acid, *meclofenamate* [me-kloe-fen-AM-ate]), and the selective COX-2 inhibitor (*celecoxib* [sel-e-KOX-ib]). They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. [Note: Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, while inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.]

A. Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It has gained much more usage at lower doses for the prevention of cardiovascular events such as stroke and myocardial infarction (MI). *Aspirin* is often differentiated from other NSAIDs, since it is an irreversible inhibitor of cyclooxygenase activity.

1. **Mechanism of action:** *Aspirin* is a weak organic acid that irreversibly acetylates (and, thus, inactivates) cyclooxygenase (Figure 36.7). The other NSAIDs are all reversible inhibitors of cyclooxygenase. The NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect; Figure 36.8). However, as outlined below, not all NSAIDs are equally effective in each of these actions.

   a. **Anti-inflammatory actions:** Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation in which prostaglandins act as mediators. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.

   b. **Analgesic action:** PGE_2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs. No single NSAID has demonstrated superior efficacy over another, and all agents are generally considered to have equivalent efficacy. The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. One exception is *ketorolac*, which can be used for more severe pain but for only a short duration.

   c. **Antipyretic action:** Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The NSAIDs lower body temperature in patients with fever by impeding PGE_2 synthesis and release. These agents essentially reset the "thermostat"

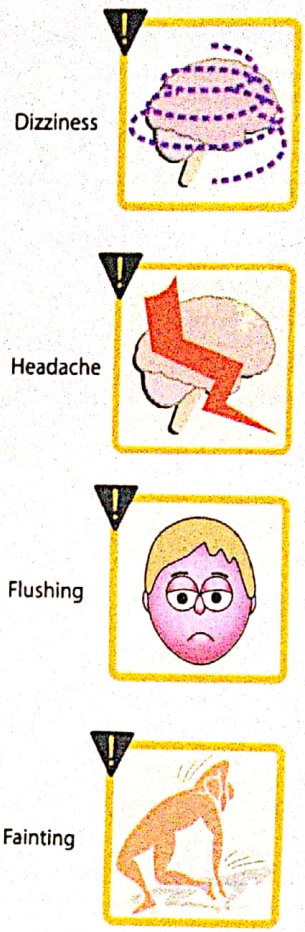


Figure 36.6
Some adverse reactions to *iloprost*.

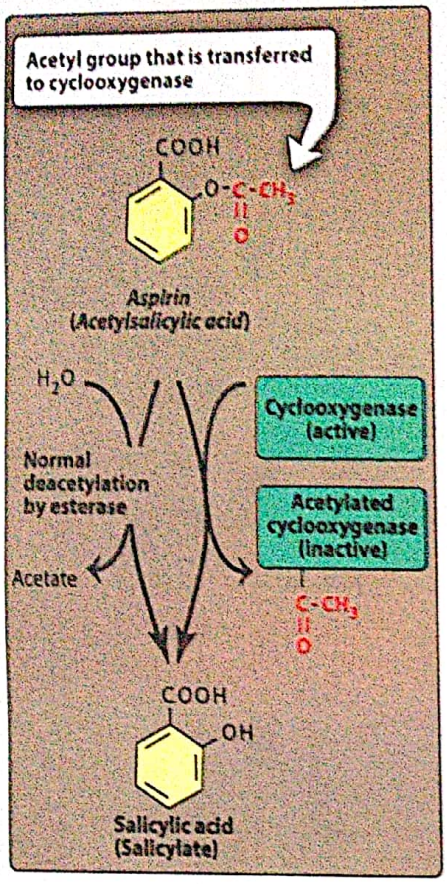
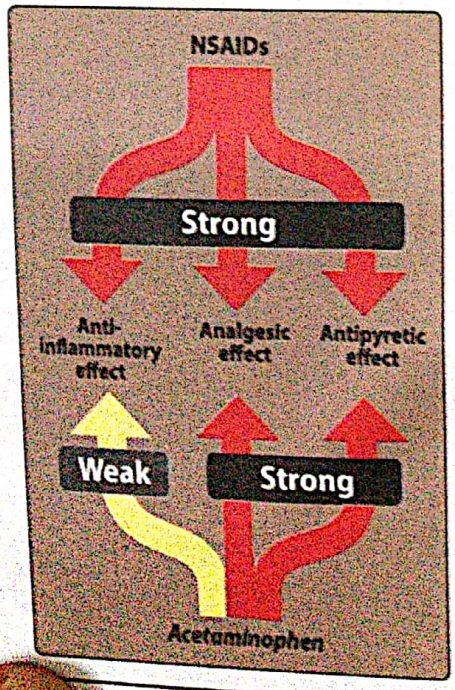


Figure 36.7
Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.



ure 36.8
ions of nonsteroidal anti-lammatory drugs (NSAIDs) and cetaminophen.

toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. NSAIDs have no effect on normal body temperature.

