Anthelmintic Drugs 36

I. OVERVIEW

Three major groups of helminths (or worms), the nematodes, trematodes and cestodes, infect humans. As in all antibiotic regimens, the anthelminthic drugs (Figure 36.1) are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host. Figure 36.2 illustrates the high incidence of helminthic infections.

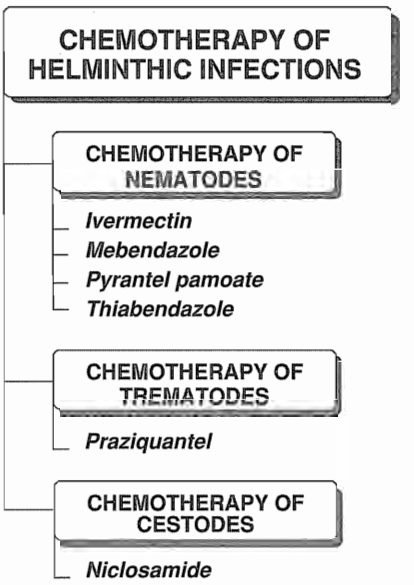


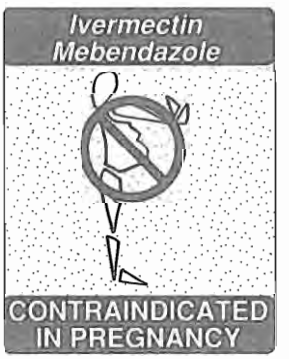
Figure 36.1
Summary of anthelminthic agents.

II. DRUGS FOR THE TREATMENT OF NEMATODES

Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus (Figure 36.3). They cause infections of the intestine as well as the blood and tissues. Figure 36.4 summarizes the infections caused by nematodes, and the common therapies used for these infections.

A. Mebendazole

Mebendazole [me BEN da zole] a synthetic benzimidazole compound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworm (Necator americanus and Ancylostoma duodenale), and roundworm (Ascariasis lumbricoides, Figure 36.5). *Mebendazole* acts by binding to and interfering with the synthesis of the parasite's microtubules and also by decreasing glucose uptake. Affected parasites are expelled with the feces. *Mebendazole* is nearly insoluble in aqueous solution, and little of an oral dose (which is chewed) is absorbed by the body unless taken with a high fat meal. Therefore, this drug is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. However, it is contraindicated in pregnant women, because it has been shown to be embryotoxic and teratogenic in experimental animals.



B. Pyrantel pamoate

Pyrantel pamoate [pi RAN tel] along with *mebendazole* is effective in the treatment of infections caused by roundworms, pinworms (see Figure 36.4), and hookworms. *Pyrantel pamoate* is poorly absorbed orally and exerts its effects in the intestinal tract. It acts as a depolarizing neuromuscular blocking agent, causing persistent activation

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

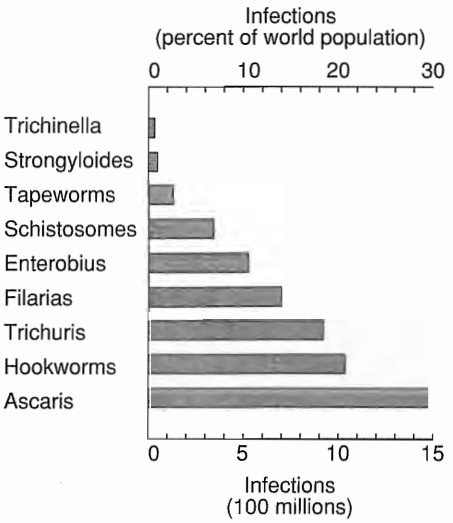


Figure 36.2
Relative incidence of helminth infections worldwide.

of the parasite's nicotinic receptors. The paralyzed worm is then expelled from the host's intestinal tract. Adverse effects are mild, and include nausea, vomiting, and diarrhea.

C. Thiabendazole

Thiabendazole [thye a BEN da zole], another synthetic benzimidazole, is effective against strongyloidiasis due to Strongyloides stercoralis (threadworm), cutaneous larva migrans (or creeping eruption) and early stages of trichinosis (caused by Trichinella spiralis). It, too, affects microtubular aggregation. Though nearly insoluble in water, the drug is readily absorbed on oral administration. The drug is hydroxylated in the liver and excreted in the urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology. Among the cases of erythema multiforme and Stevens-Johnson syndrome reportedly caused by *thiabendazole*, there have been a number of fatalities.

D. Ivermectin

Ivermectin [eye ver MEK tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and has been shown to be effective against scabies. *Ivermectin* targets the parasite's γ-aminobutyric acid (GABA) receptors. Chloride efflux is enhanced and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and has no pharmacologic effects. However, it is contraindicated in patients with meningitis, since their blood-brain barrier is more permeable, and CNS effects might be expected. *Ivermectin* is also contraindicated in pregnancy. It should be avoided in patients who are taking benzodiazepines or barbiturates—drugs that act at the GABA receptor. The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, hypotension, etc.).

Figure 36.3
Pinworms leaving the anus of a five-year-old child who presented with crying, restlessness and abdominal pain.

III. DRUGS FOR THE TREATMENT OF TREMATODES

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes.

A. Praziquantel

Trematode infections are generally treated with *praziquantel* [pray zi KWON tel]. This drug is an agent of choice for the treatment of all forms of schistosomiasis and for cestode infections like cysticercosis. Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite. *Praziquantel* is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in the bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through the urine and bile.

