Therapy of Anemias

Introduction

- **Anemia is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), which results in decreased oxygen-carrying capacity of the blood.**
- **Anemia is defined by the World Health Organization (WHO) as Hb less than 13 g/dL in men and less than 12 g/dL in women.**
- **According to the WHO, 25% of the world's population are anemic.**

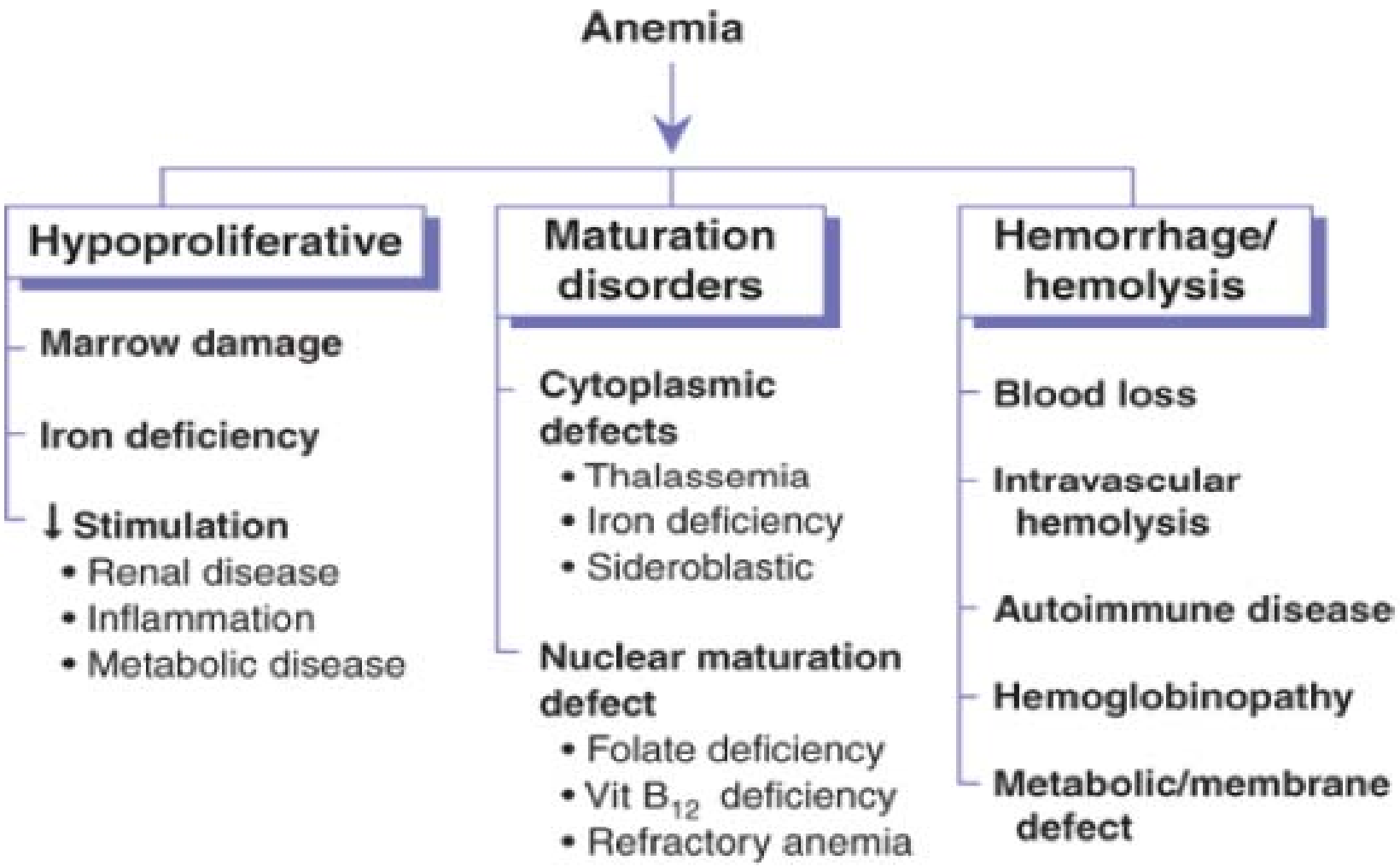
Introduction

- Acute-onset anemias present with tachycardia, lightheadedness, and dyspnea, while chronic anemia presents with weakness, fatigue, headache, vertigo, and pallor.
- Iron deficiency is the leading cause of anemia worldwide, accounting for about 50% of cases.
- It is recommended to routinely screen for iron deficiency anemia, especially in pregnant women, children, and the elderly.

