TABLE 128-2 BIOCHEMICAL REACTIONS OF FOLATE COENZYMES

Reaction	Coenzyme Form of Folate Involved	Single Carbon Unit Transferred	Importance
Formate activation	THF	–CHO	Generation of 10-formyl-THF
Purine synthesis			
Formation of glycinamide ribonucleotide	5,10-Methylene-THF	–CHO	Formation of purines needed for DNA, RNA synthesis, but reactions probably not rate-limiting
Formylation of aminoimidazole carboxamide ribonucleotide (AICAR)	10-Formyl (CHO)THF		
Pyrimidine synthesis			
Methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP)	5,10-Methylene-THF	$-CH_3$	Rate limiting in DNA synthesis Oxidizes THF to DHF Some breakdown of folate at the C-9–N-10 bond
Amino acid interconversion			
Serine–glycine interconversion	THF	$=CH_2$	Entry of single carbon units into active pool
Homocysteine to methionine	5-Methyl(M)THF	$-CH_3$	Demethylation of 5-MTHF to THF; also requires cobalamin, flavine adenine dinucleotide, ATP, and adenosylmethionine
Forminoglutamic acid to glutamic acid in histidine catabolism	THF	–HN–CH=	

Abbreviations: DHF, dihydrofolate; THF, tetrahydrofolate.

forms are hydrolyzed to the monoglutamate derivatives either in the lumen of the intestine or within the mucosa. All dietary folates are converted to 5-methylTHF (5-MTHF) within the small intestinal mucosa before entering portal plasma. The monoglutamates are actively transported across the enterocyte by a proton-coupled folate transporter (PCFT, SCL46A1). This is situated at the apical brush border and is most active at pH 5.5, which is about the pH of the duodenal and jejunal surface. Genetic mutations of this protein underlie hereditary malabsorption of folate (see below). Pteroylglutamic acid at doses >400 μg is absorbed largely unchanged and converted to natural folates in the liver. Lower doses are converted to 5-MTHF during absorption through the intestine.

About 60–90 μg of folate enters the bile each day and is excreted into the small intestine. Loss of this folate, together with the folate of sloughed intestinal cells, accelerates the speed with which folate deficiency develops in malabsorption conditions.

TRANSPORT

Folate is transported in plasma; about one-third is loosely bound to albumin, and two-thirds is unbound. In all body fluids (plasma, cerebrospinal fluid, milk, bile), folate is largely, if not entirely, 5-MTHF in the monoglutamate form. Three types of folate-binding protein are involved. A reduced folate transporter (RFC, SLC19A1) is the major route of delivery of plasma folate (5-MTHF) to cells. Two folate receptors, FR2 and FR3 embedded in the cell membrane by a glycosyl phosphatidylinositol anchor, transport folate into the cell via receptor-mediated endocytosis. The third protein, PCFT, transports folate at low pH from the vesicle to the cell cytoplasm. The reduced folate transporter also mediates uptake of methotrexate by cells.

BIOCHEMICAL FUNCTIONS

Folates (as the intracellular polyglutamate derivatives) act as coenzymes in the transfer of single-carbon units (Fig. 128-1 and Table 128-2). Two of these reactions are involved in purine synthesis and one in pyrimidine synthesis necessary for DNA and RNA replication. Folate is also a coenzyme for methionine synthesis, in which methylcobalamin is also involved and in which THF is regenerated. THF is the acceptor of single carbon units newly entering the active pool via conversion of serine to glycine. Methionine, the other product of the methionine synthase reaction, is the precursor for *S*-adenosylmethionine (SAM), the universal methyl donor involved in >100 methyltransferase reactions (Fig. 128-1).

During thymidylate synthesis, 5,10-methylene-THF is oxidized to DHF (dihydrofolate). The enzyme DHF reductase converts this to THF. The drugs methotrexate, pyrimethamine, and (mainly in bacteria) trimethoprim inhibit DHF reductase and so prevent formation of active THF coenzymes from DHF. A small fraction of the folate coenzyme is not 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 128-1). 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. An alternative theory for megaloblastic anemia in cobalamin or folate deficiency is misincorporation of uracil into DNA because of a buildup 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. 128-1). 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 size aiding retention in the cell), but the enzyme folate polyglutamate synthase can use only THF, not MTHF, as substrate. In cobalamin deficiency, MTHF accumulates in plasma, and intracellular folate concentrations fall due to failure of formation of THF, the substrate on which folate polyglutamates are built. This has been termed *THF starvation*, or the *methylfolate trap*.

This theory explains the abnormalities of folate metabolism that occur in cobalamin deficiency (high serum folate, low cell folate, positive purine precursor aminoimidazole carboxamide ribonucleotide [AICAR] excretion; Table 128-2) and also why the anemia of cobalamin deficiency responds to folic acid in large doses.

CLINICAL FEATURES

Many symptomless patients are detected through the finding of a raised mean corpuscular volume (MCV) on a routine blood count. The main clinical features in more severe cases are those of anemia. Anorexia is