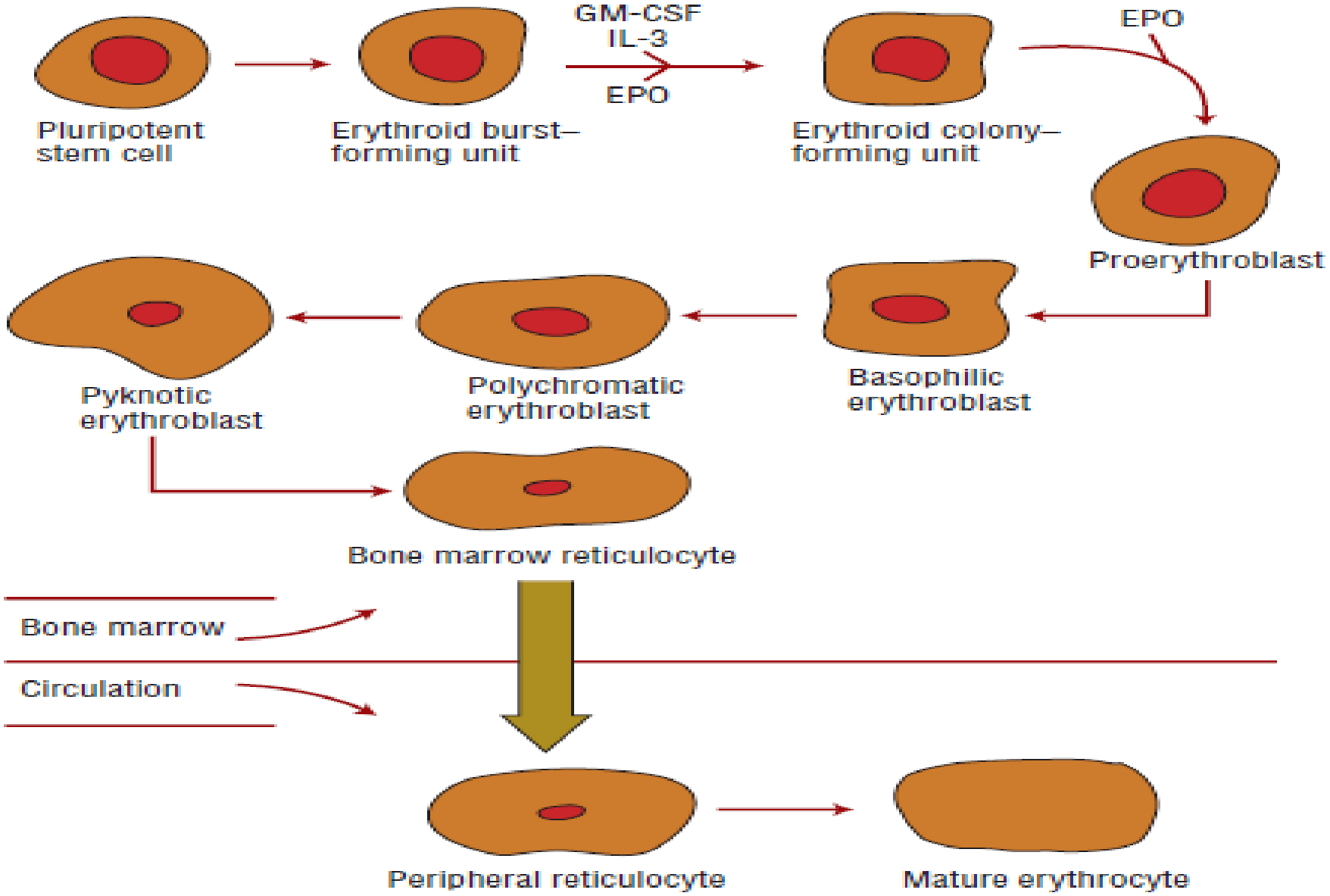
Anemia

By Dr. Swathi Swaroopa. B

- **In adults, RBCs are formed in the marrow of the vertebrae, ribs, sternum, clavicle, pelvic (iliac) crest, and proximal epiphyses of the long bones.**

- **The hormone EPO, 90% of which is produced by the kidneys, initiates and stimulates the production of RBCs.**