Introduction

- **Anemia can result from inadequate RBC production, increased RBC destruction, or blood loss.**
- **It can be a manifestation of other systemic disorders, such as infection, chronic renal disease, or malignancy.**
- **Because anemia is a sign of underlying pathology, early identification of the cause is essential.**

Introduction



Iron Deficiency Anemia

- **The reference ranges for Hb and Hct are wide, so that a patient may lose up to 15% of RBC mass and the Hct is still within the reference range.**
- **Therefore, iron deficiency may precede the appearance of anemia.**

Iron Balance:

- **The normal iron content of the body is about 3 - 4 g.**
- **It is a component of Hb, myoglobin, and cytochromes.**

Iron Deficiency Anemia

	Iron (mg)
Hb	2000
Myoglobin	130
Transferrin (plasma)	3
Ferritin (storage)	1000
Cytochromes	Rest of iron

Iron Deficiency Anemia

- **The body has an intricate system for iron absorption, transport, storage, assimilation, and elimination.**
- **Iron loss is ~ 1 mg daily.**
- **Menstruating women lose up to 0.6% - 2.5% more per day.**
- **Pregnancy requires an additional 700 mg of iron.**
- **Blood donation results in ~ 250 mg of iron loss.**

Iron Deficiency Anemia

- Iron is best absorbed in its ferrous (Fe^{2+}) form.
- The normal daily diet contains mainly the ferric (Fe^{3+}) non-absorbed form.
- Iron is ionized by gastric acid, and then reduced to the Fe^{2+} state before it is absorbed.
- It is absorbed primarily in the duodenum, and to a smaller extent in the jejunum, via intestinal mucosal cell uptake.
- Subsequently, it is transferred across the cell into the plasma.

Iron Deficiency Anemia

- **Iron absorption is NOT directly proportional to iron intake.**
- **As iron levels decrease, GI absorption of iron increases.**
- **The recommended daily intake of elemental iron is 8 mg in adult males and postmenopausal females, and 18 mg in menstruating females.**
- **Children require more iron because of growth related increases in blood volume.**

Iron Deficiency Anemia

- **Pregnant women require more iron because of fetal development.**
- **Normally, only the amount of iron lost per day is absorbed.**
- **Hem iron (in meat, fish, and poultry) is about three times more absorbable than the non-hem iron found in vegetables, fruits, dried beans, nuts, grains, and dietary supplements.**
- **Gastric acid and ascorbic acid increase the absorption of non-hem iron.**

Iron Deficiency Anemia

- **Dietary components that form insoluble complexes with iron (phytates, tannates, and phosphates) decrease absorption.**
- **Polyphenols bind iron and decrease non-hem iron absorption when large amounts of tea or coffee are consumed with a meal.**
- **Calcium inhibits absorption of both hem and non-hem iron (mechanism ?).**
- **Patients with gastrectomy or achlorhydria have decreased iron absorption.**

Iron Deficiency Anemia

- **Iron deficiency results from increased iron demand (hematopoiesis), increased loss, decreased intake or decreased absorption.**
- **Iron stores are reduced before reduced serum iron levels, and can be assessed with serum ferritin measurement.**
- **Groups at risk: children younger than 2 years, adolescent girls, pregnant and lactating females, and those older than 65 years.**

Iron Deficiency Anemia

- **In patients older than 65 years of age test for occult GI bleeding.**
- **Medications involved: alcohol, corticosteroids, anticoagulants, aspirin, and other (NSAIDs).**
- **Other causes of hypochromic microcytic anemia include: "anemia of inflammation", thalassemia, sideroblastic anemia, and heavy metal (lead) poisoning.**

Therapy of Iron Deficiency Anemia

Treatment:

