenital malformations in newborns (neural tube defect & cleft lips)



Folic acid chemistry:

- Folic acid undergoes reduction (folate reductase) → dihydrofolate; tetrahydrofolate
  - Transforms to folate cofactors possessing one-carbon units
  - Folate cofactors are inter-convertible & donate one-carbon units at various levels of oxidation
  - Tetrahydrofolate is regenerated; available for reutilization
- Dietary folates consist of polyglutamate forms of N^5-methyltetrahydrofolate
  - Converted into monoglutamates by <u>intestinal conjugase</u>

Excess: no adverse effects associated with the consumption of excess folate from foods

→ Meta-analysis of 8 trials of folic acid supplementation (>800 ug/day) showed no increased risk of cancer

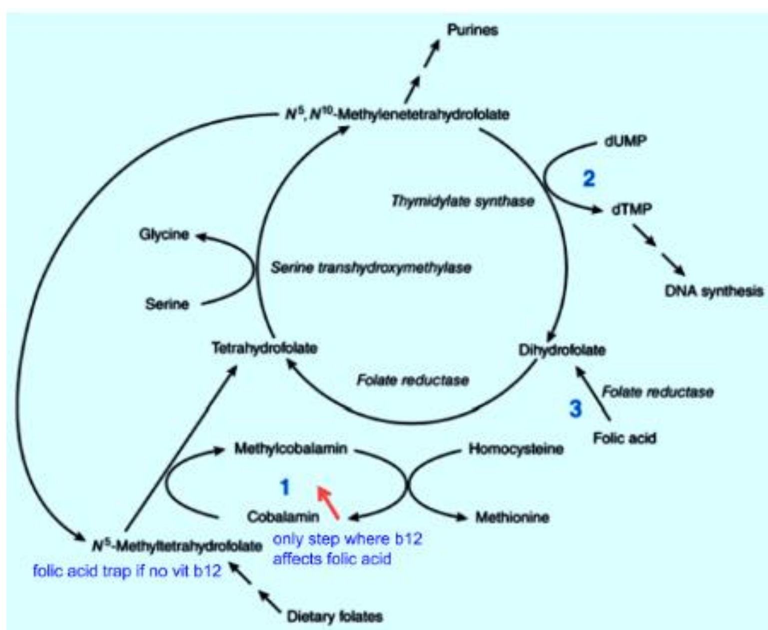
Requirements: the average American diet 500-700 ug/day (50-200 ug usually absorbed)

- Pregnant women: 300-400 ug of folic acid daily
- Sources: yeast, liver, kidney and green vegetables

Absorption & excretion:

- Unaltered folic acid absorbed in proximal jejunum
- 5-20 mg of folate stored in liver/other tissues
  → Body stores relatively low & requirements high
- Excreted through urine/stool or destroyed by catabolism
  → Serum levels fall w/in few days when intake is diminished

Folate Cofactor Pool



- Cells that are highly proliferating need a lot of folic acid
- This happens in cancer cells so if you inhibit this pathway you may be able to regulate the proliferation of cancer cells

Vitamin B_{12} (Cobalamin): a porphyrin-like ring with a central cobalt atom attached to a nucleotide

- Various organic groups (R) may be covalently bound (cobalamins)
- 5-deoxyadenosylcobalamin and methylcobalamin are the active forms of the vitamin in humans
- Inadequate supply in diet = unusual; inadequate absorption = normal
- Cofactor for several essential biochemical reactions
  - Transfer of a methyl group from N5-methyltetrahydrofolate → homocysteine (forming methionine)
  - Isomerization of nethylmalonyl-CoA to succinyl-CoA

Requirements: American diet – 5-30 ug (avg)
→ 1-5 ug usually absorbed
→ normal daily requirements: 0.5-2.6 ug/day

- Stored in liver (3000-5000 ug) = 5 year supply (only trace amounts lost in urine and stool)
- Dietary source: microbially derived Vit B12 in meat (esp. liver), eggs, dairy
  - Not synthesized by animals or plants

Excess: no toxic or adverse effects associated with large intakes of Vit B12 from food or supplements in healthy people
→ no upper limit has been set

Absorption: cyanocobalamin and hydroxycobalamin (and other cobalamins) found in food sources are converted to the active forms

- Vitamin B12 is transported – bound to a family of specialized glycoproteins (transcobalamin I, II, III)
- Intrinsic factor: protein secreted by stomach required for GI uptake of dietary Vit B12
  - IF-Vit B12 complex is absorbed in distal ileum (via cubulin)

Excretion:

- Approx.. 0.1% of Vitamin B12 lost per day
  - Secretions into gut
  - Bile main form of Vitamin B12 excretion
  - Recycled via enterohepatic circulation
- Excessive B12 typically excreted in urine (more than blood's binding capacity)