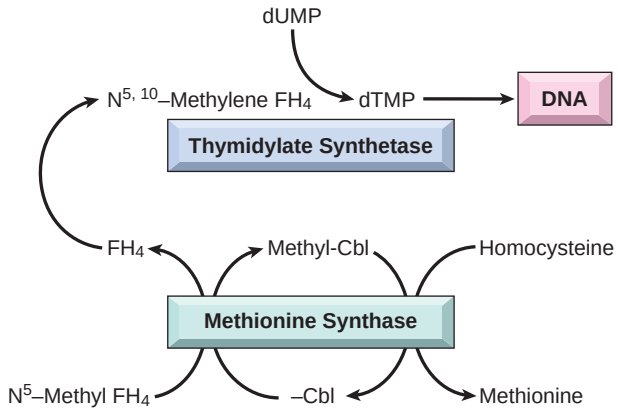

Figure 14-19 Relationship of N^5-methyl FH_4, methionine synthase, and thymidylate synthetase. In cobalamin (Cbl) deficiency, folate is sequestered as N^5-methyl FH_4. This ultimately deprives thymidylate synthetase of its folate coenzyme ($N^{5,10}$-methylene FH_4), thereby impairing DNA synthesis. FH_4, Tetrahydrofolic acid.

protein, transcobalamin II, and is secreted into the plasma. Transcobalamin II delivers vitamin B_{12} to the liver and other cells of the body, including rapidly proliferating cells in the bone marrow and the gastrointestinal tract. In addition to this major pathway, there is also a poorly understood alternative uptake mechanism that is not dependent on intrinsic factor or an intact terminal ileum. Up to 1% of a large oral dose can be absorbed by this pathway, making it feasible to treat pernicious anemia with high doses of oral vitamin B_{12}.

Biochemical Functions of Vitamin B_{12}. Only two reactions in humans are known to require vitamin B_{12}. In one, methylcobalamin serves as an essential cofactor in the conversion of homocysteine to methionine by methionine synthase (Fig. 14-19). In the process, methylcobalamin yields a methyl group that is recovered from N^5-methyltetrahydrofolic acid (N^5-methyl FH_4), the principal form of folic acid in plasma. In the same reaction, N^5-methyl FH_4 is converted to tetrahydrofolic acid (FH_4). FH_4 is crucial, because it is required (through its derivative $N^{5,10}$-methylene FH_4) for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), a building block for DNA. It is postulated that the fundamental cause of the impaired DNA synthesis in vitamin B_{12} deficiency is the reduced availability of FH_4, most of which is "trapped" as N^5-methyl FH_4. The FH_4 deficit may be further exacerbated by an "internal" folate deficiency caused by a failure to synthesize metabolically active polyglutamylated forms. This stems from the requirement for vitamin B_{12} in the synthesis of methionine, which contributes a carbon group needed in the metabolic reactions that create folate polyglutamates (Fig. 14-20). Whatever the mechanism, lack of folate is the proximate cause of anemia in vitamin B_{12} deficiency, because the anemia improves with administration of folic acid.

The neurologic complications associated with vitamin B_{12} deficiency are more enigmatic, because they are not improved (and may actually be worsened) by folate administration. The other known reaction that depends on vitamin B_{12} is the isomerization of methylmalonyl coenzyme A to succinyl coenzyme A, which requires adenosylcobalamin as a prosthetic group on the enzyme methylmalonyl-coenzyme A mutase. A deficiency of vitamin B_{12} thus leads to increased plasma and urine levels of methylmalonic acid. Interruption of this reaction and the consequent buildup of methylmalonate and propionate (a precursor) could lead to the formation and incorporation of abnormal fatty acids into neuronal lipids. It has been suggested that this biochemical abnormality predisposes to myelin breakdown and thereby produces the neurologic complications of vitamin B_{12} deficiency (Chapter 28). However, rare individuals with hereditary deficiencies of methylmalonyl-coenzyme A mutase do not suffer from the neurologic abnormalities seen in vitamin B_{12} deficiency, casting doubt on this explanation.

Pernicious Anemia

Incidence. Although somewhat more prevalent in Scandinavian and other Caucasian populations, pernicious anemia occurs in all racial groups, including blacks and Hispanics. It is a disease of older adults; the median age at diagnosis is 60 years, and it is rare in people younger than 30. A genetic predisposition is strongly suspected, but no definable genetic pattern of transmission has been discerned. As described later, many affected individuals have a tendency to form antibodies against multiple self-antigens.

Pathogenesis. Pernicious anemia is believed to result from an autoimmune attack on the gastric mucosa. Histologically, there is a *chronic atrophic gastritis* marked by a loss of parietal cells, a prominent infiltrate of lymphocytes and plasma cells, and megaloblastic changes in mucosal cells similar to those found in erythroid precursors. Three types of autoantibodies are present in many, but not all, patients. About 75% of patients have a *type I antibody* that blocks the binding of vitamin B_{12} to intrinsic factor. Type I antibodies are found in both plasma and gastric juice. *Type II antibodies* prevent binding of the intrinsic factor-vitamin B_{12} complex to its ileal receptor. These antibodies are also found in a large proportion of patients with pernicious anemia. *Type III antibodies* are present in 85% to 90% of patients and recognize the α and β subunits of the gastric proton pump, which is normally localized to the microvilli of the canalicular system of the gastric parietal cell. Type III

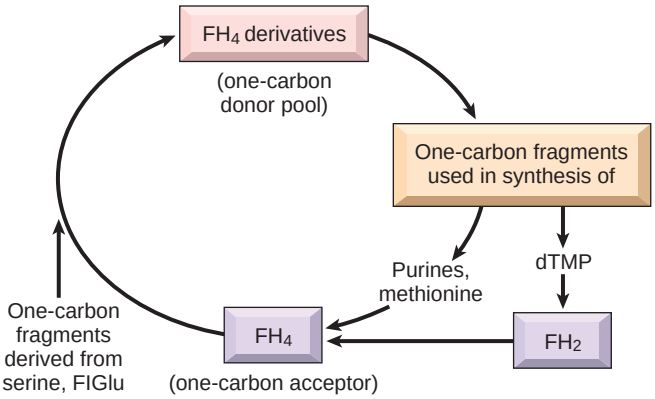

Figure 14-20 Role of folate derivatives in the transfer of one-carbon fragments for synthesis of biologic macromolecules. FH_4, Tetrahydrofolic acid; FH_2, dihydrofolic acid; FIGlu, formiminoglutamate; dTMP, deoxythymidine monophosphate.