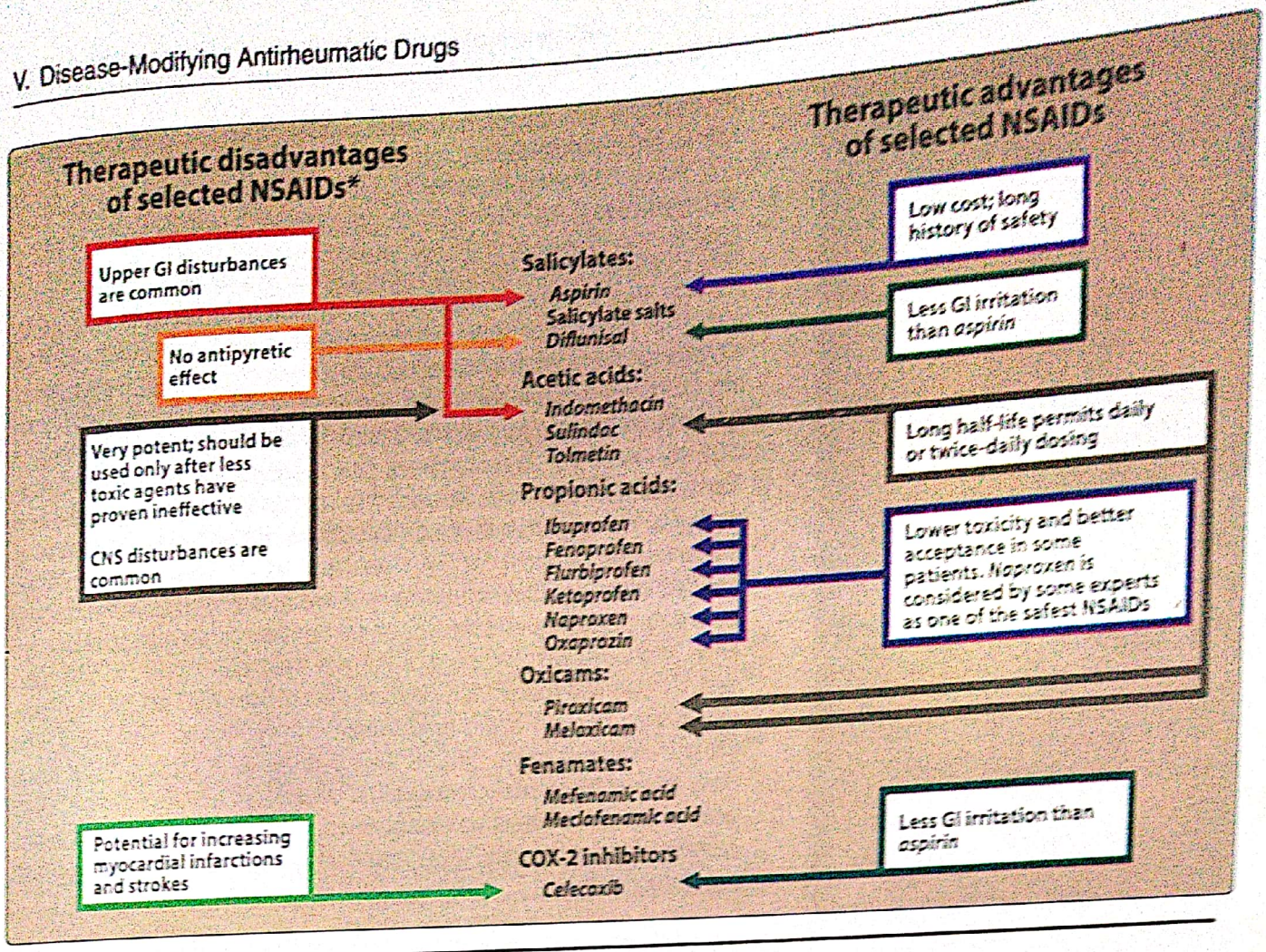

Figure 36.15
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke.

in cases of overdose (see Chapter 48).] *Acetaminophen* should be avoided in patients with severe hepatic impairment.

V. DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. When a patient is diagnosed with RA, DMARDs should be started within 3 months to help stop the progression of the disease at the earlier stages. NSAIDs or corticosteroids may also be used for relief of symptoms if needed.