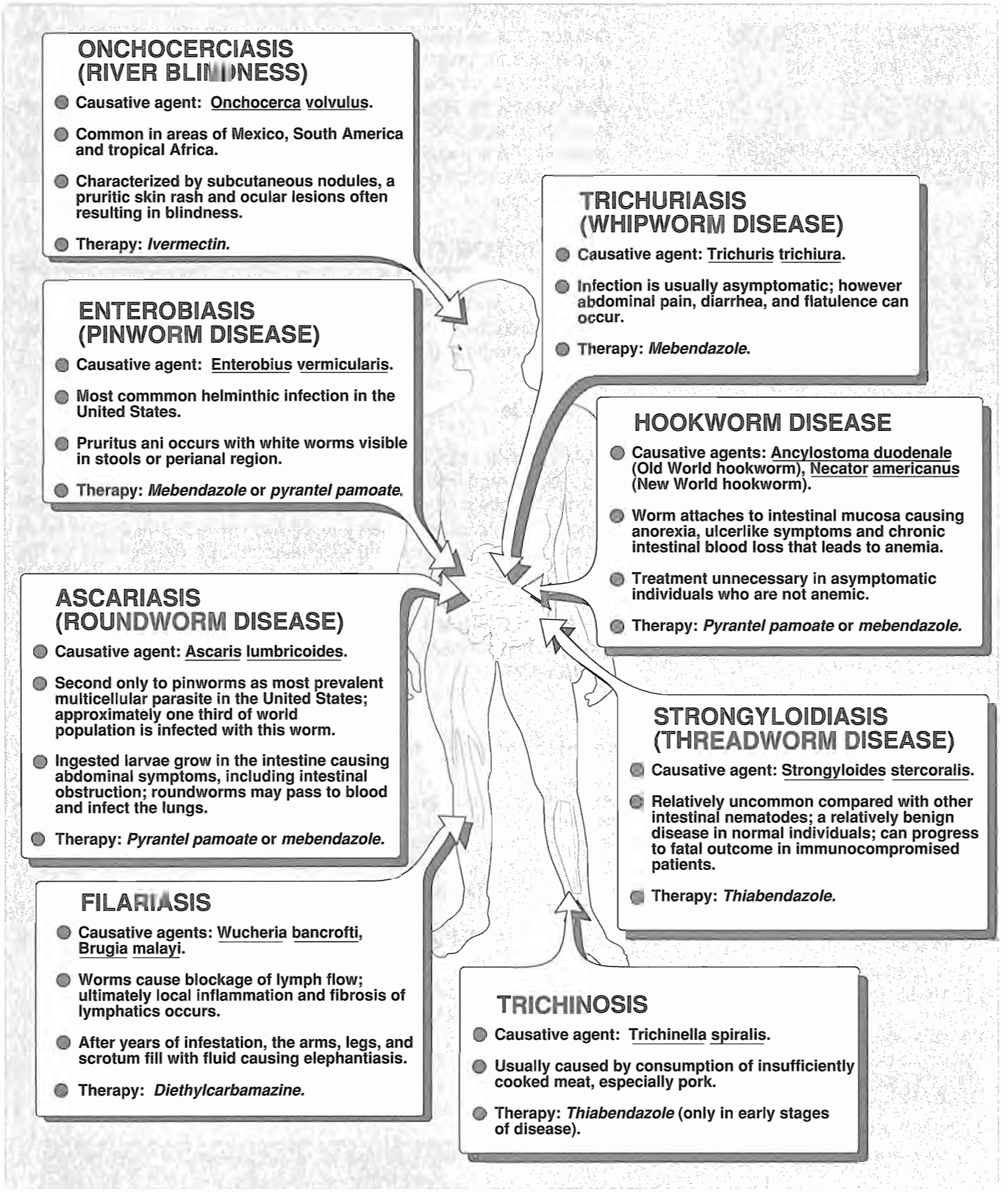


Figure 36.4
Characteristics and therapy for commonly encountered nematode infections.

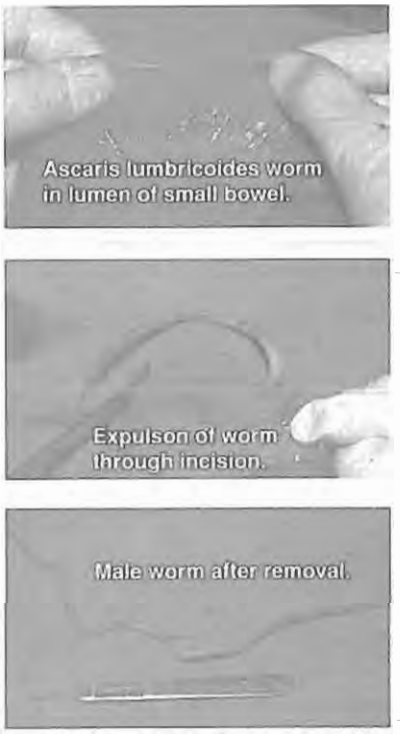


Figure 36.5
Ascaris lumbricoides worm in lumen of small bowel of 52-year-old woman from Africa.

Common adverse effects include drowsiness, dizziness, malaise, and anorexia, as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers. Drug interactions due to increased metabolism have been reported with *dexamethasone*, *phenytoin,* and *carbamazepine*. *Cimetidine*, known to inhibit cytochrome P-450 isozymes, causes increased *praziquantel* levels. *Praziquantel* is contraindicated for the treatment of ocular cysticercosis since destruction of the organism in the eye may damage the organ.

IV. DRUGS FOR THE TREATMENT OF CESTODES

The cestodes, or "true tapeworms," typically have a flat, segmented body and attach to the host's intestine. Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

A. Niclosamide

Niclosamide [ni KLOE sa mide] is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the parasite's mitochondrial anaerobic phosphorylation of ADP which produces usable energy in the form of ATP. The drug is lethal for the cestode's scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of *niclosamide*. This is done to purge the bowel of all dead segments in order to preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of *niclosamide*.

Study Questions

Questions 35.1 - 35.4: For each numbered phrase, select the ONE drug (A-E) that is most closely associated with it. Each drug (A-E) may be selected once, more than once, or not at all.

A. Mebendazole
B. Praziquantel
C. Niclosamide
D. Pyrantel pamoate
E. Thiabendazole

35.1 A drug which affects microtubular function in roundworm, pinworm, and hookworm.

Correct answer = A (mebendazole)

35.2 Acts as a depolarizing neuromuscular blocking agent.

Correct answer = D (pyrantel pamoate)

35.3 A drug of choice for the treatment of all forms of schistosomiasis.

Correct answer = B (praziquantel)

35.4 Drug of choice for the treatment of most tapeworm infections.

Correct answer = C (niclosamide)

Choose the ONE best answer.