- **Desired outcomes: reversal of hematologic parameters to normal, return of normal function and quality of life, and prevention or reversal of long-term complications.**
- **Treatment is focused on replenishing iron stores.**
- **Treatment of the underlying cause is needed and it aids in the correction of iron deficiency.**

Therapy of Iron Deficiency Anemia

- **Treatment consists of use of soluble and absorbable Fe^{2+} iron salts.**
- **Meat, fish, and poultry, and certain iron-fortified cereals can help treat IDA.**
- **Fe^{2+} salts (sulfate, succinate, lactate, fumarate, glutamate, and gluconate) are absorbed similarly.**
- **The dose of iron replacement therapy depends on the patient's ability to tolerate the administered iron.**

Therapy of Iron Deficiency Anemia

- **Tolerance of iron salts may improve with a small initial dose and gradual escalation to the full dose.**
- **The recommended dose is about 150 to 200 mg of elemental iron daily, in two or three divided doses.**
- **Iron preferably is administered at 1 hour before meals because food can interfere with absorption. (???)**

Therapy of Iron Deficiency Anemia

- **Many patients take iron with food because of GI upset when iron is administered on an empty stomach.**
- **Treatment should continue for 3 to 6 months after the anemia is resolved to allow for repletion of iron stores and to prevent relapse.**

Iron Salt	Percent Elemental Iron	Common: Formulations and Elemental Iron Provided
Ferrous sulfate	20	60-65 mg/324-325 mg tablet 60 mg/5 mL syrup 44 mg/ 5 mL elixir 15 mg/1 mL
Ferrous sulfate (disiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28-29 mg/240-246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324-325 mg tablet

Therapy of Iron Deficiency Anemia

Adverse reactions:

- **At therapeutic doses: dark discoloration of feces, constipation or diarrhea, nausea, and vomiting.**
- **GI adverse effects are dose-related and are similar among iron salts when equivalent amounts of elemental iron are administered.**

Drug Interactions with Iron Salts

Drugs That Decrease Iron Absorption	Drugs Affected by Iron
1. Al^{+3} -, Mg^{+2} - , and Ca^{2+} - containing antacids. 2. Tetracycline and doxycycline. 3. Histamine H_2 -receptor antagonists. 4. Proton-pump inhibitors. 5. Cholestyramine.	1. Levodopa ↓ (chelates with iron). 2. Methyldopa ↓ (decreases efficacy of methyldopa). 3. Levothyroxine ↓ (decreased efficacy of levothyroxine). 4. Penicillamine ↓ (chelates with iron). 5. Fluoroquinolones ↓ (forms ferric ion quinolone complex). 6. Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt). 7. Mycophenolate ↓ (decreases absorption).

Therapy of Iron Deficiency Anemia

Common causes of treatment failure:

1. **Poor patient adherence.**
2. **Inability to absorb iron (due to previous gastrectomy, gastric bypass surgery, or celiac disease).**
3. **Conditions that impairs full reticulocyte response.**
4. **Persistance of a coexisting cause of anemia (continued bleeding. …).**
5. **Incorrect diagnosis.**

Therapy of Iron Deficiency Anemia

Parenteral Iron Therapy:

Indications:

1. Intolerance to oral iron.
2. Malabsorption.
3. Nonadherence.
4. Patients with significant blood loss who refuse transfusions and cannot take oral iron (??!!).
5. Patients with chronic kidney disease especially those undergoing hemodialysis.

Therapy of Iron Deficiency Anemia

6. **Patients with inflammatory bowel disease and those with gastric bypass/gastric resection due to poor oral absorption (first-line).**
7. **Cancer patients receiving chemotherapy and erythropoiesis-stimulating agents.**

Therapy of Iron Deficiency Anemia

Parenteral iron preparations:

1. **Iron dextran.**
2. **Sodium ferric gluconate.**
3. **Iron sucrose.**
4. **Ferumoxytol.**
5. **Ferric carboxymaltose.**

- **They differ in their molecular size, pharmacokinetics, bioavailability, and adverse effect profiles.**
- **They are all effective.**