A. Choice of drug

No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary. Monotherapy may be initiated with any of the DMARDs (*methotrexate*, *leflunomide*, *hydroxychloroquine*, or *sulfasalazine*) for patients with low disease activity. For patients with moderate to high disease activity or inadequate response to monotherapy, combination DMARD therapy (usually *methotrexate* based) or use of anti-TNF drugs (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*) may be needed. For patients with more established disease, use of other biologic therapies

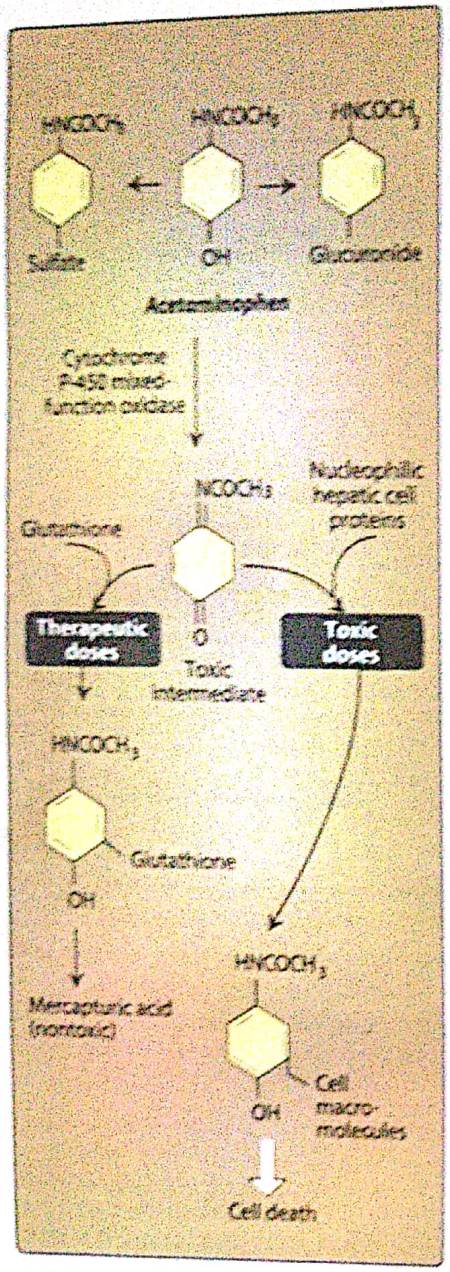

Figure 36.16
Metabolism of *acetaminophen*.

(for example, *abatacept*, *rituximab*) can be considered. Most of these agents are contraindicated for use in pregnant women.

B. Methotrexate

Methotrexate [meth-oh-TREX-ate], used alone or in combination therapy, has become a mainstay of treatment in patients with rheumatoid or psoriatic arthritis. *Methotrexate* is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. Response to *methotrexate* occurs within 3 to 6 weeks of starting treatment; it can also slow the appearance of new erosions within involved joints. The other DMARDs can be added to *methotrexate* therapy if there is partial or no response to maximum doses of *methotrexate*. Doses of *methotrexate* required for RA treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects. The most common side effects observed after *methotrexate* treatment of RA are mucosal ulceration and nausea. Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [*Note:* Taking *leucovorin* (*folinic acid*) once daily after *methotrexate* reduces the severity of adverse effects. *Folic acid* taken on off-days is widely used.] Periodic liver enzyme tests, complete blood counts, and monitoring for signs of infection are recommended.

C. Hydroxychloroquine

Hydroxychloroquine [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA, often combined with *methotrexate*. This agent is also used in the treatment of lupus and malaria. Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. *Hydroxychloroquine* has less effects on the liver and immune system than other DMARDs; however, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits. It may also cause CNS disturbances, GI upset, and skin discoloration and eruptions.

D. Leflunomide

Leflunomide [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). Activated proliferating lymphocytes require constant DNA synthesis to proliferate. Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis. After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH (Figure 36.17). *Leflunomide* is approved for the treatment of RA. It can be used as monotherapy or in combination with *methotrexate*. The most common adverse effects are headache, diarrhea, and nausea. Other untoward effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia. It is *not* recommended in patients with liver disease, because of a risk of hepatotoxicity. Monitoring parameters include signs of infection, complete blood counts, and liver enzymes.

E. Minocycline

Minocycline [mi-noe-SYE-kleen], a tetracycline antibiotic, is considered to be a DMARD. Although *minocycline* has been shown to be effective in the treatment of early RA, it is generally not utilized as first-line therapy. *Minocycline* can be used as monotherapy or in combination with other DMARDs.

F. Sulfasalazine

Sulfasalazine [sul-fa-SAH-la-zeen] is also used for early, mild RA in combination with *methotrexate* and/or *hydroxychloroquine*. Onset of activity is 1 to 3 months, and it is associated with leukopenia. Its mechanism of action in treating RA is unclear.

G. Glucocorticoids

Glucocorticoids (see Chapter 27) are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until DMARDs are effective. Timely dose reductions and cessation are necessary to avoid adverse effects associated with long-term use.

VI. BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF-α inhibitors (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy. As with DMARDs, the decision to continue or stop a biological agent can often be made within 3 months after initiation of therapy. If a patient has failed therapy with one TNF-α inhibitor, a trial with a different TNF-α inhibitor or a non-TNF biologic therapy (*abatacept*, *rituximab*, *tocilizumab*, *tofacitinib*) is appropriate. TNF-α inhibitors can be administered with any of the other drugs for RA, except for the non-TNF biologic therapies (due to increased risk of infection).

