restriction are not effective in reducing homogentisic acid production. By contrast, nitisone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione), a drug used in tyrosinemia type I, reduces urinary excretion of homogentisic acid and, in conjunction with a low-protein diet, might prevent the long-term complications of alkaptonuria.

UREA CYCLE DEFECTS

Excess ammonia generated from protein nitrogen is removed by the urea cycle, a process mediated by several enzymes and transporters (Table 434e-1). Complete absence of any of these enzymes usually causes severe hyperammonemia in newborns, while milder variants can be seen in adults. The accumulation of ammonia and glutamine leads to brain edema and direct neuronal toxicity. Deficiencies in urea cycle enzymes are individually rare, but as a group, they affect about 1:25,000 individuals. They are all transmitted as autosomal recessive traits, with the exception of ornithine transcarbamylase deficiency, which is X-linked. Hepatocytes of females with ornithine transcarbamylase deficiency express either the normal or the mutant allele due to random X-inactivation and may be unable to remove excess ammonia if mutant cells are predominant.

Infants with classic urea cycle defects present at 1–4 days of life with refusal to eat and lethargy progressing to coma and death. Milder enzyme deficiencies present with protein avoidance, recurrent vomiting, migraine, mood swings, chronic fatigue, irritability, and disorientation that can progress to coma. Females with ornithine transcarbamylase deficiency can present at time of childbirth due to the combination of involuntary fasting and stress that favors catabolism. The diagnosis requires measurement of plasma ammonia, plasma amino acids, and urine orotic acid, useful for differentiating ornithine transcarbamylase deficiency from carbamyl phosphate synthase-1 and *N*-acetylglutamate synthase deficiency. Hyperammonemia can also be caused by liver disease from any cause and several organic acidemias and fatty acid oxidation defects (the latter two excluded by the analysis of urine organic acids and plasma acylcarnitine profile).

TREATMENT UREA CYCLE DEFECTS

Therapy is aimed at stopping catabolism and ammonia production by providing adequate calories (as IV glucose and lipids in the comatose patient) and, if needed, insulin. Excess nitrogen is removed by IV phenylacetate and benzoate (0.25 g/kg for the priming dose and subsequently as an infusion over 24 h) that conjugate with glutamine and glycine, respectively, to form phenylacetylglutamine and hippuric acid, water-soluble molecules efficiently excreted in urine. Arginine (200 mg/kg per day) becomes an essential amino acid (except in arginase deficiency) and should be provided intravenously to resume protein synthesis. If these measures fail to reduce ammonia, hemodialysis should be initiated promptly. Chronic therapy consists of a protein-restricted diet, phenylbutyrate, glycerol phenylbutyrate (a liquid drug better tolerated by most patients), arginine, or citrulline supplements, depending on the specific diagnosis. Liver transplantation should be considered in patients with severe urea cycle defects that are difficult to control medically.

Hyperammonemia due to a functional deficiency of glutamine synthase can occur in patients receiving chemotherapy for different malignancies or undergoing solid organ transplants. It can also be seen with hepatic cirrhosis. Several of these patients have been successfully rescued from hyperammonemia using the protocol described above for urea cycle defects.