35.5 All of the following statements about mebendazole are correct EXCEPT:

A. It is contraindicated in pregnant women.
B. It is the drug of choice in the treatment of whipworm infections.
C. It is effective by oral administration.
D. It is active against cestodes.
E. It interferes with glucose uptake by the parasite.

Correct answer = D. Mebendazole is effective against nematodes, in part by decreasing glucose uptake, and thus causing the parasite to starve. Mebendazole has been shown to be embryotoxic and teratogenic in experimental animals

Antiviral Drugs

37

I. OVERVIEW

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane and do not carry out metabolic processes. Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host. For example, viruses are not affected by antimicrobial agents. Nevertheless, some drugs sufficiently discriminate between cellular and viral reactions to be effective and yet relatively nontoxic. Unfortunately, only a few virus groups, including those that cause the viral infections discussed in this chapter, respond to these drugs (Figure 37.1).

II. TREATMENT OF VIRAL RESPIRATORY INFECTIONS

Viral respiratory tract infections for which treatments exist include those of influenza types A and B, and respiratory syncytial virus (RSV). [Note: Immunization against influenza A is the preferred approach. However, antiviral agents are employed when patients are allergic to the vaccine or when the outbreak is due to an immunologic variant of the virus not covered by vaccines, or when outbreaks occur among unvaccinated individuals at risk who are in closed settings, for example, in a nursing home.]

A. Amantadine and rimantadine

In many viral infections the clinical symptoms appear late in the course of the disease at a time when most of the virus particles have replicated. [Note: This contrasts with bacterial diseases in which the clinical symptoms are usually coincident with bacterial proliferation.] At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication have limited effectiveness. However, some antiviral agents are useful as prophylactic agents. For example, *amantadine* [a MAN ta deen] and its congener, *rimantadine* [rih MAN ta deen] have been shown to be equally effective in preventing influenza A infections. [Note: *Amantadine* is also effective in the treatment of some cases of Parkinson's disease (see p. 87).]

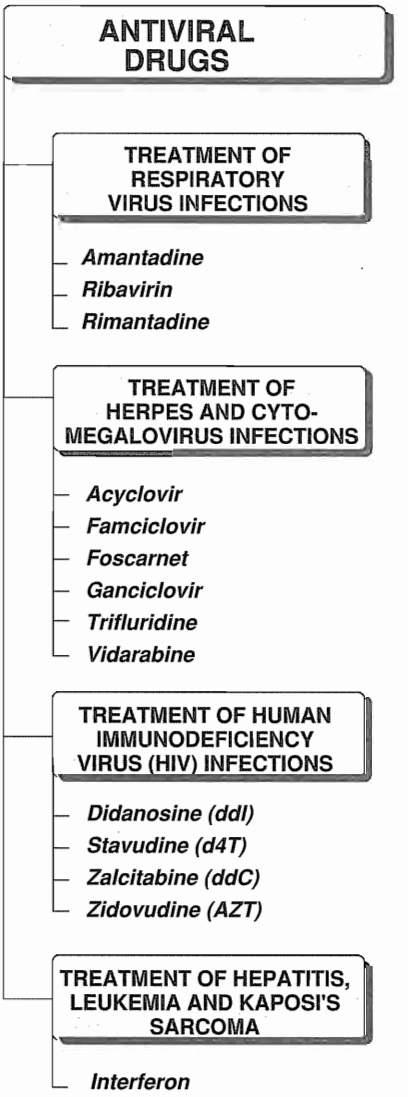


Figure 37.1
Summary of antiviral drugs.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

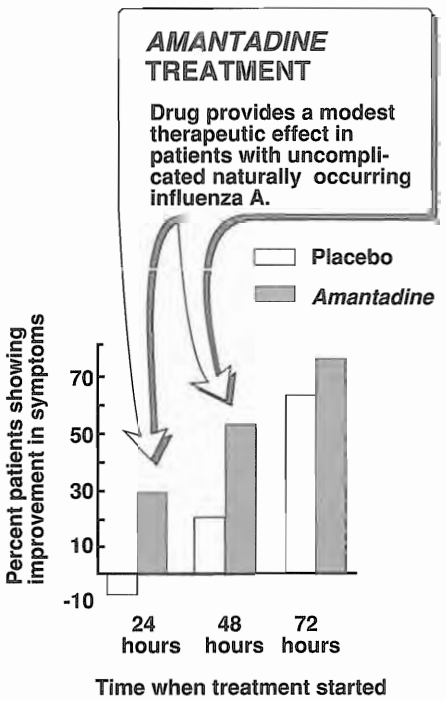


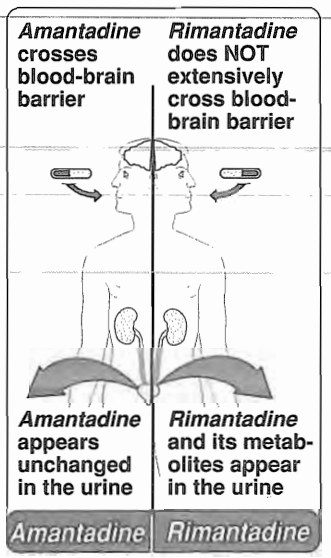
Figure 37.2
Improvement in symptoms of individuals with naturally occurring influenza infection treated with *amantadine*.

1. **Mode of action:** The precise antiviral mechanism of *amantadine* and *rimantadine* remains to be established. Recent evidence points to a blockade of the viral membrane matrix protein, M2, which functions as an ion channel. This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (created when the virus is internalized by endocytosis). [Note: The acid environment of the endosome is required for viral uncoating.] These drugs may also interfere with the release of new virions.

2. **Resistance:** Influenza A resistance to *amantadine* and *rimantadine* is not a clinical problem as yet, although some viral isolates have shown a high incidence of resistance. Resistance has been shown to be due to a change in one amino acid of the M2 matrix protein. Cross-resistance occurs between the two drugs.