Erythrocyte maturation sequence

- **Hb and iron are incorporated into the gradually maturing RBC, which eventually is released from the marrow into the circulating blood as a reticulocyte.**

- **More than 90% of the protein content of the erythrocyte consists of the oxygen-carrying molecule Hb.**

- **Normal survival time is 120 days.**

- **Under normal conditions, the body produces approximately 6.25 g of Hb daily.**
- **The normal iron content of the body is approximately 3 to 4 g. Iron is a component of Hb**
- **Approximately 2.5 g of the iron exists in the form of Hb**
- **Iron is a component of Hb, myoglobin, and cytochromes.**

- Another 3 to 7 mg of iron is bound to transferrin in plasma, and the remaining iron exists as storage iron in the form of ferritin or hemosiderin

- Hepcidin is a regulator of intestinal iron absorption, iron recycling and iron mobilization from hepatic stores.

- **Hepcidin is induced during infections and inflammation, which allows iron to sequester in macrophages, hepatocytes, and enterocytes**

- **Plasma transport protein transferrin delivers iron to the bone marrow for incorporation into the Hb molecule.**

Introduction

- **Anemia is defined as an abnormally low number of circulating red blood cells or level of hemoglobin, or both, resulting in diminished oxygen-carrying capacity**

Anemia usually results from

- **Excessive loss (bleeding) or**
- **Destruction (hemolysis) of red blood cells or**
- **Deficient red blood cell production because of a lack of nutritional elements or bone marrow failure.**

Anemia may result from the decreased production of erythrocytes by the bone marrow.

- A deficiency of nutrients for hemoglobin synthesis (iron) or DNA synthesis (cobalamin or folic acid) may reduce red cell production by the bone marrow

- A deficiency of red cells also results when the marrow itself fails or is replaced by nonfunctional tissue.

Anemia's of Deficient Red Cell Production

IRON DEFICIENCY ANEMIA

Iron Deficiency Anemia

- **Iron deficiency is a common worldwide cause of anemia affecting people of all ages.**

- **Because iron is a component of heme, a deficiency leads to decreased hemoglobin synthesis and consequent impairment of oxygen delivery.**

- **Malabsorptive syndromes**
- **Diets limited in meat or fresh fruits and vegetables**
- **Diets high in substances that form complexes with iron**
- **Situations that increase the demand for iron (menstruation, lactation, infancy, adolescence, pregnancy)**
- **Blood loss (trauma, hemorrhoids, peptic ulcers, gastritis, gastrointestinal malignancies, postpartum Bleeding)**
- **ACD, Thalassemia, Sideroblastic anemia, and heavy metal (mostly lead) poisoning**

IDA Etiopathogenesis

Risk of iron deficiency is related to

- **levels of iron loss,**
- **Iron intake,**
- **Iron absorption, and**
- **Physiologic demands.**

- **Iron deficiency usually is the result of a long period of negative iron balance**

- **Manifestations of iron deficiency occur in three stages: prelatent, latent, and IDA.**

- **Prelatent iron deficiency: This first stage, iron stores can be depleted without causing anemia.**

- **Once stores are depleted, there still is adequate iron from daily RBC turnover for Hb synthesis.**

- **Further iron losses would make the patient vulnerable to anemia development.**

- **Latent iron deficiency occurs when iron stores are depleted, but Hb is above the lower limit of normal for the population.**

- **IDA occurs when the Hb falls to less than normal values.**

- When red cells become senescent and are broken down, their iron is released and reused in the production of new red cells.
- Despite this efficiency, small amounts of iron are lost in the feces and need to be replaced by dietary uptake.
- Iron balance is maintained by the absorption of 1 to 2 mg daily to replace the iron lost in the feces.
- The usual reason for iron deficiency in adults is chronic blood loss because iron cannot be recycled to the pool.

