

 Gout is a disorder in which sodium urate crystals are deposited in and around joints. (The name *gout* is derived from “gutta,” the Latin word for “drop.” According to ancient belief, a poisonous substance falls drop by drop into joints.) This deposition, which occurs because of **hyperuricemia** (high blood levels of uric acid, greater than 7 mg/dL in men and 6 mg/dL in women), causes a form of arthritis (joint inflammation). The initial attacks of gouty arthritis are usually acute (sudden) and most frequently affect the big toe, although other joints in the foot or leg may also be involved. The inflammation caused by urate crystal deposition attracts white blood cells, which engulf the crystals. Further tissue destruction is caused when urate crystals disrupt the lysosomal membranes in the white blood cells, resulting in the leakage of lysosomal enzymes into the tissues. In addition, visible structures called tophi (urate crystal “stones”) may form near joints and cause grotesque deformities. The deposition of urate crystals within the kidney causes impaired renal function. Although hyperuricemia is a necessary predisposing factor to gout, for unknown reasons only a small percentage of individuals with high blood urate levels ever display classic gout symptoms. Circumstances that may provoke gouty arthritis include excessive food and/or alcohol consumption or starvation.

There are two forms of gout: primary and secondary. *Primary gout* is most often caused by genetic defects in purine metabolism. For example, several variants of ribose-5-phosphate pyrophosphokinase are not effectively regulated by allosteric inhibitors (e.g., P_i , GDP, or ADP). Consequently, PRPP concentrations rise, causing the increased synthesis of purine nucleotides. (Recall that PRPP concentration is an important regulator of purine nucleotide synthesis.) The overproduction of purine nucleotides then leads to increased uric acid synthesis. HGPRT deficiency also causes hyperuricemia because of decreased salvage of purine bases. Hyperuricemia can also be caused by genetic defects in other pathways. For example, in glucose-6-phosphatase deficiency, hypoglycemia develops in affected individuals because they cannot produce blood glucose from glucose-6-phosphate. Consequently, high liver concentrations of glucose-6-phosphate stimulate the synthesis of ribose-5-phosphate and PRPP.

Secondary (or acquired) *gout* is caused by seemingly unrelated disorders. These conditions may cause hyperuricemia by either overproduction of uric acid or its undersecretion by the kidneys. For example, leukemia patients overproduce uric acid either because of massive cell destruction or the chemotherapy treatment required to destroy the cancerous cells. Hyperuricemia also results when certain drugs interfere with the renal secretion of uric acid into the urine. Patients with lead poisoning are also likely to develop gout because of renal damage.

Gout is treated with diet and with several drugs. Dietary control (i.e., reduced consumption of food that is rich in nucleic acids such as liver and sardines) depresses uric acid synthesis in some individuals who are susceptible to primary gout. Allopurinol and colchicine are often used in gout therapy. Because allopurinol

inhibits xanthine oxidase, it depresses uric acid synthesis. (Allopurinol is converted to alloxanthine by xanthine oxidase. Alloxanthine acts as a competitive inhibitor of the enzyme.) Hypoxanthine and xanthine, whose levels increase with allopurinol treatment, are easily excreted because of their solubility properties. In addition, the conversion of allopurinol to allopurinol ribonucleotide by HGPRT reduces PRPP levels. This circumstance depresses purine nucleotide synthesis. Colchicine, an alkaloid that is known to disrupt microtubules, reduces joint inflammation. It is currently believed that colchicine acts against inflammation by disrupting white blood cell activity.

Saturnine Gout

In years past, gout was associated with rich diets and especially with excessive consumption of alcoholic beverages. In recent years this association has been discounted because so many individuals lead overindulgent lives without developing gout. However, recent clinical research and some historical detective work indicate that the old connection between gout and alcoholic beverages may have been accurate.

Until well into the nineteenth century many bottles of wine and other alcoholic beverages were likely to be contaminated with lead. For example, the large-scale consumption of port wine by the English gentry during the eighteenth century is now believed to have been largely responsible for a gout epidemic that occurred among this population. (Port wines were imported from Portugal. To maximize their profits, Portuguese exporters added lead salts, which are very effective preservatives. In recent years, port wine bottles from this era were tested and found to contain large amounts of lead.) Similarly, in the past, rum was often stored in containers lined with lead-containing glazes.

The term *saturnine gout* reflects the connection made between gout and lead exposure by several nineteenth-century physicians. (The medieval alchemists believed that the planet Saturn had lead-like properties.) Proving the connection has been more difficult. Because bone is the major reservoir for lead (both calcium and lead are divalent), chronic lead exposure may often not be easily diagnosed. Lead can be transferred in small amounts from bone to tissues such as the kidney over long periods. Consequently, tissue damage may continue for years after the original lead exposure. Long before tissue damage becomes obvious, blood lead levels have returned to near normal values. Saturnine gout is now believed to be caused by hyperuricemia from kidney damage. Although the kidney damage is irreversible, further damage can be avoided by removing lead from the body with chelation therapy. A chelating agent such as ethylenediaminetetraacetic acid (EDTA) binds to lead with a higher affinity than it does to calcium. (Chelating agents are molecules with carboxylate groups that bind to metal cations. EDTA binds to metals with two or more positive charges.) Because lead-EDTA chelate is soluble, it is excreted in the urine.

SPECIAL INTEREST BOX 15.2 Hyperammonemia



Hyperammonemia is a condition in which the concentration of 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 NH_4^+ inactivates Cl^- channels. NH_4^+ prevents the binding of glutamate, an excitatory neurotransmitter, to its postsynaptic receptors. Glutamate metabolism can also be compromised by its reaction with NH_4^+ catalyzed by glutamine synthase (see p. 459), which may cause nerve tissue to become depleted of glutamate. Depletion of α -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.