3. **Antiviral spectrum:** *Amantadine's* and *rimantadine's* therapeutic antiviral spectrum is limited to influenza A virus. Their effectiveness is directly related to their administration relative to infection, for example, these drugs are 70-90% effective in preventing infection if treatment is begun at the time of exposure to the virus. Neither impairs the immune response to influenza A vaccine, and either can be administered as a supplement to vaccination, thus providing protection until antibody response occurs (usually 2 weeks in healthy adults). Treatment is particularly useful in high-risk patients who have not been vaccinated, or during epidemics. In individuals with influenza A infection, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus (Figure 37.2).

4. **Pharmacokinetics:** Both drugs are well absorbed orally. *Amantadine* distributes throughout the body and readily penetrates into the central nervous system (CNS), whereas *rimantadine* does not cross the blood-brain barrier to the same extent. *Amantadine* is not extensively metabolized. It is excreted into the urine and may accumulate to toxic levels in patients with renal failure. On the other hand, *rimantadine* is extensively metabolized by the liver. Metabolites and parent drug are eliminated by the kidney.



5. **Adverse effects:** *Amantadine's* side effects are mainly associated with the CNS. Minor neurologic symptoms include insomnia, dizziness, and ataxia. More serious side effects have been reported (for example, hallucinations, seizures). The drug should be employed cautiously in patients with psychiatric problems, cerebral atherosclerosis, renal impairment, or epilepsy. *Rimantadine* causes fewer CNS reactions since it does not efficiently cross the blood-brain barrier. *Amantadine* and *rimantadine* should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats.

B. Ribavirin

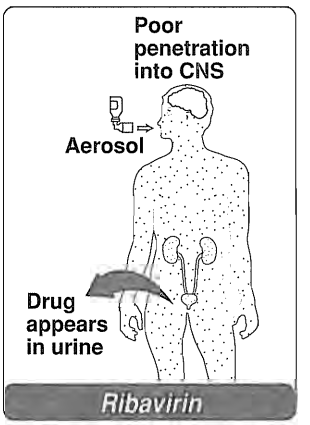
Ribavirin [rye ba VYE rin] is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses.

1. **Mode of action:** The mode of action has been studied only for the influenza viruses. *Ribavirin* is first converted to the 5'-phosphate derivatives, the major product being the compound ribavirin-triphosphate (RTP), which has been postulated to exert its antiviral action by inhibiting viral mRNA synthesis. [Note: Rhinoviruses and enteroviruses, which contain preformed mRNA and do not need to synthesize mRNA in the host cell to initiate the infection, are relatively resistant to the action of *ribavirin*.]

2. **Antiviral spectrum:** *Ribavirin* is used in treating infants and young children infected with severe RSV infections. [Note: It is not indicated for use in adults.] Favorable responses of acute hepatitis A virus and influenza A and B infections have also been reported. *Ribavirin* may reduce the mortality and viremia of Lassa fever.

3. **Pharmacokinetics:** *Ribavirin* is effective orally and intravenously. Its current use is as an aerosol in certain respiratory viral conditions, such as the treatment of RSV infection. Studies of drug distribution in primates showed retention in all tissues, except brain. The drug and its metabolites are eliminated in the urine.

4. **Adverse effects:** Side effects reported for oral or parenteral use of *ribavirin* have included dose-dependent transient anemia in Lassa fever victims. Elevated bilirubin has been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment and therefore, monitoring is essential. Because of teratogenic effects in experimental animals, *ribavirin* is contraindicated in pregnancy.



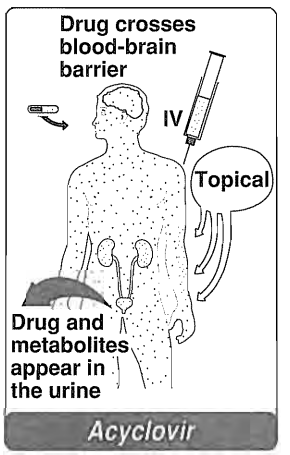
III. TREATMENT OF HERPESVIRUS INFECTIONS

Herpesviruses are associated with a broad spectrum of diseases, e.g., cold sores, viral encephalitis, and genital infections, the latter being a hazard to the newborn during parturition. The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect in the latent phase. Except for *foscarnet*, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

A. Acyclovir

Acyclovir [ay SYE kloe ver] (*acycloguanosine*) has become one of the most prescribed antiviral drugs because of its effectiveness against herpesviruses.

1. **Mode of action:** *Acyclovir*, a guanosine analog that lacks a true sugar moiety, is monophosphorylated in the cell by the herpes virus-encoded enzyme, thymidine kinase. Therefore virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cells (Figure 37.3). Acyclovir triphosphate competes with deoxyguanosine triphosphate (dGTP) as a substrate for viral DNA polymerase, and is itself incorporated into the viral DNA causing premature DNA-chain termination (see Figure 37.3). Irreversible binding of the *acyclovir*-containing template primer to viral DNA polymerase inactivates the enzyme. It is less effective against the host enzyme.