Patients receiving TNF-α inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia. Live vaccinations should not be administered while on TNF-α inhibitor therapy. These agents should be used very cautiously in those with heart failure, as they can cause and/or worsen preexisting heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors. Characteristics of the TNF-α inhibitors and other biologic therapies are outlined below.

A. Adalimumab

Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF-α, thereby interfering with endogenous TNF-α

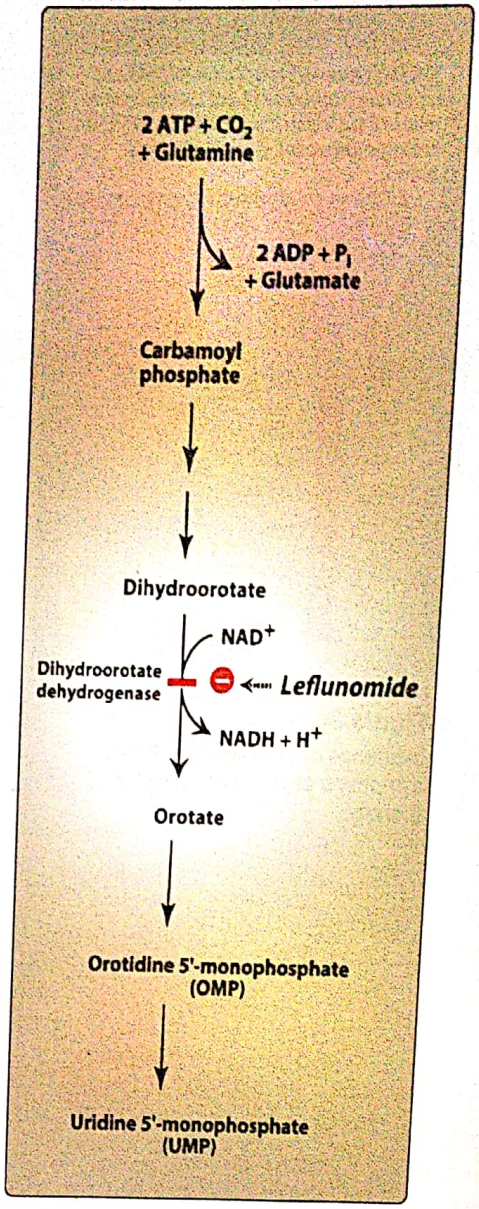

Figure 36.17
Site of action of *leflunomide*.

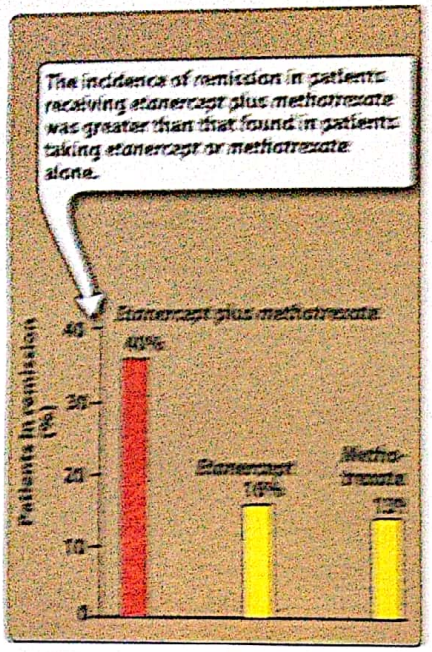

Figure 36.13
Incidence of remission from the symptoms of RA after 1 year of therapy.

activity by blocking its interaction with cell surface receptors. This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with *methotrexate*. It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease. *Adalimumab* is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infections such as urinary tract infections, upper respiratory tract infections, and sinusitis.

E. Certolizumab pegol

Certolizumab [ser-tol-LIZ-ue-mab] is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions. It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. It has similar indications to *adalimumab*. Adverse effects are similar to other TNF-α inhibitors.

C. Etanercept

Etanercept [et-TAN-er-cept] is a genetically engineered, soluble, recombinant, fully human receptor fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with *methotrexate*. It is also approved for use in ankylosing spondylitis and psoriasis. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in reducing the RA disease process, improving function, and achieving remission (Figure 36.13). *Etanercept* is given subcutaneously twice a week. The drug is generally well tolerated. As with all TNF-α inhibitors, it can increase the risk for infections, malignancy, and new or worsening heart failure.

D. Golimumab

Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. This compound is administered subcutaneously once a month in combination with *methotrexate* or other nonbiologic DMARDs. *Golimumab* may increase hepatic enzymes. Reactivation of hepatitis B may occur in chronic carriers. As with other TNF-α inhibitors, this drug may increase the risk of malignancies and serious infections.

E. Infliximab

Infliximab [in-FLIK-si-mab] is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α and inhibits binding with its receptors. *Infliximab* is approved for use in combination with *methotrexate* in patients with RA who have had inadequate response to *methotrexate* monotherapy. This agent is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies, resulting in reduced efficacy. Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease. *Infliximab* is administered as an IV infusion every 8 weeks. Infusion