Therapy of Iron Deficiency Anemia

- **All parenteral iron preparations carry a risk for severe anaphylactic reactions, which is more with iron dextran and ferumoxytol products.**
- **Resuscitation equipment and trained staff should be available during administration of all iron dextran preparations.**
- **Iron may be released too quickly and overload the ability of transferrin to bind it, leading to free iron reactions that can interfere with neutrophil function.**

Therapy of Iron Deficiency Anemia

$$\text{Dose of iron (mg)} = \text{whole blood hemoglobin deficit (g/L)} \times \text{body weight (kg)} \times 0.22$$

An additional quantity of iron to replenish stores should be added (about 600 mg for women and 1,000 mg for men).

Megaloblastic Anemias

- **Macrocytosis seen in megaloblastic anemias is caused by abnormal DNA metabolism resulting from vitamin B_{12} or folate deficiency.**
- **With adequate folate and vitamin B_{12} levels and the absence of liver disease, high alcohol intake may produce macrocytosis.**
- **Cessation of alcohol results in resolution of the macrocytosis within ~ 2 months.**

Megaloblastic Anemias

- **Drug-induced macrocytosis:**

  hydroxyurea, zidovudine, cytarabine, methotrexate, azathioprine, 6-mercaptopurine, cladribine.

- **In vitamin B_{12}- or folate-deficiency anemia, megaloblastosis results from interference with folic acid- and vitamin B_{12}-interdependent nucleic acid synthesis in the immature erythrocyte.**

Megaloblastic Anemias

- **The maturation process is impaired, resulting in immature large RBCs (macrocytosis).**
- **RNA and DNA synthesis depend on a series of reactions catalyzed by vitamin B_{12} and folic acid because of their role in the conversion of uridine to thymidine.**