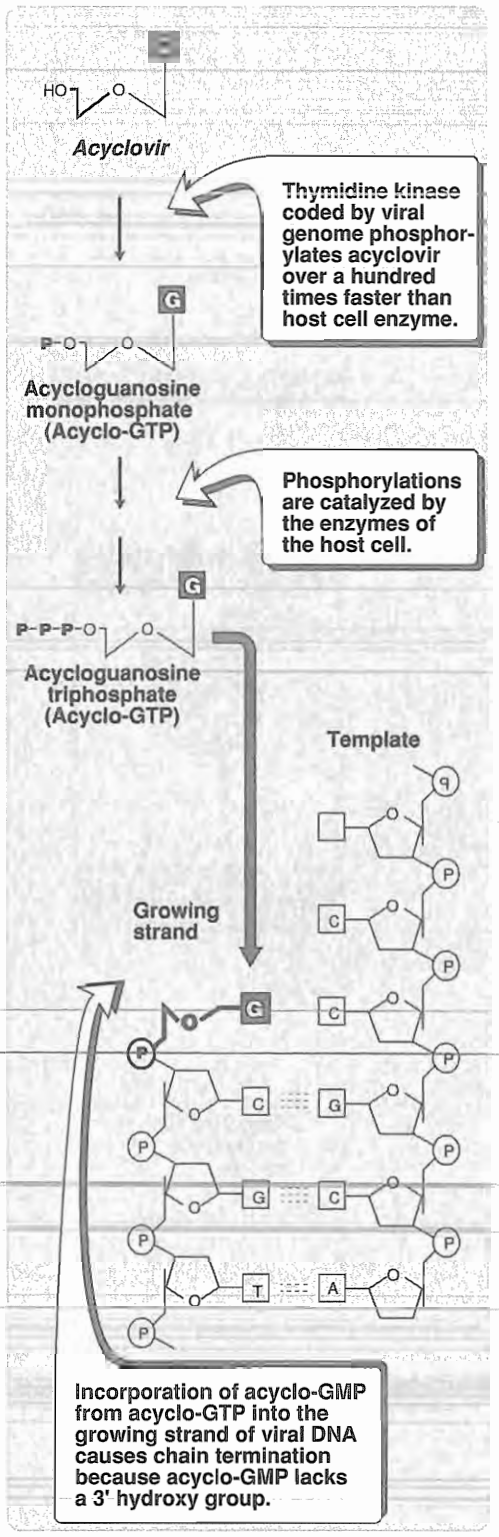


Figure 37.3
Incorporation into viral DNA, causing chain termination.

2. **Resistance:** Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains. [Note: Cytomegalovirus (CMV) is resistant because it lacks a specific viral thymidine kinase.]

3. **Antiviral spectrum:** *Acyclovir* has a greater specificity than *vidarabine* against herpesviruses. Herpes simplex virus-1 (HSV-1), HSV-2, varicella-zoster virus, and some Epstein-Barr virus-mediated infections are sensitive to *acyclovir*, but CMV is resistant. *Acyclovir* is the treatment of choice in herpes simplex encephalitis, and is more efficacious than *vidarabine* in increasing the rate of survival (Figure 37.4). The most common use of *acyclovir* is in therapy of genital herpes infections. [Note: In all cases, *acyclovir* inhibits only actively replicating viruses and has no effect on latent viruses.] It is also given prophylactically to seropositive patients before bone marrow and after heart transplants to protect such individuals during posttransplant immunosuppressive treatments.

4. **Pharmacokinetics:** Administration can be by an intravenous, oral, or topical route. The efficacy of topical applications is doubtful. The drug distributes well throughout the body, including the cerebrospinal fluid. *Acyclovir* is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and tubular secretion. *Acyclovir* accumulates in patients with renal failure.

5. **Adverse effects:** Side effects depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration; transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

B. Ganciclovir (DHPG)

The lack of effect of available nucleoside analogs on cytomegalovirus (CMV) infection led to the synthesis of the *acyclovir* analog, *ganciclovir* [gan SYE kloe ver] (*9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, DHPG*). It is currently available for treatment of cytomegalic retinitis in immunocompromised patients.

1. **Mode of action:** Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes, the actual pathway depending on the virus. Cytomegalovirus is deficient in thymidine kinase, and therefore forms the triphosphate by another route. The nucleotide competitively inhibits viral DNA polymerase and can be incorporated into the DNA to decrease the rate of chain elongation.

2. **Resistance:** Resistant CMV strains have been detected, but the mechanism of resistance is not yet known.

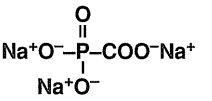
3. **Antiviral spectrum:** Its activity in vitro is the same as that of *acyclovir*, but *ganciclovir* is approved only for treatment of cytomegalic retinitis.

4. **Pharmacokinetics:** *Ganciclovir* is administered intravenously and distributed throughout the body, including the cerebrospinal fluid. Excretion into the urine occurs through glomerular filtration and tubular secretion. Like *acyclovir*, *ganciclovir* accumulates in patients with renal failure.

5. **Adverse effects:** Adverse effects include severe, dose-dependent neutropenia. [Note: Combined treatment with *zidovudine* can result in additive neutropenia.] *Ganciclovir* is carcinogenic as well as embryotoxic and teratogenic in experimental animals.

C. Famciclovir

Famciclovir [fam SYE kloe ver], another acyclic analog of 2'-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir* (pen SYE kloe ver). The antiviral spectrum is similar to that of *ganciclovir* but it is presently approved only for treatment of acute herpes zoster. The drug is effective orally. Adverse effects include headaches and nausea. Studies in experimental animals have shown an increased incidence in mammary adenocarcinomas and testicular toxicity.



Foscarnet sodium

D. Foscarnet

Unlike most of the antiviral agents, *foscarnet* [FOS car ney] is not a purine or pyrimidine analog; it is phosphonoformate, a pyrophosphate derivative. Despite its broad antiviral activity in vitro, it is approved only as a treatment for cytomegalic retinitis in immunocompromised HIV-infected patients, especially if the infection is resistant to *ganciclovir*. *Foscarnet* works by reversibly inhibiting viral DNA and RNA polymerases, thereby terminating chain elongation. Mutation of the polymerase structure is responsible for resistant viruses. [Note: Cross-resistance between *foscarnet* and *ganciclovir* or *acyclovir* is uncommon.] *Foscarnet* is poorly absorbed orally and must be injected intravenously, and must be given frequently to avoid relapse when levels fall. It is dispersed throughout the body, Greater than 10% enters the bone matrix from which it slowly leaves. The parent drug is eliminated by glomerular filtration and tubular secretion into the urine. Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent cations, hypocalcemia, and hypomagnesemia are also seen. In addition, hypokalemia, hypophosphatemia, seizures, and arrhythmias have been reported.

