

In ureotelic organisms, the ammonia deposited in the mitochondria of hepatocytes is converted to urea in the **urea cycle**. This pathway was discovered in 1932 by Hans Krebs (who later also discovered the citric acid cycle) and a medical student associate, Kurt Henseleit. Urea production occurs almost exclusively in the liver and is the fate of most of the ammonia channeled there. The urea passes into the bloodstream and thus to the kidneys and is excreted into the urine.

The urea cycle begins inside liver mitochondria, but three of the subsequent steps take place in the cytosol; the cycle thus spans two cellular compartments. The first amino group to enter the urea cycle is derived from ammonia in the mitochondrial matrix—most of this  $\text{NH}_4^+$  arises by the pathways described in the previous section. The liver also receives some ammonia via the portal vein from the intestine, from the bacterial oxidation of amino acids. Whatever its source, the  $\text{NH}_4^+$  generated in liver mitochondria is immediately used, together with  $\text{CO}_2$  (as  $\text{HCOO}^-$ ) produced by mitochondrial respiration, to form carbamoyl phosphate in the matrix.

This

ATP-dependent reaction is catalyzed by **carbamoyl phosphate synthetase I**, a regulatory enzyme (see below). The mitochondrial form of the enzyme is distinct from the cytosolic (II) form, which has a separate function in pyrimidine biosynthesis. The carbamoyl phosphate, which functions as an activated carbamoyl group donor, now enters the urea cycle. The cycle has only four enzymatic steps. First, carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline, with the release of  $\text{P}_i$ . The reaction is catalyzed by **ornithine transcarbamoylase**. Ornithine plays a role resembling that of oxaloacetate in the citric acid cycle, accepting material at each turn of the urea cycle. The citrulline produced in the first step of the urea cycle passes from the mitochondrion to the cytosol.

The next two steps bring in the second amino group. The source is aspartate generated in mitochondria by transamination and transported into the cytosol. A condensation reaction between the amino group of aspartate and the ureido (carbonyl) group of citrulline forms argininosuccinate. This cytosolic reaction, catalyzed by **argininosuccinate synthetase**, requires ATP and proceeds through a citrullyl-AMP intermediate. The argininosuccinate is then cleaved by **argininosuccinase** (step 3 in Fig. 18–10) to form free arginine and fumarate, the latter being converted to malate before entering mitochondria to join the pool of citric acid cycle intermediates. This is the **only reversible step** in the urea cycle. In the last reaction of the urea cycle, the cytosolic enzyme **arginase** cleaves arginine to yield **urea** and ornithine. Ornithine is transported into the mitochondrion to initiate another round of the urea cycle.

In the urea cycle, the mitochondrial and cytosolic enzymes seem to be clustered. The citrulline transported out of the mitochondrion is not diluted into the general pool of metabolites in the cytosol but is passed directly to the active site of argininosuccinate synthetase. This channeling between enzymes continues for argininosuccinate, arginine, and ornithine. Only urea is released into the general cytosolic pool of metabolites.

# urea cycle