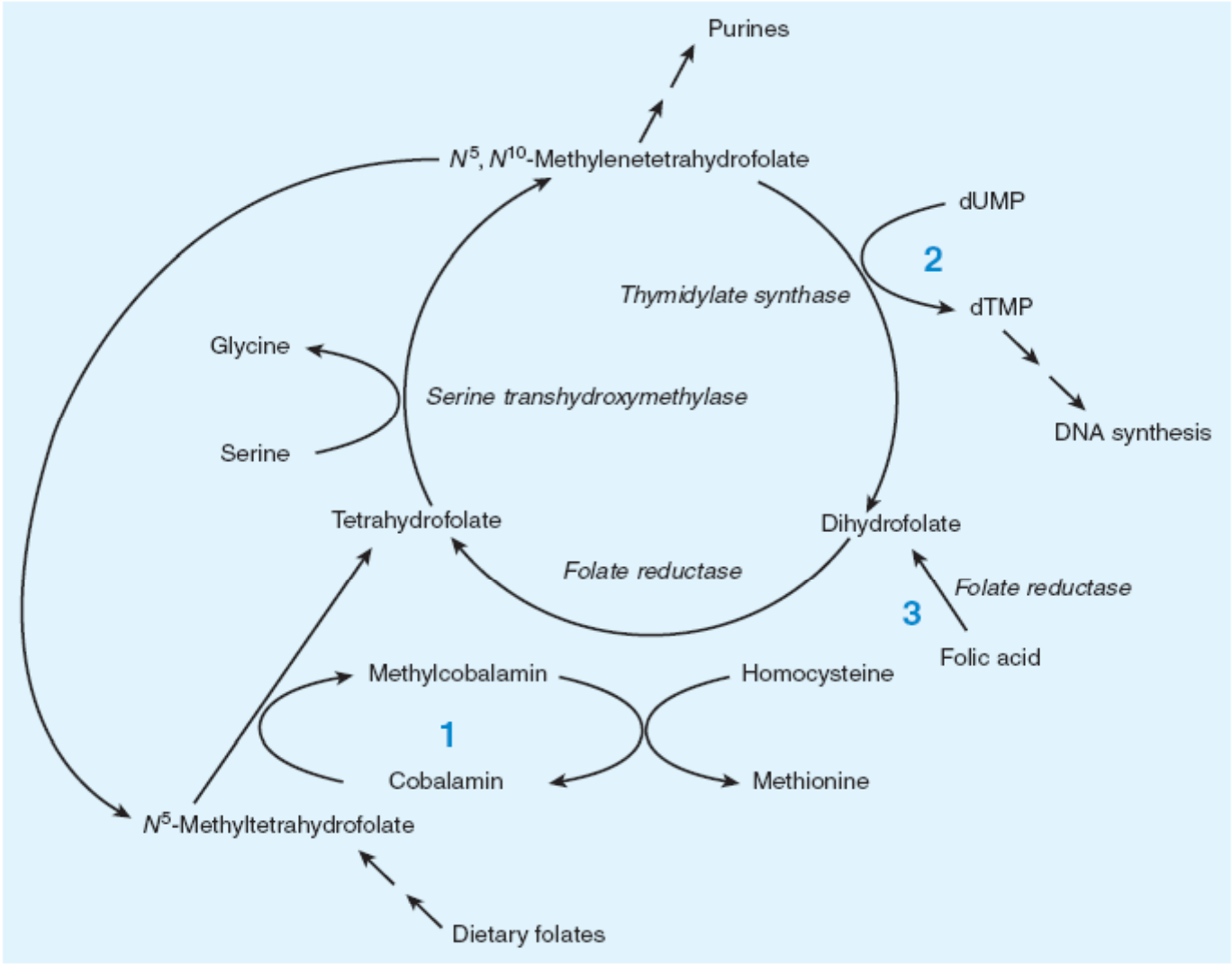


FIGURE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the dTMP cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows indicate pathways with more than one intermediate step.

Vitamin B_{12} Deficiency Anemia

Causes:

1. **Inadequate intake.**

- **In strict vegans and their breast-fed infants, chronic alcoholics, and elderly patients who consume a “tea and toast” diet because of financial limitations or poor dentition.**

Vitamin B_{12} Deficiency Anemia

2. **Decreased absorption.**

- **With loss of intrinsic factor by autoimmune mechanisms (pernicious anemia, in which gastric parietal cells are selectively damaged).**
- **Inadequate gastric acid production, or use of antacid drugs (proton pump inhibitors and histamine H_2-receptor antagonists), leading to failure of cleavage and release of vitamin B_{12} from proteins in food.**

Vitamin B_{12} Deficiency Anemia

- In chronic atrophic gastritis, or gastric surgery.
- *Helicobacter pylori* infection (a cause of chronic gastritis).
- Overgrowth of bacteria and parasites that use vitamin B_{12} in the bowel.
- Metformin may reversibly decrease B_{12} absorption, due to its effects on the mechanism of absorption of vitamin B_{12} -receptor complex in the terminal ileum.

Vitamin B_{12} Deficiency Anemia

- **Injury or surgical removal of ileal receptor sites where vitamin B_{12} and the intrinsic factor complex are absorbed (Crohn's disease or small bowel surgery).**

Vitamin B_{12} Deficiency Anemia

- Vitamin B_{12} is a water-soluble vitamin obtained by ingestion of meat, fish, poultry, dairy products, and fortified cereals.
- The body stores vitamin B_{12} is in the liver (~50%) for several years (2000 – 4000 µg).
- The recommended daily requirement is 2 µg in adults and 2.6 µg in pregnant or breast-feeding women.
- Vitamin B_{12} deficiency usually takes several years to develop following vitamin deprivation.

Vitamin B_{12} Deficiency Anemia

Vitamin B_{12} deficiency also causes :

1. **Neurologic complications (bilateral paraesthesia in extremities, and deficits in proprioception and vibration). If not treated, symptoms progress to ataxia, dementia-like symptoms, psychosis, and vision loss.**
2. **In children prolonged deficiency can lead to poor brain development.**

- **Patients with unexplained neuropathies should be screened for vitamin B_{12} deficiency.**

Vitamin B_{12} Deficiency Anemia

Megaloblastic anemia is associated with:

1. **Elevated MCV.**
2. **Mild leukopenia and thrombocytopenia.**
3. **Low serum vitamin B_{12} level, less than 200 pg/mL.**
4. **Subclinical vitamin B_{12} deficiency is sometimes seen with vitamin B_{12} levels 200 - 300 pg/mL.**

