Pathogenesis. **Hyperuricemia (plasma urate level above 6.8 mg/dL) is necessary, but not sufficient, for the development of gout.** Elevated uric acid can result from overproduction or reduced excretion or both (Table 26-7). Uric acid metabolism can be summarized as follows:

- Synthesis: Uric acid is the end product of purine catabolism. Increased urate synthesis typically reflects some abnormality in purine production. The synthesis of purine nucleotides, in turn, involves two interlinked pathways. In the de novo pathway, purine nucleotides are synthesized from nonpurine precursors, and in salvage pathways they are synthesized from free purine bases from dietary intake and catabolism of purine nucleotides.
- Excretion: Uric acid is filtered from the circulation by the glomerulus and virtually completely resorbed by the proximal tubule of the kidney. A small fraction of the resorbed uric acid is secreted by the distal nephron and excreted in the urine.

Hyperuricemia can result from either overproduction or reduced excretion. The vast majority of *primary gout* is caused by increased uric acid biosynthesis for unknown reasons. A small minority of patients have overproduction because of identifiable enzymatic defects. For example, partial deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) interrupts the salvage pathway, so purine metabolites cannot be savaged and are, instead, degraded into uric acid. Complete absence of HGPRT also results in hyperuricemia, but the significant neurologic manifestations of this condition (*Lesch-Nyhan syndrome*) dominate the clinical picture so it is classified as *secondary gout*. Secondary gout can also be caused by increased production (e.g., rapid cell lysis during chemotherapy for leukemia) or decreased excretion (chronic renal disease).

The inflammation in gout is triggered by precipitation of monosodium urate (MSU) crystals into the joints, which result in the production of cytokines that recruit leukocytes (Fig. 26-46). Macrophages phagocytose the MSU and the intracellular sensor, the inflammasome (Chapter 3), recognizes the crystals. The inflammasome activates caspase-1, which is involved in the production of some biologically active cytokines, most notably IL-1. IL-1 is proinflammatory, and promotes accumulation of neutrophils and macrophages in the joint. These cells, in turn, release other cytokines, free radicals, proteases and arachidonic acid metabolites, all of which recruit more leukocytes and damage the joint. Urate crystals may also activate the complement system, leading to the generation of chemotactic complement byproducts. These cascades trigger an acute arthritis, which typically remits spontaneously in days to weeks.

The solubility of MSU in a joint is modulated by temperature and the chemical composition of the fluid. Synovial fluid is inherently a poorer solvent for monosodium urate than plasma. The lower temperature of the peripheral joints also favors precipitation. Crystallization is dependent on the presence of nucleating agents such as insoluble collagen fibers, chondroitin sulfate, proteoglycans and cartilage fragments.

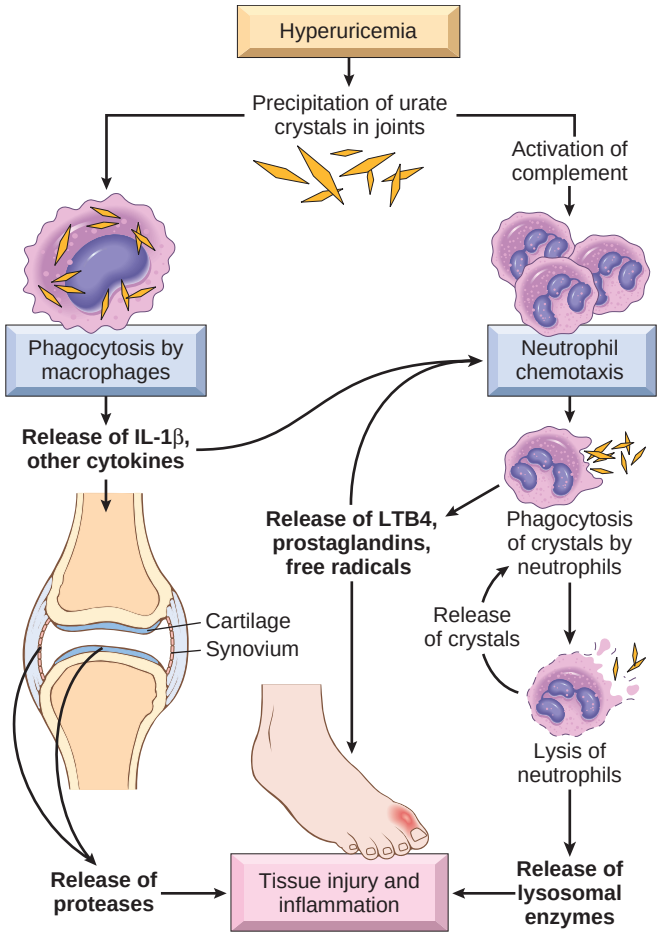

Figure 26-46 Pathogenesis of acute gouty arthritis. LTB4, Leukotriene B4; IL-1β, interleukin 1β.

Hyperuricemia does not necessarily lead to gouty arthritis. Many factors contribute to the conversion of asymptomatic hyperuricemia into primary gout, including the following:

- Age of the individual and duration of the hyperuricemia. Gout usually appears after 20 to 30 years of hyperuricemia.
- Genetic predisposition. In addition to the well-defined X-linked abnormalities of HGPRT, primary gout follows multifactorial inheritance and runs in families. Polymorphisms in genes involved in urate transport and homeostasis (URAT1 and GLUT9) are also associated with gout.
- Heavy alcohol consumption
- Obesity
- Drugs (e.g., thiazides) that reduce excretion of urate
- Lead toxicity (so-called saturnine gout)

Repeated attacks of acute arthritis lead eventually to chronic tophaceous arthritis and the formation of tophi in the inflamed synovial membranes and periarticular tissue. Severe damage to the cartilage develops and the function of the joints is compromised.