2. Therapeutic uses:

a. Anti-inflammatory and analgesic uses: NSAIDs are used in the treatment of osteoarthritis, gout, and RA. These agents are also used to treat common conditions (for example, headache, arthralgia, myalgia, and dysmenorrhea) requiring analgesia. Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized. The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 36.9). For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

b. Antipyretic uses: *Aspirin*, *ibuprofen*, and *naproxen* may be used to treat fever. [Note: *Aspirin* should be avoided in patients less than 20 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome (a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death).]

c. Cardiovascular applications: *Aspirin* is used to inhibit platelet aggregation. Low-dose *aspirin* inhibits COX-1–mediated production of TXA_2, thereby reducing TXA_2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events. Low doses (doses less than 325 mg; many classify it as doses of 75 to 162 mg—commonly 81 mg) of *aspirin* are used prophylactically to 1) reduce the risk of recurrent cardiovascular events and/or death in patients with previous MI or unstable angina pectoris, 2) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had a prior TIA or stroke, and 3) reduce the risk of cardiovascular events or death in high-risk patients such as those with chronic stable angina or diabetes. As *aspirin* irreversibly inhibits COX-1 (Figure 36.10) the antiplatelet effects persist for the life of the platelet. Chronic use of low doses allows for continued inhibition as new platelets are generated. *Aspirin* is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.

d. External applications: *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs.

3. Pharmacokinetics:

a. Aspirin: After oral administration, *aspirin* is rapidly deacetylated by esterases in the body, thereby producing salicylate. Unionized salicylates are passively absorbed mostly from the upper small

intestine (dissolution of the tablets is favored at the higher pH of the gut). Salicylates (except for *diflunisal*) cross both the blood–brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more (Figure 36.11). Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion. At low doses of *aspirin* (less than 2 g/day), uric acid secretion is decreased, whereas at high doses, uric acid secretion may be unchanged or increased. Therefore, *aspirin* is avoided in gout or in patients taking *probenecid*.

b. **Other NSAIDs:** Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example, *nabumetone* and *sulindac*) have active metabolites. Elimination of active drug and metabolites is primarily via the urine.

4. **Adverse events:** Because of the associated adverse events below, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. **Gastrointestinal:** The most common adverse effects of NSAIDs are GI related, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI_2) inhibits gastric acid secretion, and PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients with a high risk for GI events, proton pump inhibitors or *misoprostol* should be used concomitantly to prevent NSAID-induced ulcers (see Chapter 31).

b. **Increased risk of bleeding (antiplatelet effect):** TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. *Aspirin* irreversibly inhibits COX-1–mediated TXA_2 formation, while other NSAIDs reversibly inhibit the production of TXA_2. Because platelets lack nuclei, they cannot synthesize new enzyme when inhibited by *aspirin*, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days). Because of the decrease in TXA_2 production, platelet aggregation (the first step in thrombus formation) is reduced, producing an antiplatelet effect with a prolonged bleeding time. For this reason, *aspirin* is often held, or not given, at least 1 week prior to surgery. NSAIDs other than *aspirin* are not utilized for their antiplatelet effect but can still prolong bleeding time. [Note: As agents become more COX-2 selective, they are

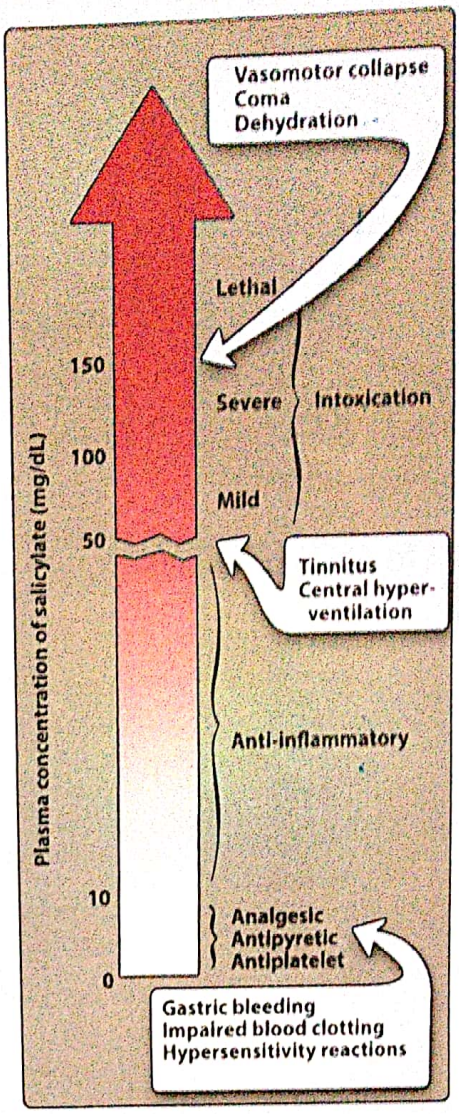


Figure 36.9
Dose-dependent effects of salicylate.