- **Pregnant women with iron deficiency anemia without iron supplementation had a slightly higher rate of preterm infants and lower birth rates than those supplemented with iron.**

- **The manifestations of anemia depend on its severity, the rapidity of its development, and the person's age and health status.**

- Lethargy
- Pale complexion
- Shortness of breath
- Heart palpitations
- Altered sense of taste
- Rapid heartbeat
- Headache
- Craving for ice or clay - "picophagia”
- Sore or smooth tongue
- Brittle nails or hair loss

Clinical presentation

MEGALOBLASTIC ANEMIA

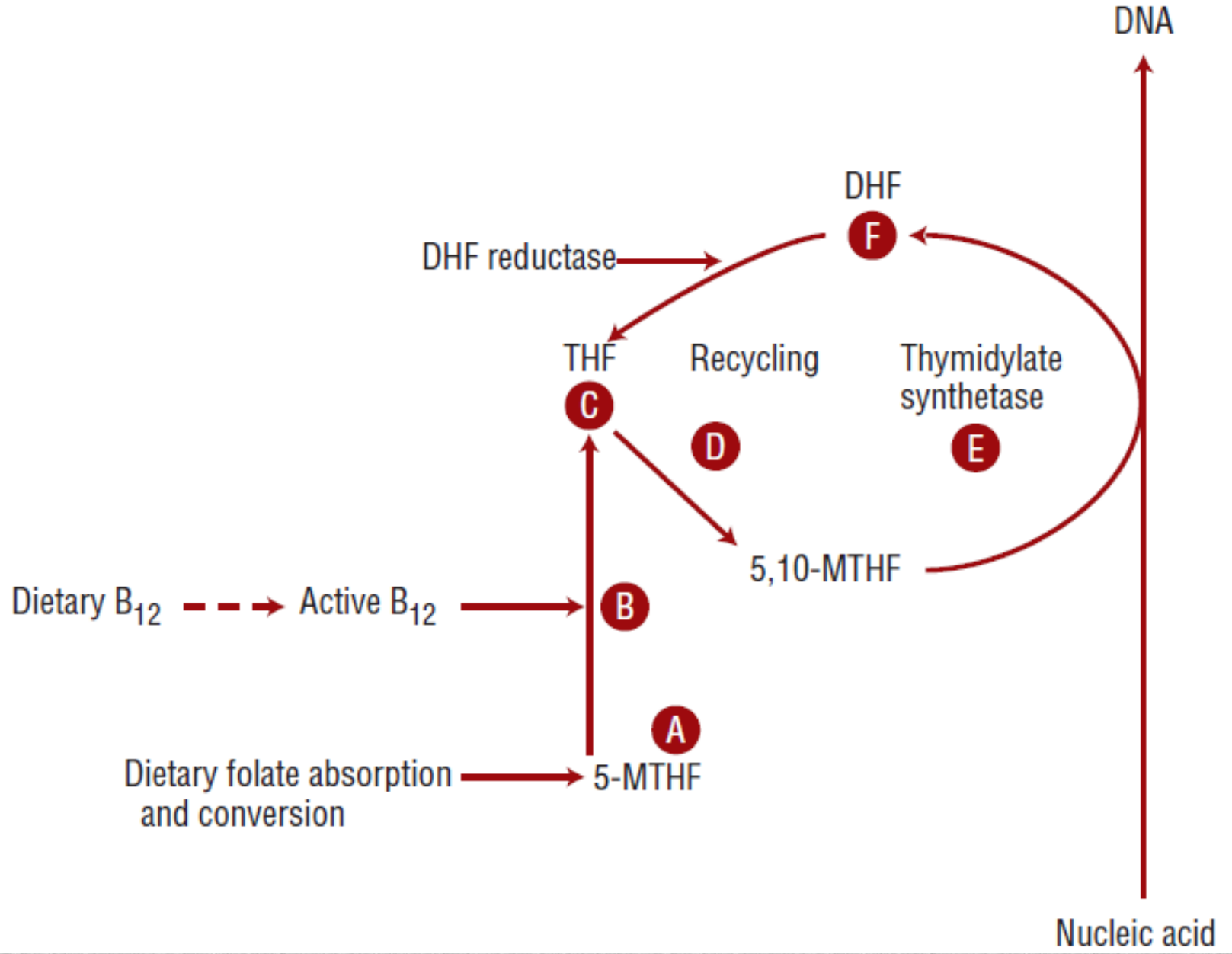
- **Macrocytic anemia divided into megaloblastic and nonmegaloblastic anemias.**

- **Megaloblastic anemias are caused by impaired DNA synthesis that results in enlarged red cells due to impaired maturation and division**