Vitamin B_{12} Deficiency Anemia

- **Methylmalonic acid (MMA) and homocysteine are first to accumulate in vitamin B_{12} deficiency.**
- **Elevations in MMA are more specific for vitamin B_{12} deficiency.**

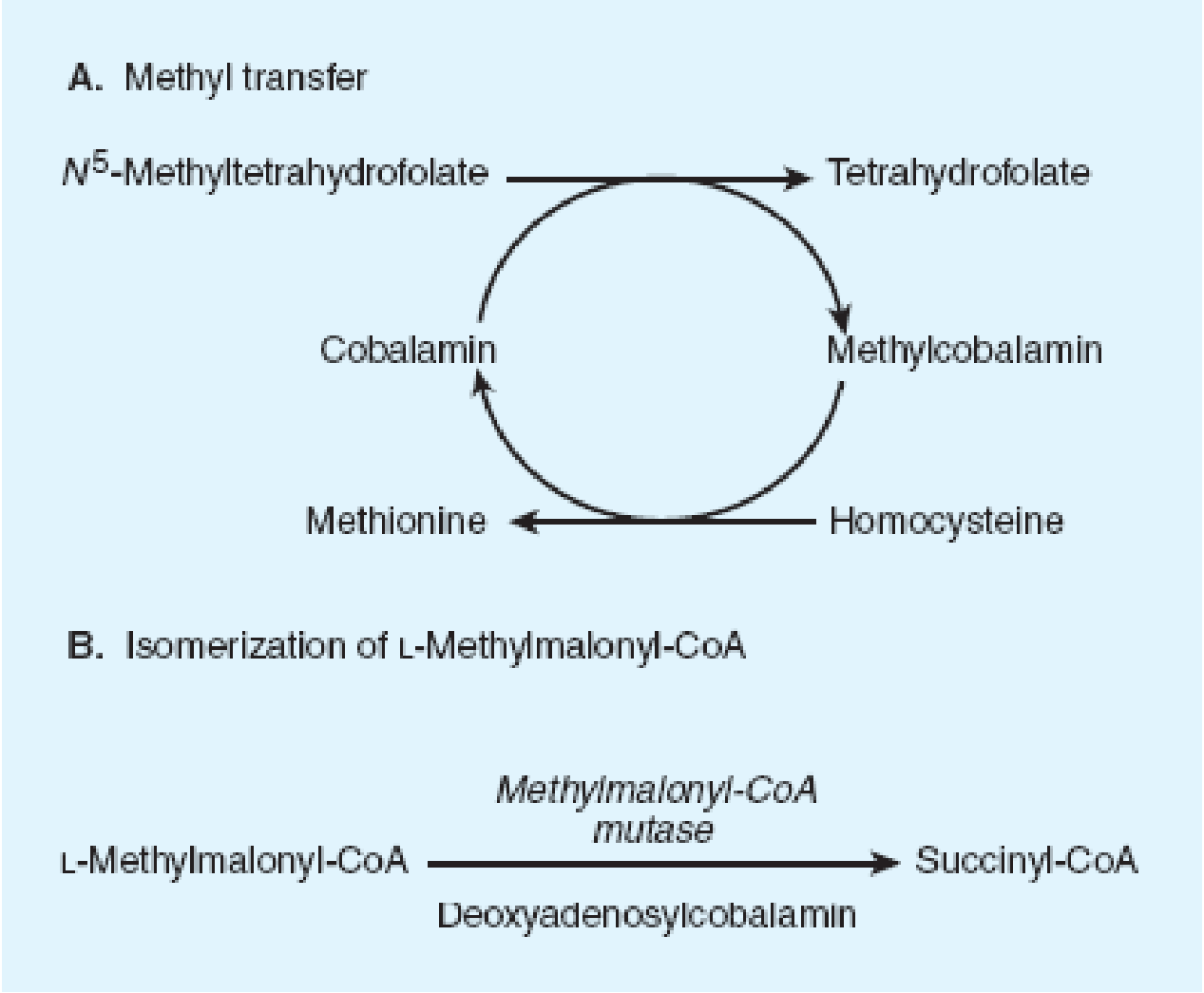


FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}. See text for details.

