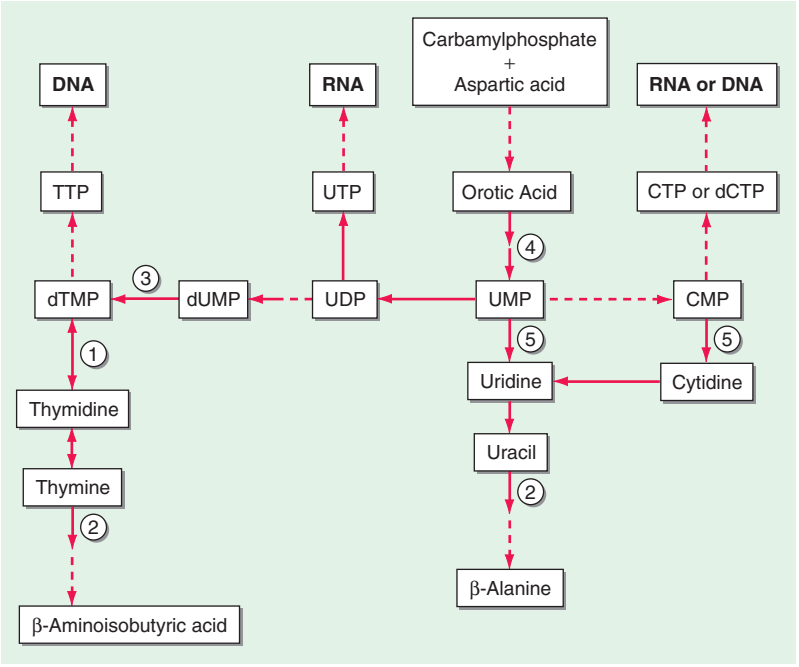


**FIGURE 431e-4 Abbreviated scheme of pyrimidine metabolism.** (1) Thymidine kinase, (2) dihydropyrimidine dehydrogenase, (3) thymidylate synthase, (4) UMP synthase, (5) 5′-nucleotidase. CMP, cytidine-5′-monophosphate; UMP, uridine-5′-monophosphate; UDP, uridine-5′-diphosphate; dUMP, deoxyuridine-5′-monophosphate; dTMP, deoxythymidine-5′-monophosphate; TTP, thymidine triphosphate; UTP, uridine triphosphate.



individuals have some measurable enzyme activity (type II). Expression of the defect is similar in the two populations, as is the frequency of the heterozygous state (0.4–1.1 per 100). Allopurinol treatment prevents stone formation.

**Hereditary Xanthinuria** A deficiency of xanthine oxidase causes all purine in the urine to occur in the form of hypoxanthine and xanthine. About two-thirds of deficient individuals are asymptomatic. The remainder develop kidney stones composed of xanthine.

**Myoadenylate Deaminase Deficiency** Primary (inherited) and secondary (acquired) forms of myoadenylate deaminase deficiency have been described. The primary form is inherited as an autosomal recessive trait. Clinically, some persons may have relatively mild myopathic symptoms with exercise or other triggers, but most individuals with this defect are asymptomatic. Therefore, another explanation for the myopathy should be sought in symptomatic patients with this deficiency. The acquired deficiency occurs in association with a wide variety of neuromuscular diseases, including muscular dystrophies, neuropathies, inflammatory myopathies, and collagen vascular diseases.

**Adenylosuccinate Lyase Deficiency** Deficiency of this enzyme is due to an autosomal recessive trait and causes profound psychomotor retardation, seizures, and other movement disorders. All individuals with this deficiency are mentally retarded, and most are autistic.

**Adenosine Deaminase Deficiency and Purine Nucleoside Phosphorylase Deficiency** See Chap. 374.

## PYRIMIDINE DISORDERS

The pyrimidine cytidine is found in both DNA and RNA; it is a complementary base pair for guanine. Thymidine is found only in DNA, where it is paired with adenine. Uridine is found only in RNA and can pair with either adenine or guanine in RNA secondary structures. Pyrimidines can be synthesized by a de novo pathway (Fig. 431e-4) or reused in a salvage pathway. Although more than 25 different enzymes are involved in pyrimidine metabolism, disorders of these pathways are rare. Seven disorders of pyrimidine metabolism have been discovered (Table 431e-4), three of which are discussed below.

**Orotic Aciduria** Hereditary orotic aciduria is caused by mutations in a bifunctional enzyme, uridine-5′-monophosphate (UMP) synthase, which converts orotic acid to UMP in the de novo synthesis pathway (Fig. 431e-4). The disorder is characterized by hypochromic megaloblastic anemia that is unresponsive to vitamin $B_{12}$ and folic acid, growth retardation, and neurologic abnormalities. Increased excretion of orotic acid causes crystalluria and obstructive uropathy. Replacement of uridine (100–200 mg/kg per day) corrects anemia, reduces orotic acid excretion, and improves the other sequelae of the disorder.

**Pyrimidine 5′-nucleotidase Deficiency** Pyrimidine 5′-nucleotidase catalyzes the removal of the phosphate group from pyrimidine ribonucleoside monophosphates (cytidine-5′-monophosphate or UMP) (Fig. 431e-4). An inherited deficiency of this enzyme causes hemolytic anemia with prominent basophilic stippling of erythrocytes. The accumulation of pyrimidines or cytidine diphosphate choline is thought to induce hemolysis. There is no specific treatment. Acquired pyrimidine 5′-nucleotidase deficiency has been reported in lead poisoning and in thalassemia.

**Dihydropyrimidine Dehydrogenase Deficiency** Dihydropyrimidine dehydrogenase is the rate-limiting enzyme in the pathway of uracil and thymine degradation (Fig. 431e-4). Deficiency of this enzyme causes excessive urinary excretion of uracil and thymine. In addition, this deficiency causes nonspecific cerebral dysfunction with convulsive disorders, motor retardation, and mental retardation. No specific treatment is available.

**Medication Effect on Pyrimidine Metabolism** A variety of medications can influence pyrimidine metabolism. The anticancer agents fluorodeoxyuridine and 5-fluorouracil and the antimicrobial agent fluorocytosine cause cytotoxicity when converted to fluorodeoxyuridylate, a specific suicide inhibitor of thymidylate synthase. Fluorocytosine must be converted to 5-fluorouracil to be effective. This conversion is catalyzed by cytosine deaminase activity. Fluorocytosine's action is selective because cytosine deaminase is present in bacteria and fungi but not in human cells. Dihydropyrimidine dehydrogenase is involved in the degradation of 5-fluorouracil. Consequently, deficiency of this enzyme is associated with 5-fluorouracil neurotoxicity.

Leflunomide, which is used to treat rheumatoid arthritis, inhibits de novo pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase, resulting in an antiproliferative effect on T cells. Allopurinol, which inhibits xanthine oxidase in the purine metabolic pathway, also inhibits the activity of orotidine-5′-phosphate decarboxylase, a step in UMP synthesis. Consequently, allopurinol use is associated with increased excretion of orotidine and orotic acid. There are no known clinical effects of this inhibition.