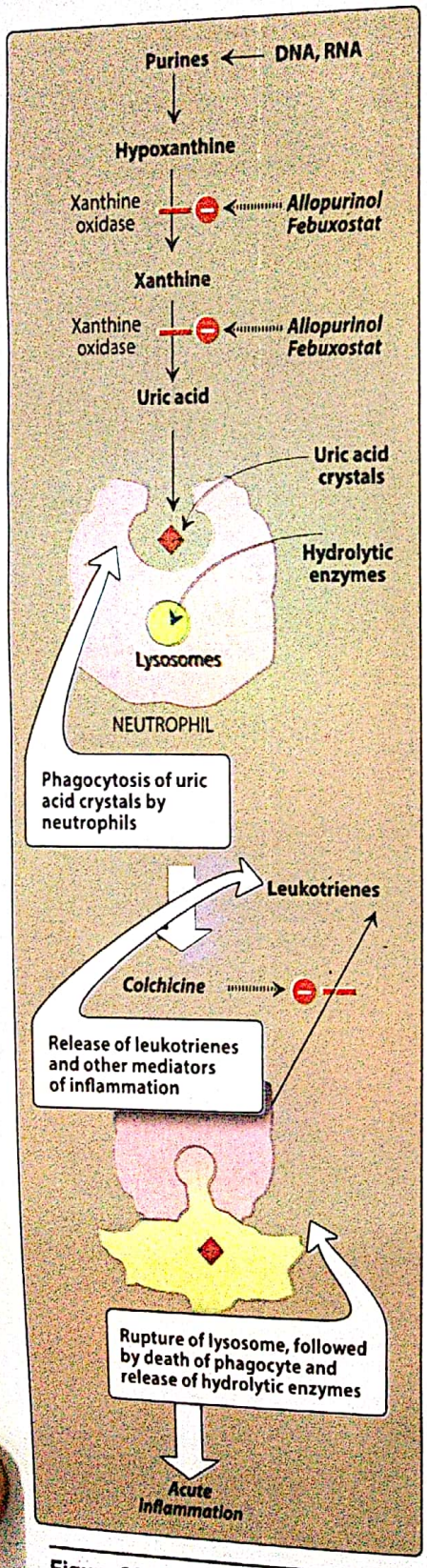

Figure 36.19
Role of uric acid in the inflammation of gout.

or intolerance to *methotrexate.* Metabolism of *tofacitinib* is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is taken with potent inhibitors or inducers of this isoenzyme. Hemoglobin concentrations must be greater than 9 g/dL to start *tofacitinib* and must be monitored during therapy due to the risk for anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. *Tofacitinib* treatment may also increase the risk for secondary malignancy, opportunistic infections, renal, or hepatic dysfunction.

J. Anakinra

IL-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption. *Anakinra* [an-a-KIN-ra] is an IL-1 receptor antagonist. *Anakinra* treatment leads to a modest reduction in the signs and symptoms of moderate to severe RA in patients who have failed one or more DMARDs. This agent is associated with neutropenia and is infrequently used in the treatment of RA.

VII. DRUGS USED FOR THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 36.19). The cause of hyperuricemia is an imbalance between overproduction of uric acid and/or the inability of the patient to excrete it via renal elimination. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

A. Treatment of acute gout

Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, or *colchicine* are effective alternatives for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, with systemic corticosteroid therapy for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

B. Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the

use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol, febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.]

C. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.

1. **Mechanism of action:** *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles.

2. **Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: *Colchicine* must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks for safety reasons. *Colchicine* is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.

3. **Pharmacokinetics:** *Colchicine* is administered orally and is rapidly absorbed from the GI tract. *Colchicine* is recycled in the bile and is excreted unchanged in feces or urine.

4. **Adverse effects:** *Colchicine* may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 36.20). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. Dosage adjustments are required in patients taking CYP3A4 inhibitors, like *clarithromycin, itraconazole*, and protease inhibitors. For patients with severe renal impairment, the dose should be reduced.

Figure 36.20
Some adverse effects of colchicine. GI = gastrointestinal.

D. Allopurinol

Allopurinol [al-oh-PURE-i-nole], a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (Figure 36.19).

1. **Therapeutic uses:** *Allopurinol* is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

2. **Pharmacokinetics:** *Allopurinol* is completely absorbed after oral administration. The primary metabolite is alloxanthine (oxypurinol), which is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosage. The drug and its active metabolite are excreted in the feces and urine. The dosage should be reduced if the creatinine clearance is less than 50 mL/min.

3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, *colchicine*, NSAIDs, or corticosteroids can be administered concurrently. *Allopurinol* interferes with the metabolism of *6-mercaptopurine*, the immunosuppressant *azathioprine*, and *theophylline*, requiring a reduction in dosage of these drugs.

E. Febuxostat

Febuxostat [feb-UX-oh-stat], a xanthine oxidase inhibitor, is structurally unrelated to *allopurinol*; however, it has the same indications. In addition, the same drug interactions with *6-mercaptopurine*, *azathioprine*, and *theophylline* apply. Its adverse effect profile is similar to that of *allopurinol*, although the risk for rash and hypersensitivity reactions may be reduced. *Febuxostat* does not have the same degree of renal elimination as *allopurinol* and thus requires less adjustment in those with reduced renal function.

F. Probenecid

Probenecid [proe-BEN-a-sid] is a uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. *Probenecid* blocks the tubular secretion of *penicillin* and is sometimes used to increase levels of β-lactam antibiotics. It also inhibits the excretion of *methotrexate*, *naproxen*, *ketoprofen*, and *indomethacin*. *Probenecid* should be avoided if the creatinine clearance is less than 50 mL/min.

G. Pegloticase

Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. *Pegloticase* is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks.

VIII. DRUGS USED TO TREAT HEADACHE

The most common types of headaches are migraine, tension-type, and cluster headaches. Migraine can usually be distinguished from cluster headaches and tension-type headaches by its characteristics as shown