E. Vidarabine (ara-A)

Vidarabine [vye DARE a been] (*arabinofuranosyl adenine*, *ara-A*, *adenine arabinoside*) is one of the most effective of the nucleoside analogs and is also the least toxic. However, it has been supplanted clinically by *acyclovir*, which is more efficacious and safe. Although *vidarabine* is active against herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV), its use is limited to treatment of immunocompromised patients with herpes simplex keratitis or encephalitis, or VZV infections. *Vidarabine*, an adenosine analog, is converted in the cell to its 5'-triphosphate analog (ara-ATP), which is postulated to inhibit viral DNA synthesis. Some resistant herpes virus

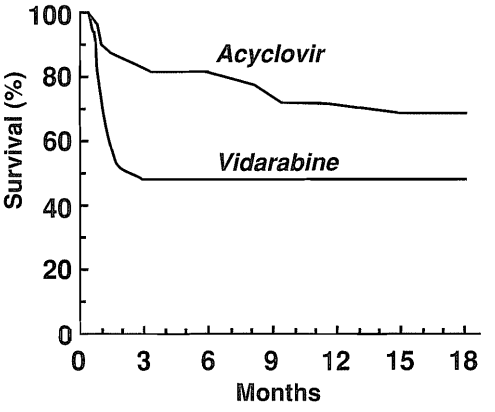
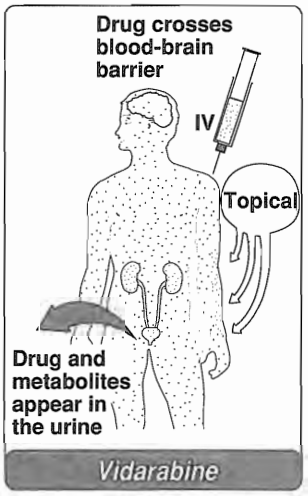


Figure 37.4
Comparison of survival in patients with biopsy-proved herpes simplex encephalitis treated with *vidarabine* or *acyclovir*.

mutants have been detected that have altered DNA polymerase. To be effective systemically, poorly soluble *vidarabine* must be administered intravenously in large volumes over a prolonged time, usually 12 hours. *Vidarabine* penetrates into the brain and thus is effective in the treatment of herpes simplex encephalitis. *Vidarabine* ointment is effective in the treatment of herpetic and vaccinial keratitis and in herpes simplex keratoconjunctivitis. *Vidarabine* and its metabolites are found in the urine. Adverse effects during short-term use are not serious. CNS disturbances and fluid overload, however, can be a problem in patients with impaired hepatic or renal function.



F. Trifluridine

Trifluridine [try FLOO ri deen] has replaced the earlier drug, *idoxuridine* [eye dox Yoor i deen], in the topical treatment of keratoconjunctivitis due to herpes simplex viruses. Like *idoxuridine*, this pyrimidine analog is incorporated into the viral DNA to disrupt its function.

IV. TREATMENT FOR ACQUIRED IMMUNODEFICIENCY DISEASE (AIDS)

Presently six drugs are approved to fight human immunodeficiency virus (HIV) infection. Five are either pyrimidine or purine nucleoside analogs, and must be converted to their nucleotide forms to exert their antiviral effect. [Note: The 3' position of their deoxyribose moiety either lacks a hydroxyl group or is blocked by an azide substituent (Figure 37.5) thus preventing chain elongation.] The sixth drug is an HIV protease inhibitor. Although not curative, these agents interfere in the multiplication of the virus and slow progression of the disease to possibly prolong survival.

A. Zidovudine (3'-Azido-3'-Deoxythymidine, AZT)

One of the most effective drugs currently approved for treatment of HIV infection and AIDS is the pyrimidine analog, *3'-azido-3'-deoxythymidine* (*AZT*). *AZT* has the generic name of *zidovudine* [zye DOE vyoo deen]. *AZT* is presently employed in patients shown to have documented HIV infection. Improvement in immunologic status (increase in absolute number of helper-induced T cells) has been reported. Most encouraging is the protection of fetuses from becoming infected by the virus when HIV-infected pregnant mothers have been maintained on the drug.

1. **Mode of action:** *AZT* must be converted to the corresponding nucleoside triphosphate by mammalian thymidine kinase in order for it to exert its antiviral activity. AZT-triphosphate is then incorporated into the growing chain of viral (but not mammalian nuclear) DNA by reverse transcriptase[1]. Because *AZT* lacks a hydroxyl at the 3' position, another 5'-3' phosphodiester linkage cannot be formed. Thus, synthesis of the DNA chain is terminated, and replication of the virus cannot take place. The relative lack of discrimination of the viral reverse transcriptase is believed to favor the introduction of the *AZT* into the viral-catalyzed process; the cellular DNA polymerase is more selective. In addition, the phosphory-

[1]See p. 372 for Infolink references to other books in this series.

lation of deoxythymidylic acid (dTMP) to the corresponding diphosphate (dTDP) is inhibited by the azido-thymidine monophosphate (AZT-MP).

2. **Resistance:** Effectiveness decreases with time. Some resistant isolates have mutated reverse transcriptase, which has a lower affinity for the AZT-triphosphate.

3. **Antiviral spectrum:** Presently the only clinical use for *AZT* is in the treatment of patients infected with HIV.

4. **Pharmacokinetics:** The drug is well absorbed after oral administration. If taken with food, peak levels may be lower but total drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. Most of the *AZT* is glucuronidated by the liver and then excreted in the urine.

5. **Adverse effects:** In spite of its seeming specificity, *AZT* is toxic to bone marrow. For example, severe anemia and leukopenia occur in patients receiving high doses. Headaches are also common. Seizures have been reported in patients with advanced AIDS. *AZT's* toxicity is potentiated if glucuronidation is decreased by co-administration of drugs like *probenecid*, *acetaminophen*, *lorazepam*, *indomethacin*, and *cimetidine*. [Note: These drugs are themselves glucuronidated and thus can interfere with the glucuronidation of *AZT*. They should be avoided or used with caution in patients receiving *AZT*.]

B. Didanosine (ddI)

The second drug approved to treat HIV-1 infection was *didanosine* [dye DAH no seen] (*dideoxyinosine*, *ddI*), which is also missing the 3' hydroxyl. It is not recommended for initial treatment of HIV disease, but rather is used for *AZT*-resistant HIV infections.