- **Megaloblastic anemias, results from vitamin B12 or folate deficiency.**

Megaloblastic anemia is of two types

- **Vitamin B12 deficiency anemia**
- **Folate deficiency anemia**


DNA
DHF
F
DHF reductase
THF
C
Recycling
D
Thymidylate synthetase
E
5,10-MTHF
Dietary B_{12}
Active B_{12}
B
A
Dietary folate absorption and conversion
5-MTHF
Nucleic acid

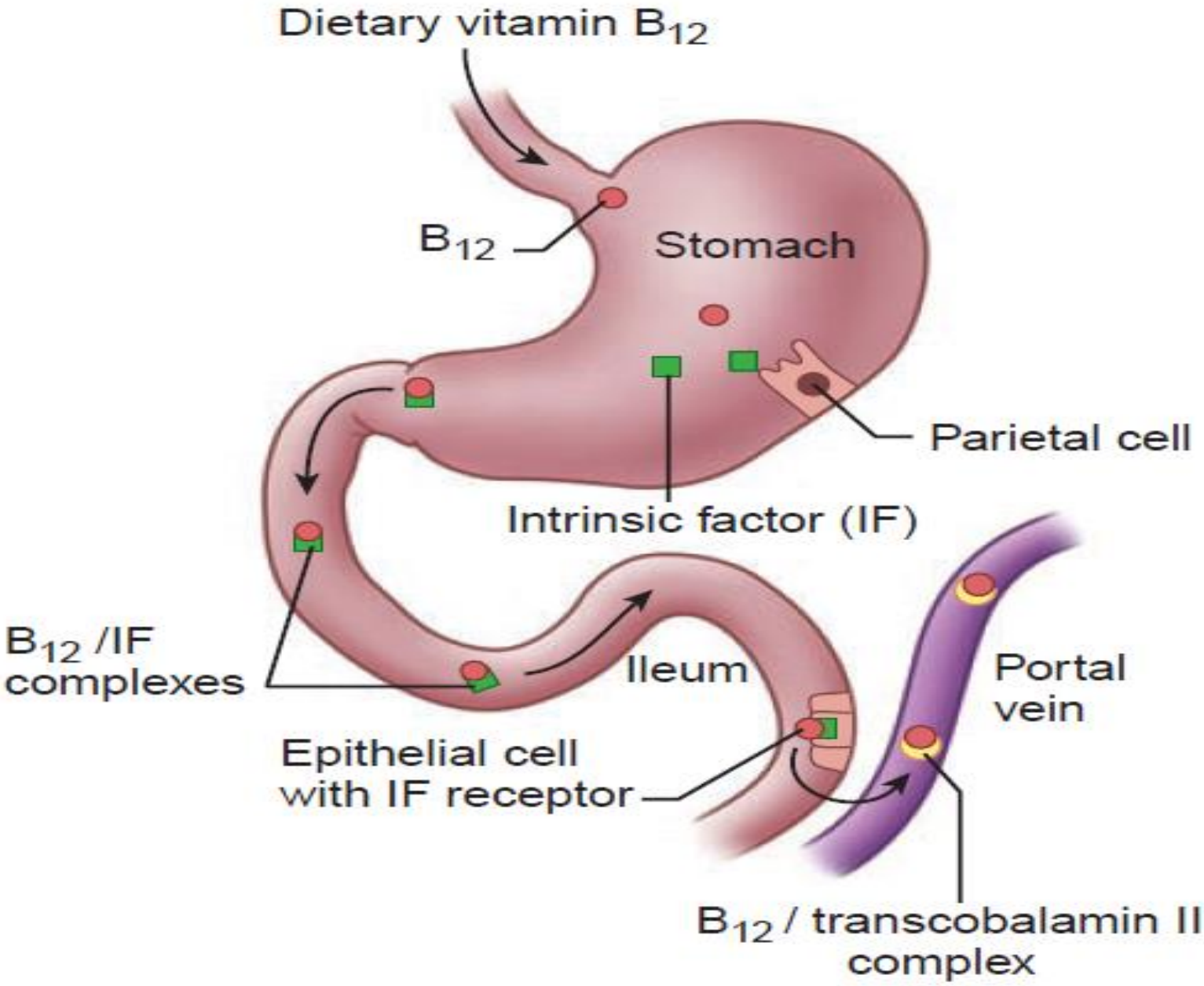
- Dietary folates are absorbed in this process and converted to 5- methyl-tetrahydrofolate (A), which then is converted via a B12- dependent reaction (B) to tetrahydrofolate (C). After gaining a carbon, tetrahydrofolate is converted to 5,10-methyl- tetrahydrofolate (D), a folate cofactor used by thymidylate synthetase (E) in the biosynthesis of nucleic acids. The 5,10-methyl-tetrahydrofolate cofactor is converted to dihydrofolate (F) during biosynthesis.Dihydrofolate reductase normally reduces dihydrofolate back to tetrahydrofolate (C), which can again pick up a carbon and be recycled to produce more 5,10-methyl-tetrahydrofolate (D).

