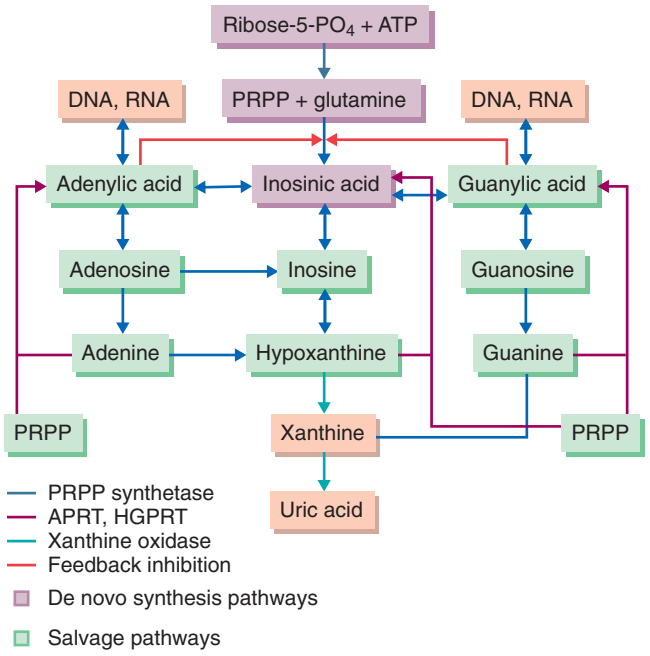

FIGURE 82-1 Biochemical pathways of purine synthesis, interconversion, and degradation. APRT, Adenine phosphoribosyl transferase; ATP, adenosine triphosphate; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; PRPP, 5′-phosphoribosyl 1-pyrophosphate.

acid overproduction result from increased reutilization of purine bases through salvage pathways (see Fig. 82-1). The de novo synthesis of purine is driven by the enzyme 5′-phosphoribosyl 1-pyrophosphate (PRPP) synthetase. In PRPP synthetase overactivity, overproduction of PRPP increases purine production. In salvage pathways, tissue-derived intermediate purine products (hypoxanthine, guanine, and adenine) are reutilized rather than undergoing further degradation to xanthine and uric acid. Deficiencies of hypoxanthine-guanine phosphoribosyltrasferase (HGPRT) activity result in impaired purine salvage and increased substrate for uric acid generation (Lysch-Nyhan syndrome and Kelley-Seegmiller syndrome).

Diseases associated with increased cell turnover (e.g., hemolysis, ineffective hematopoiesis, psoriasis) or with other causes of enhanced purine nucleotide breakdown (ethanol or fructose ingestion) can lead to hyperuricemia. Purine-rich foods comprise a significant portion of the daily purine load and can worsen hyperuricemia. On the other hand, consumption of low-fat dairy products is associated with reduced serum urate levels and may decrease the risk of gout.

A very small proportion of serum urate is bound to plasma proteins; therefore, urate is almost completely filtered in the glomeruli. Subsequent reabsorption and secretion occur through various organic acid transporters located on the luminal side of the proximal convoluted tubule epithelium. Only about 10% of the total filtered uric acid is excreted in the urine.

In addition to the bidirectional transport of uric acid, organic acid transporters are also responsible for eliminating other organic acids and certain medications. The function of these transporters is affected by certain medications, including thiazides, low-dose aspirin, and cyclosporine, leading to decreased uric acid excretion and hyperuricemia. Conversely, medications such as probenecid and losartan, when excreted in the tubular lumen, exert their uricosuric effect by displacing uric acid from the transporter and increasing uric acid excretion. Certain genetic mutations affecting these transporters may lead to uric acid underexcretion. Renal insufficiency can cause hyperuricemia though decreased uric acid filtration.

Pathophysiology of Acute Gouty Attack

In some patients with prolonged hyperuricemia, tissue deposits of MSU crystals, called *microtophi*, form in the synovium and on the surface of cartilage. During an acute attack, microtophi break apart, shedding a large number of MSU crystals into the joint space and activating synovial macrophages and fibroblasts that phagocytize the crystals. This, in turn, leads to the activation of a cytosolic multiprotein complex, the NALP3 (NACHT, LRR, and PYD domains–containing protein 3) inflammasome, which generates interleukin-1β. Interleukin-1β production activates bloodstream neutrophils and endothelial cells, allowing neutrophils to cross the capillary endothelium into the joint space. Inflammation is propagated by further activation of the newly recruited neutrophils, which leads to the clinical signs of inflammation characteristic of the acute gouty attack.

MSU crystals undergo clearance by inflammatory cells that then undergo apoptosis. This, along with other mechanisms, eventually leads to resolution of the acute inflammatory process, typically after 10 to 14 days. Even after complete resolution of symptoms, a low-grade level of inflammation (intercritical inflammation) can persist in the otherwise asymptomatic joint. This inflammation may become clinically apparent in long-standing gout, and it contributes to chronic synovitis, cartilage loss, and bony erosions.

CLINICAL FEATURES

Gout has three stages: asymptomatic hyperuricemia, acute intermittent gout, and chronic gout.

Acute Gouty Attacks

The classic picture of acute gout is rapid development of an inflammatory arthritis involving one (or occasionally two) joints. Severe pain, erythema, swelling and exquisite tenderness typically occur. The most commonly involved joints are the first metatarsophalangeal joint (podagra), followed by the joints of the ankle, midfoot, and knee. The pain intensifies over 8 to 24 hours. Acute attacks usually resolve, even without therapy, within 5 to 14 days. The clinical resolution is complete, and the patient is asymptomatic between attacks. This clinical picture can be easily confused with that of septic arthritis or cellulitis, because many patients can mount an intense systemic inflammatory response with fever, chills, and elevated inflammatory markers.

Attack-provoking factors include use of diuretics, alcohol, surgery, trauma, and consumption of foods containing high purine levels. Each of these can cause fluctuation in serum urate levels. Initiation of urate-lowering therapy can trigger attacks in the early phase by the same mechanism.

Subsequently, involvement of the upper extremities can occur, affecting the small joints of the hands, wrists, and elbows.

Chronic Gout

Transition to the chronic phase can occur if hyperuricemia is inadequately treated. This phase, called *chronic gout* (also referred