Vitamin B_{12} Deficiency Anemia

- **Homocysteine can also be elevated in folate deficiency, chronic renal disease, alcoholism, smoking, and use of steroid or cyclosporine therapy.**
- **Hyperhomocysteinemia may be an independent risk factor for cerebrovascular, peripheral vascular, coronary, and venous thromboembolic diseases.**

Vitamin B_{12} Deficiency Anemia

Treatment:

- **The goals of treatment for vitamin B_{12} deficiency include:**

a. **reversal of hematologic manifestations.**

b. **replacement of body stores.**

c. **prevention or resolution of neurologic manifestations.**

- **Early treatment is very important because neurologic damage may be reversible if the deficiency is detected and corrected early.**

Vitamin B_{12} Deficiency Anemia

- **The underlying etiology should be corrected also.**
- **Parenteral vitamin B_{12} regimen consists of daily injections of 1,000 µg of cyanocobalamin for 1 week to saturate vitamin B_{12} stores in the body and resolve clinical manifestations of the deficiency.**
- **Thereafter, it can be given weekly for 1 month, and then monthly for maintenance.**

Vitamin B_{12} Deficiency Anemia

- **Parenteral therapy is indicated in the presence of neurologic symptoms.**
- **Vitamin B_{12} should be continued for life in patients with pernicious anemia.**

Adverse effects:

- **Are rare, and include hyperuricemia and hypokalemia due to marked increase in potassium utilization during production of new hematopoietic cells.**

Folic Acid Deficiency Anemia

- **Folic acid deficiency is one of the most common vitamin deficiencies.**
- **It is associated with excessive alcohol intake and pregnancy.**

Major causes of folic acid deficiency:

1. **Inadequate intake.**

- **Poor eating habits in elderly patients, teenagers ("junk food"), alcoholics, the poor, and those who are chronically ill, or demented.**

Folic Acid Deficiency Anemia

2. **Decreased absorption:**

- **In patients with malabsorption syndromes.**
- **In alcoholics with poor dietary habits, alcohol interferes with folic acid absorption, interferes with folic acid utilization at the cellular level, and decreases hepatic stores of folic acid.**

Folic Acid Deficiency Anemia

3. **Increased requirements:**

- **When the rate of cellular division is increased as seen in:**

a) **Pregnant women.**
b) **Patients with hemolytic anemia.**
c) **Adolescents and infants during their growth spurts.**
d) **Malignancy.**
e) **Others**

Folic Acid Deficiency Anemia

Drug induced folic acid deficiency:

1. **Azathioprine, 6-mercaptopurine, 5-fluorouracil, hydroxyurea, and zidovudine directly inhibit DNA synthesis.**
2. **Folate antagonists; methotrexate; pentamidine, trimethoprim, and triamterene.**
3. **Phenytoin, phenobarbital, and primidone may reduce absorption through the intestine.**

Folic Acid Deficiency Anemia

- **Folic acid is a water-soluble vitamin readily destroyed by cooking or processing.**
- **Because 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.**

Folic Acid Deficiency Anemia

- **The minimum daily requirement is 50 to 100 µg.**
- **In the general population, the recommended daily allowance for folate is 600 µg for pregnant females, 400 µg in nonpregnant females, and 500 µg for lactating women.**
- **Because the body stores about 5 to 10 mg of folate, primarily in the liver, cessation of dietary folate intake can result in deficiency within 3 to 4 months.**

Folic Acid Deficiency Anemia

- It is important to rule out vitamin B_{12} deficiency when folate deficiency is suspected.
- Laboratory changes associated with folate deficiency are similar to those seen in vitamin B_{12} deficiency, except vitamin B_{12} and MMA levels are normal.
- Serum folate levels decrease to less than 3 ng/mL within a few days of reduced dietary folate intake.