1. **Mechanism of action:** Upon entry into the host cell, *didanosine* is biotransformed into *ddATP* through a series of reactions that involve phosphorylation of the *ddI*, amination to ddAMP and further phosphorylation. The resulting *ddATP* is incorporated into the DNA chain like *AZT*, causing termination of chain elongation.

2. **Resistance:** Viral isolates from patients who have undergone prolonged therapy with *ddI* contain reverse transcriptase with amino acid substitutions. Cross-resistance with the other nucleoside agents has not been reported.

3. **Antiviral spectrum:** Its activity is confined to retroviruses, specifically HIV-1.

4. **Pharmacokinetics:** Due to its acid lability, *didanosine* is administered as either chewable, buffered tablets or in a buffered solution. Absorption is good if taken in the fasting state; food causes decreased absorption. The drug penetrates into the CSF but to a lesser extent than *AZT*. About 55% of the parent drug appears in the urine.

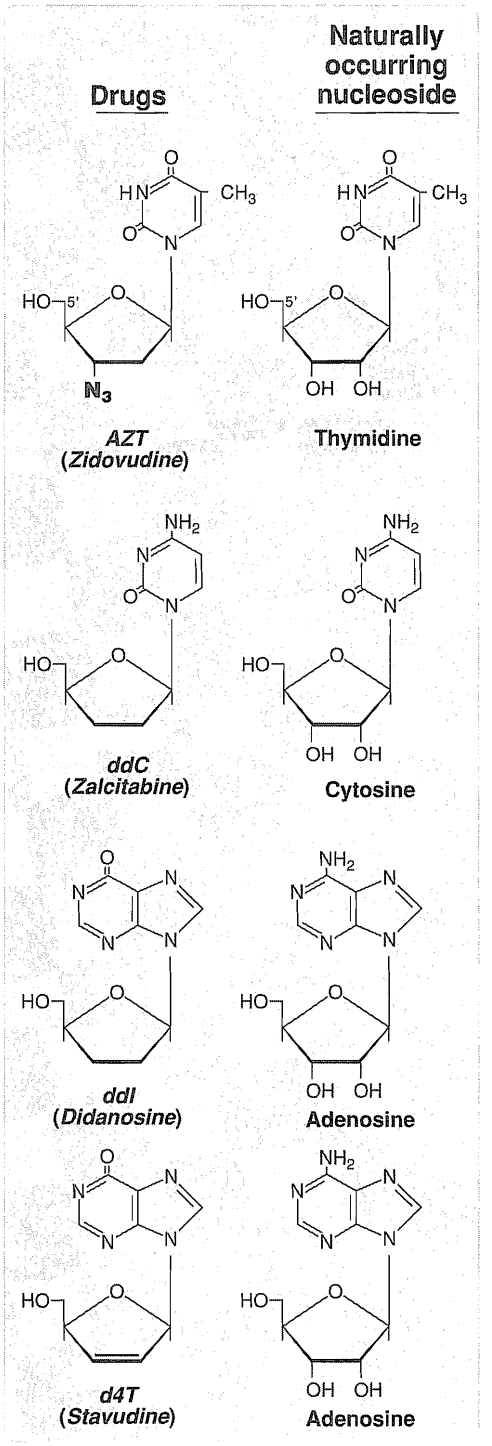
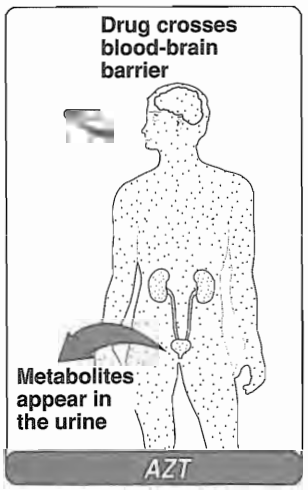


Figure 37.5
Nucleoside analogues used in HIV therapy.



5. **Adverse effects:** Pancreatitis, which may be fatal, is a major toxicity of *ddI* treatment, and requires monitoring of serum amylase. The dose-limiting toxicity of *didanosine* is peripheral neuropathy. [Note: The buffering of stomach contents may interfere in the absorption of other drugs that require an acidic milieu for absorption, such as *ketoconazole*.]

C. Zalcitabine (ddC)

An analog of deoxycytidine, *zalcitabine* [zal SIT a been] (*dideoxycytidine*, *ddC*) is used either in conjunction with *AZT* or as monotherapy in patients who cannot tolerate *AZT*. Like other drugs in this group, it is converted to the active triphosphate (ddCTP), which terminates chain elongation when incorporated into viral DNA and also inhibits viral reverse transcriptase. Point mutations in the reverse transcriptase lead to resistance. *Zalcitabine* is very well absorbed orally, but food or MAALOX TC reduces absorption. The drug is distributed throughout the body but penetration into the CSF is lower than that obtained with *AZT*. Some of the drug is metabolized to the inactive dideoxyuridine (ddU). The urine is the main route of excretion of *ddC,* although fecal elimination of *ddC*, along with its metabolite ddU, occurs. Rash and stomatitis are common but resolve on continued treatment. Peripheral neuropathy is the major toxicity and is probably a consequence of the inhibition of the mammalian mitochondrial DNA polymerase γ. Pancreatitis resulting in death has occurred, especially if *ddC* is given with *pentamidine* (see p. 354).

D. Stavudine (d4T)

Stavudine [STAY vue deen] is an analog of thymidine in which a double bond joins the 2' and 3' carbon of the sugar (see Figure 37.5. Like the others in this group *stavudine* must be converted by the intracellular kinases to the triphosphate (d4TTP) which inhibits the reverse-transcriptase to cause DNA chain termination. In addition it inhibits cellular enzymes such as the β and γ DNA polymerases thus reducing mitochondrial DNA synthesis. It is too early to assess the clinical advantage or resistance to *stavudine*. The drug is almost completely absorbed on oral ingestion and is not affected by food. *Stavudine* penetrates the blood brain barrier. About half the parent drug can be accounted for in the urine. Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy.