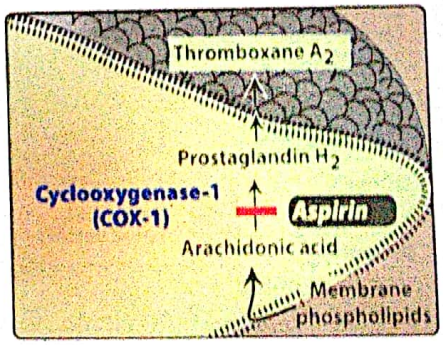


Figure 36.10
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

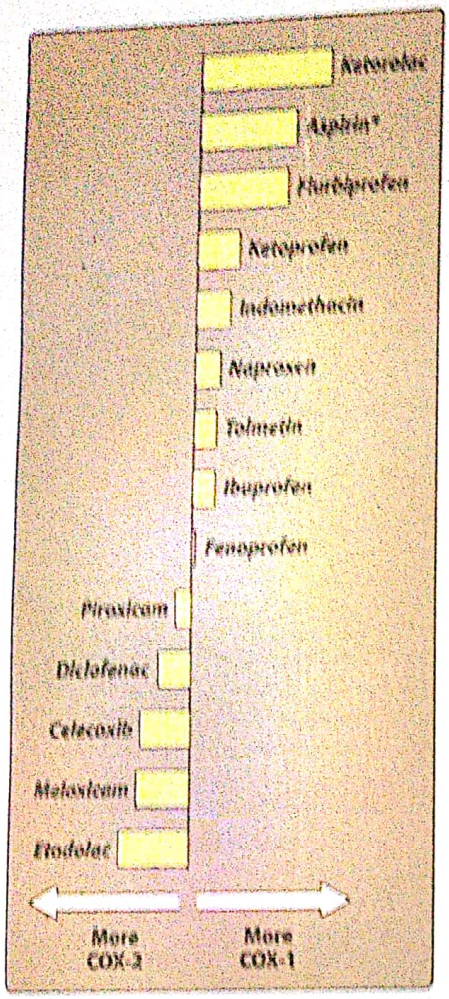


Figure 36.14
Relative selectivity of some commonly used NSAIDs. Data shown as the logarithm of their ratio of IC_{80} (drug concentration to achieve 80% inhibition of cyclooxygenase). **Aspirin* graphed for IC_{80} value due to it showing significantly more COX-1 selectivity at lower doses and graph using higher concentrations does not accurately reflect the usage or selectivity of *aspirin*.

drug has a similar risk for cardiovascular events. Celecoxib should be used with caution in patients who are allergic to sulfonamides. Patients who have had anaphylactoid reactions to *aspirin* or non-selective NSAIDs may be at risk for similar effects with celecoxib. Inhibitors of CYP2C9, such as *fluconazole* and *fluvastatin*, may increase serum levels of *celecoxib*.

Figure 36.15 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

IV. ACETAMINOPHEN

Acetaminophen [a-SEET-a-MIN-oh-fen] (*N*-acetyl-*p*-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. *Acetaminophen* has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. *Acetaminophen* does not affect platelet function or increase bleeding time. It is not considered to be an NSAID.

A. Therapeutic uses

Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti-inflammatory action of NSAIDs. *Acetaminophen* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with *aspirin*).

B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal circumstances, *acetaminophen* is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *acetaminophen* is hydroxylated to form *N*-acetyl-*p*-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of *acetaminophen*, NAPQI reacts with the sulfhydryl group of glutathione, which is produced by the liver, forming a non-toxic substance (Figure 36.16). *Acetaminophen* and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

C. Adverse effects

At normal therapeutic doses, *acetaminophen* is virtually free of significant adverse effects. With large doses of *acetaminophen*, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (Figure 36.16). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of *acetaminophen*-induced hepatotoxicity. [Note: *N-acetylcysteine*, which contains sulfhydryl groups to which the toxic metabolite can bind, is an antidote