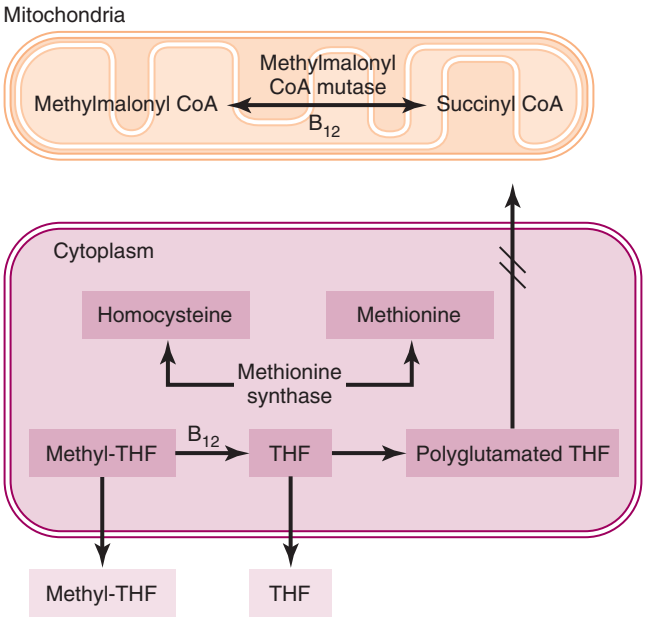

FIGURE 47-3 Metabolic pathways of folic acid and cobalamin. CoA, Coenzyme A; THF, tetrahydrofolate.

Methylmalonyl-CoA mutase is a mitochondrial enzyme that functions in the citric acid cycle to convert methylmalonyl-CoA to succinyl-CoA. The cytoplasmic enzyme homocysteine-methionine methyltransferase is necessary for the transfer of methyl groups from *N*-methyltetrahydrofolate to homocysteine to form methionine. Demethylated tetrahydrofolate is necessary as a carbon donor in the conversion of deoxyuridine to deoxythymidine. Absence of cobalamin results in a *trapping* of tetrahydrofolate in its methylated form, which blocks the synthesis of thymidine 5′-triphosphate for incorporation into DNA. The megaloblastic changes induced by cobalamin deficiency are mediated through this functional folate deficiency, which explains the similarity in the hematologic abnormalities induced by cobalamin and folate deficiency.

Causes of Cobalamin Deficiency

The most common cause of cobalamin deficiency is pernicious anemia, an autoimmune disease associated with gastric parietal cell atrophy, defective gastric acid secretion, and absence of IF. Antiparietal cell and anti-IF antibodies are frequently found in patients with pernicious anemia and other autoimmune conditions such as type 1 diabetes, viteligo, Graves' disease, Addison's disease, and hypoparathyroidism. Many other lesions in the gastrointestinal tract can interfere with absorption of cobalamin (Table 47-3). Gastrectomy causes loss of parietal cell function and IF secretion. Pancreatic insufficiency interferes with digestion of the haptocorrin-cobalamin complex, thus hindering the binding of cobalamin to IF and ileal absorption. Resection of the terminal ileum prevents vitamin B_{12} absorption, as do diseases that affect ileal mucosal function, such as Crohn's disease, sprue, intestinal tuberculosis, and lymphoma. Because the body stores of cobalamin are large and daily loss of cobalamin is low, the stores of cobalamin are adequate for 3 to 4 years if intake stops abruptly; signs of cobalamin deficiency do not develop until defective absorption has occurred for several years. Nutritional cobalamin deficiency is rare and is seen only in individuals who have been on strict vegan diets that exclude all animal products for many years. Infants born to vegan mothers who are breastfed are also at risk for development of cobalamin deficiency.

TABLE 47-3 CAUSES OF COBALAMIN DEFICIENCY

Malabsorption of Vitamin B_{12}	Tapeworm infection
Pernicious anemia	Nutritional (vegans)
Partial or total gastrectomy	Congenital deficiency of intrinsic factor or haptocorrin
Pancreatic insufficiency	
Bacterial overgrowth	
Diseases of the terminal ileum	

TABLE 47-4 CAUSES OF FOLATE DEFICIENCY

DIETARY INSUFFICIENCY	MALABSORPTION
INCREASED FOLATE REQUIREMENTS	Sprue
Pregnancy	Crohn's disease
Lactation	Short bowel syndrome
Hemolysis	**ANTIFOLATE MEDICATIONS**
Exfoliative dermatitis	Chemotherapy agents (e.g., methotrexate, pemetrexed)
Malignancy	Sulfa drugs

Folate Deficiency

Folate is widely present in foods such as leafy vegetables, fruits, and animal protein. However, because it is destroyed by prolonged cooking, fresh fruits and vegetables are the most reliable sources of folate. Consequently, nutritional folate deficiency is common in malnourished individuals who eat very little fresh fruits and vegetables. Folate deficiency can also be caused by increased demand, as occurs with pregnancy, hemolysis, or exfoliative dermatitis, and by increased losses, which occur with dialysis (Table 47-4). Folate is absorbed in the proximal small intestine, and malabsorption of folate can also lead to folate deficiency.

Other Causes of Megaloblastic Anemia

Drugs and toxins are common causes of megaloblastic anemia. Some drugs, such as methotrexate and sulfa drugs, act as direct folate antagonists and mimic folate deficiency. Purine and pyrimidine analogue chemotherapeutic agents (e.g., azathioprine, 5-fluorouracil) are direct DNA-synthesis inhibitors. Antiviral agents cause megaloblastic changes by unclear mechanisms. Alcohol interferes with folate metabolism, increasing the effect of frequent concomitant nutritional folate deficiency. Myelodysplasia commonly appears as a macrocytic anemia, with megaloblastic changes primarily in the erythroid series.

Clinical Manifestations of Megaloblastic Anemia

The development of megaloblastic anemia is usually gradual, allowing adequate time for concomitant plasma expansion to prevent hypovolemia. Consequently, patients are frequently severely anemic at presentation. They may have yellowish skin as the result of a combination of pallor and jaundice. Some patients have glossitis and cheilosis. With severe anemia, patients usually have an MCV greater than 110 fL/cell, although concomitant iron deficiency, caused by malabsorption secondary to