VIT B12 deficiency anemia

- **Vitamin B12, also known as cobalamin**
- **Serves as a cofactor for two important reactions in humans.**
- **It is essential for DNA synthesis and nuclear maturation, which in turn leads to normal red cell maturation and division.**

Etiology

- **Inadequate Intake**
- **Malabsorption syndromes,**
- **Inadequate utilization**
- **Chronic alcoholics**
- **Pernicious anemia (Absence of intrinsic factor due to autoimmune destruction of the gastric parietal cells, atrophy of the gastric mucosa, or stomach surgery)**
- **Inadequate gastric acid production (subtotal gastrectomy, Atrophic gastritis, Acid suppression therapy)**
- **Helicobacter pylori**
- **Blind loop syndrome, Whipple disease, Zollinger-Ellison syndrome,**
- **Tapeworm Infestations**
- **Inflammatory bowel disease**



Absorption of vitamin B12

Pathophysiology

- **Vitamin B12 works closely with folate in the synthesis of building blocks for DNA and RNA, is essential in maintaining the integrity of the neurologic system, and plays a role in fatty acid biosynthesis and energy production.**

- **Once dietary cobalamin enters the stomach, pepsin and hydrochloric acid release the cobalamin from animal proteins.**

- **The free cobalamin then binds to R-protein, which is released from parietal and salivary cells.**

- **In the duodenum, the cobalamin bound to R-protein is joined by cobalamin–R-protein complexes that have been secreted in the bile.**

- **Pancreatic enzymes degrade both biliary and dietary cobalamin– R-protein complexes, releasing free cobalamin.**

- **The cobalamin then binds with intrinsic factor that serves as a cell-directed carrier protein similar to transferrin for iron.**

- This complex attaches to mucosal cell receptors (cubilin) in the distal ileum, the intrinsic factor is discarded, and the cobalamin is bound to transport proteins (transcobalamin I, II, and III).

- The cobalamin bound to transcobalamin II is secreted into the circulation and is taken up by the liver, bone marrow, and other cells via endocytosis

- The cobalamin then is converted into its two coenzyme forms (methylcobalamin and adenosylcobalamin).

- All three of the transport proteins prevent loss of vitamin B12 in the urine, sweat, and other body secretions.

- In the liver, vitamin B12 is converted to coenzyme B12, which is essential for hematopoiesis, maintenance of myelin throughout the entire nervous system, and production of epithelial cells

- **An alternate pathway for vitamin B12 absorption independent of intrinsic factor or an intact terminal ileum accounts for a small amount of vitamin B12 absorption.**

- **This alternate pathway involves passive diffusion and accounts for approximately 1% absorption of the ingested vitamin B12.**

- **When vitamin B12 is deficient, the red cells that are produced are abnormally large because of excess cytoplasmic growth and structural proteins**

- **The cells have immature nuclei and show evidence of cellular destruction.**

- **They have flimsy membranes and are oval rather than biconcave.**

- **These oddly shaped cells have a short life span that can be measured in weeks rather than months.**

Clinical Manifestations

- **MCV is elevated**
- **MCHC is normal**
- **Mild jaundice**
- **Mild leukopenia and thrombocytopenia,pancytopenia**
- **Symmetric paresthesias of the feet and Fingers loss of vibratory and position sense, eventual spastic ataxia**
- **More advanced cases, cerebral function may be altered**
- **Confusion and dementia and other neuropsychiatric changes may precede hematologic changes.**

