

## SPECIAL INTEREST BOX 15.2 Hyperammonemia



**Hyperammonemia** is a condition in which the concentration of  $\text{NH}_4^+$  is excessive (i.e., greater than  $60 \mu\text{M}$ ) in blood. Elevated concentrations of ammonia are serious; the consequences of **ammonia intoxication** include lethargy, tremors, slurred speech, blurred vision, protein-induced vomiting (vomiting caused by the consumption of dietary protein), coma, and death.

Hyperammonemia may be caused by genetic defects or cirrhosis of the liver. In congenital (inherited) hyperammonemia, a relatively rare condition, one or more of the urea cycle enzymes is missing or defective. Complete absence of a urea cycle enzyme is fatal soon after birth. Brain damage can be minimized in infants who have partial deficiencies in urea synthesis if aggressive therapy is initiated immediately after birth. (Therapy consists of diets with severe restrictions on protein intake.) In cirrhosis, loss of liver function is devastating because of wide spread inflammation and necrosis (cell death). It is most commonly caused by prolonged, excessive consumption of ethanol. Less common causes of cirrhosis include prolonged exposure to toxic chemicals such as carbon tetrachloride, hepatitis (an inflammation

of the liver that is often caused by viral infections), and amebiasis (an infection with parasitic amebas).

Because most of the symptoms of ammonia intoxication are manifested in brain tissue, ammonia is considered a neurotoxic agent. Although significant research effort has been devoted to elucidating the effects of ammonia on brain cells, the mechanism of the damage is still unclear. Concentrations of ammonium ions as low as  $1\text{--}2 \mu\text{M}$  have been observed to disrupt both inhibitory and excitatory nerve transmission. Inhibitory neurotransmitters such as glycine become ineffective because  $\text{NH}_4^+$  inactivates  $\text{Cl}^-$  channels.  $\text{NH}_4^+$  prevents the binding of glutamate, an excitatory neurotransmitter, to its postsynaptic receptors. Glutamate metabolism can also be compromised by its reaction with  $\text{NH}_4^+$  catalyzed by glutamine synthase (see p. 459), which may cause nerve tissue to become depleted of glutamate. Depletion of  $\alpha$ -ketoglutarate, a citric acid cycle intermediate, has also been implicated. Other toxic effects of ammonia on the brain may include inhibition of amino acid transport and the  $\text{Na}^+\text{-K}^+$  ATPase.