

recycled during thymidylate synthesis but is degraded at the C9-N10 bond.

BIOCHEMICAL BASIS OF MEGALOBlastic ANEMIA

The common feature of all megaloblastic anemias is a defect in DNA synthesis that affects rapidly dividing cells in the bone marrow. All conditions that give rise to megaloblastic changes have in common a disparity in the rate of synthesis or availability of the four immediate precursors of DNA: the deoxyribonucleoside triphosphates (dNTPs)—dA(adenine)TP and dG(guanine)TP (purines), dT(thymine)TP, and dC(cytosine)TP (pyrimidines). In deficiencies of either folate or cobalamin, there is failure to convert deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), the precursor of dTTP ([Fig. 99-1](#)). This is the case because folate is needed as the coenzyme 5,10-methylene-THF polyglutamate for conversion of dUMP to dTMP; the availability of 5,10-methylene-THF is reduced in either cobalamin or folate deficiency. DNA replication from multiple origins along the chromosome is slower than normal during mitosis, and there is failure of joining up the incomplete replicons with resulting single-stranded DNA breaks. An alternative theory for megaloblastic anemia in cobalamin or folate deficiency is misincorporation of uracil into DNA because of the accumulation of deoxyuridine triphosphate (dUTP) at the DNA replication fork as a consequence of the block in conversion of dUMP to dTMP.

■ COBALAMIN-FOLATE RELATIONS

Folate is required for many reactions in mammalian tissues. Only two reactions in the body are known to require cobalamin. Methylmalonyl-CoA isomerization requires adocobalamin, and the methylation of homocysteine to methionine requires both methylcobalamin and 5-MTHF ([Fig. 99-1](#)). This reaction is the first step in the pathway by which 5-MTHF, which enters bone marrow and other cells from plasma, is converted into all the intracellular folate coenzymes. The coenzymes are all polyglutamated (the larger