Food	Serving Size	Amount (mcg)
Beef liver, cooked	3 oz	70
Breakfast cereal, fortified (100%)	¾ cup	6
Rainbow trout, cooked	3 oz	3.5
Sockeye salmon, cooked	3 oz	4.9
Beef, cooked	3 oz	2.1
Breakfast cereal, fortified (25%)	¾ cup	1.5
Clams, cooked	3 oz	84.1
Oysters, breaded and fried	6 pieces	1
Tuna, canned in water	3 oz	2.5
Milk	1 cup	1.2
Yogurt	8 oz	1.1

DIETARY VIT B12

TABLE 12-7

Cyanocobalamin (Vitamin B_{12}) Supplementation Regimens for Macrocytic Anemia[31]

	Initial Supplementation			Chronic Supplementation (lifelong)		
Patient Population	Dose	Frequency	Route	Dose	Frequency	Route
US regimens	100 mcg	Daily for 7 days, then on alternate days for 14 days, then q 3–4 days for 2–3 weeks	IM or SQ	100–200 mcg Up to 1,000 mcg[a] 500 mcg	Monthly Daily Weekly	IM or SQ Oral Intranasal
	1,000 mcg	Weekly for 4–6 weeks	IM or SQ	1,000 mcg	Monthly	IM or SQ
	1,000–2,000 mcg	Daily for 1 month	Oral	125–500 mcg	Daily	Oral
UK regimen, without neurological involvement	250–1,000 mcg	On alternating days for 1–2 weeks, then 250 mcg weekly until counts normalize	IM or SQ	1,000 mcg	Monthly	IM or SQ
UK regimen, with neurological involvement	1,000 mcg	On alternating days as long as symptoms occur	IM or SQ			

[a]In patients with normal gastrointestinal absorption, doses of 1–25 mcg daily are considered sufficient as a dietary supplement.

IM, intramuscular; SQ, subcutaneous.

FOLIC ACID DEFICIENCY ANEMIA

- **Folic acid is also required for DNA synthesis and red cell maturation**

- **Adults need to absorb approximately 400 mcg of folate per day in order to replenish the daily degradation and loss through urine and bile.**

- Inadequate intake
- Decreased absorption
- Hyperutilization (rate of cellular division is increased--- adolescents and infants, psoriasis, rheumatoid arthritis, chronic inflammatory Disorders, malignancy, myelofibrosis, hemolytic anemia, pregnant women)
- Inadequate utilization
- Malabsorption syndromes
- Alcoholics (interferes with folic acid absorption, folic acid utilization at the cellular level, decreases hepatic stores of folic acid)
- Drugs (azathioprine, 6-mercaptopurine, 5-fluorouracil, hydroxyurea, zidovudine, methotrexate)

Etiopathogenesis

- **Humans are unable to synthesize sufficient folate to meet total daily requirements, they depend on dietary sources.**

- **Major dietary sources of folate include fresh, green, leafy vegetables, citrus fruits, yeast, mushrooms, dairy products, and animal organs such as liver and kidney.**

- **Most folate in food is present in the polyglutamate form, which must be broken down into the monoglutamate form prior to absorption in the small intestine.**

- **Once absorbed, dietary folate must be converted to the active form tetrahydrofolate through a cobalamin- dependent reaction.**

- **The recommended daily allowance for folate is 600 mcg for pregnant females, and 500 mcg for lactating females.**

Clinical presentation

- **Fatigue**
- **Headache**
- **Pallor**
- **Sore mouth and tongue**
- **Nausea, vomiting, abdominal pain, and diarrhea**
- **Anorexia**
- **Symptoms similar to vit B12 def anemia except neurological manifestations.**

Food	Serving	Amount (mcg)
Beef liver	3 oz	215
Cereal, 25% fortified	½ to 1½ cups	100–400
Lentils, cooked	½ cup	180
Chickpeas	½ cup	141
Asparagus	½ cup	132
Spinach, cooked	½ cup	131
Pasta, enriched	½ cup	83
Kidney beans	½ cup	46
White rice, cooked	½ cup	90
Tomato juice	1 cup	48
Brussels sprouts	½ cup	78
Orange	1 medium	47