Folic Acid Deficiency Anemia

- **The RBC folate level also declines, and levels remain constant throughout the life span of the erythrocyte.**
- **If serum or erythrocyte folate levels are borderline, serum homocysteine usually is increased with a folic acid deficiency.**
- **If serum MMA levels also are elevated, vitamin B_{12} deficiency must be ruled out given that folate does not participate in MMA metabolism.**

Folic Acid Deficiency Anemia

- **Therapy for folic acid deficiency consists of administration of exogenous folic acid to:**

1. **induce hematologic remission.**
2. **replace body stores.**
3. **resolve signs and symptoms.**

- **In most cases, 1 mg daily orally is sufficient to replace stores.**

Folic Acid Deficiency Anemia

- **In cases of deficiency due to malabsorption, doses of 1 to 5 mg daily may be necessary.**
- **Folic acid is completely absorbed by the GI tract and is converted to tetrahydrofolate.**
- **Therapy should continue for about 4 months.**

Folic Acid Deficiency Anemia

- **Foods high in folic acid should also be encouraged (Beef liver, cooked lentils, chickpeas, fortified cereals, cooked spinach, kidney beans, tomato juice, orange, ..).**
- **Long-term folate administration may be necessary in increased folate requirements.**
- **Low-dose folate therapy (500 mcg daily) can be given in combination with anticonvulsant drugs.**
- **Adverse effects have not been reported.**

Folic Acid Deficiency Anemia

- **Periconceptional folic acid supplementation is recommended to decrease the occurrence and recurrence of neural tube defects, specifically anencephaly and spinal bifida.**
- **Folic acid supplementation at a dose of 400 mcg daily is recommended for all women.**

Folic Acid Deficiency Anemia

- **Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg daily of folic acid.**
- **Folic acid supplementation should NOT be attained via ingestion of excess multivitamins because of the risk of fat soluble vitamin toxicity.**

Anemia of Inflammation

- **It describes both “anemia of chronic disease” and “anemia of critical illness”, to reflect the inflammatory process that underlies both of those types of anemia.**
- **The onset of anemia of critical illness is quicker, over days, and typically occurs in a hospital setting.**
- **A nemia of chronic disease has a similar mechanism, but it develops over months to years from a chronic condition.**

Anemia of Inflammation

- **It is especially important in the differential diagnosis of iron deficiency.**
- **Various conditions associated with "anemia of chronic disease" may predispose patients to blood loss (malignancy, GI blood loss from treatments with aspirin, NSAIDs, or corticosteroids).**

Common Causes of Anemia of Inflammation

1. Chronic infections
   Tuberculosis
   Other chronic lung infections (eg, lung abscess, bronchiectasis)
   Human immunodeficiency virus
   Subacute bacterial endocarditis
   Osteomyelitis
   Chronic urinary tract infections

2. Chronic inflammation
   Rheumatoid arthritis
   Systemic lupus erythematosus
   Inflammatory bowel disease
   Inflammatory osteoarthritis
   Gout
   Other (collagen vascular) diseases
   Chronic inflammatory liver diseases

3. Malignancies
   Carcinoma
   Lymphoma
   Leukemia
   Multiple myeloma

Anemia of Inflammation

Treatment:

- **The goals of therapy should include treating the underlying disorder and correcting reversible causes of anemia.**
- **Erythropoiesis-stimulating agent have been used to stimulate erythropoiesis for patients with anemia of inflammation, because a relative erythopoetin (EPO) deficiency exists.**

Anemia of Inflammation

Two agents are available:

1. **Recombinant epoetin alfa.**
2. **Recombinant darbepoetin alfa (has a longer half-life).**

- **Patients with chronic disease may have a relatively impaired response.**
- **Treatment is effective when the marrow has an adequate supply of iron, cobalamin, and folic acid.**

Anemia of Inflammation

Toxicities of erythropoetin administration:

- **Increases in blood pressure, nausea, headache, fever, bone pain, and fatigue.**
- **Less commonly, seizures, thrombotic events, allergic reactions (rashes), and local reactions at the injection site.**

Anemia of Inflammation

Monitoring of erythropoetin therapy:

- **Ensure the patient's Hb does NOT exceed 12 g/dL with treatment, or that Hb does NOT rise greater than 1 g/dL every 2 weeks.**
- **These cases have been associated with:**

➢ **increased mortality.**

➢ **cardiovascular events.**

➢ **tumor progression.**