E. Lamivudine (3TC)

Recently, *lamivudine* [LAM ih vue deen] or (-)-2'-deoxy-3'-thiacytidine (3TC) has been approved for treatment of HIV in combination with zidovudine. This dideoxynucleoside terminates the synthesis of the proviral DNA chain and also inhibits reverse-transcriptase of both HIV and hepatitis B virus (HBV). However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells. Resistance to *zidovudine* develops more slowly with the combination. *Lamivudine* has good bioavailability on oral administration and depends on the kidney for excretion. Though generally well tolerated, pancreatitis develops in a significant number of pediatric

patients, requiring stoppage of the drug. Administration with trimethoprim/sulfamethoxazole increases the area under the curve (AUC) of *lamivudine*.

F. HIV Protease Inhibitors

Development of toxicity and resistance to the reverse-transcriptase inhibitors led to the targeting of the HIV protease. This aspartate proteinase is essential for the final step of viral proliferation. It is encoded in the HIV genome and thus is absent in uninfected CD4 cells. It is translated as part of the large gag-pol 160-kDA precursor protein and undergoes autocatalytic cleavage from this precursor Figure 37.6). The active enzyme then hydrolytically attacks the precursor protein to generate proteins which are necessary to the virus. The HIV protease inhibitors interfere in this process and lead to the assembly of nonfunctional virions.

Recently, three HIV protease inhibitors have been approved—*saquinavir* [sah KWIN a veer], *ritonavir* [rih TONE a veer] and *indinavir* [in DIN a veer]. It is critical that these drugs be given in dosages high enough to completely suppress viral replication, otherwise resistant virus can emerge. They are frequently given in combination with *zidovudine* and *lamivudine*. Some cross-resistance occurs with the protease inhibitors. Cessation of treatment results in reemergence of the virus.

All are very specific for the viral enzyme and generally much higher concentrations are required to inhibit mammalian proteases. They are orally effective and undergo metabolism partly by the hepatic cytochrome P-450 family of enzymes. Thus many interactions with other drugs have been either identified or suggested. In early studies, these agents have been fairly well-tolerated but nausea, vomiting and diarrhea do occur. Elevated hepatic aminotransferase levels and triglycerides and paresthesias around the mouth have been reported for *ritonavir*.

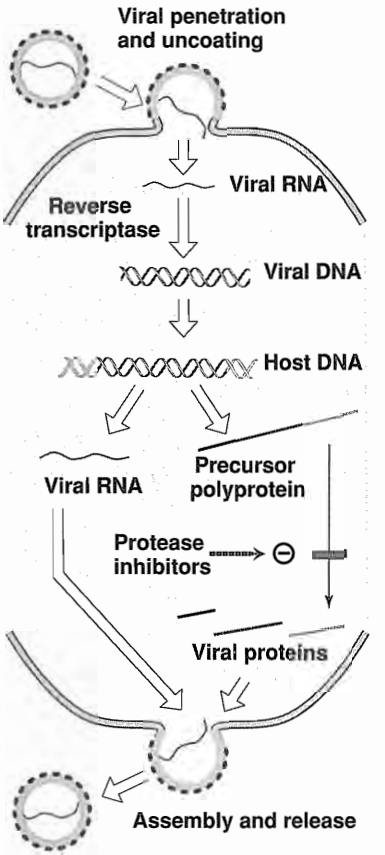


Figure 37.6
Role of HIV protease in viral replication.

V. INTERFERON

Interferon [in ter FEER on] is a family of naturally occurring inducible glycoproteins that interfere with the ability of viruses to infect cells. Although *interferon* inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing. At present the interferons are synthesized by recombinant DNA technology. At least three types of *interferon* exist, α, β, and γ (Figure 37.7). One of the 15 α-interferons, α-2b has been approved for treatment of hepatitis B and C, as well as against cancers such as hairy cell leukemia and Kaposi's sarcoma (see p. 398). Its antiviral mechanism is incompletely understood but appears to involve the induction of host cell enzymes (e.g., a protein kinase, 2',5'-oligoadenylate synthase, and a phosphodiesterase) that inhibit viral RNA translation, and ultimately lead to the degradation of viral mRNA and tRNA. *Interferon* is given intravenously and crosses into the CSF. Adverse effects include fever, lethargy, bone marrow depression, cardiovascular problems such as congestive heart failure, and acute hypersensitivity reactions. Hepatic failure and pulmonary infiltrates are rare.

Interferon-α	*Interferon-β*	*Interferon-γ*
Chronic hepatitis B and C	**Relapsing-remitting multiple sclerosis**	**Chronic granulomatous disease**
Genital warts caused by papilloma-virus		
Hairy-cell leukemia		
Kaposi's sarcoma		

Figure 37.7
Some approved indications for *interferons*.

Choose the ONE best answer.

37.1 All of the following statements about acyclovir are correct EXCEPT:

A. It is the treatment of choice for influenza infections.
B. It is incorporated into the viral DNA causing premature DNA chain termination.
C. It is the treatment of choice in herpes simplex encephalitis.
D. It reduces the duration of lesions associated with genital herpes infections.
E. It inhibits only actively replicating viruses, not latent ones.

Correct choice = A. Amantadine is the drug of choice for influenza infections.

37.2 All of the following statements about amantadine are correct EXCEPT:

A. It is effective in the prophylaxis of influenza A infections.
B. It causes CNS disturbances at high doses.
C. It reduces the duration and severity of systemic symptoms of active influenza A.
D. It is extensively metabolized.
E. It is effective in the treatment of some cases of Parkinson's disease.

Correct choice = D. Amantadine is effective in the prophylaxis of influenza A infections only if administered before exposure to the virus. If amantadine is started within 48 hr after the onset of the disease, the drug will reduce the duration and severity of systemic symptoms of influenza A infection.

37.3 Which one of the following antiviral agents exhibits the greatest selective toxicity for the invading virus?

A. Interferon
B. Amantadine.
C. Acyclovir.
D. Zidovudine.
E. Ribavirin.

Correct answer = C. Acyclovir is monophosphorylated in the cell by the herpesvirus-coded enzyme, thymidine kinase. Thus, uninfected cells show little activation of the drug, and the toxicity is therefore highly selective for herpesvirus-infected cells

37.4 All of the following statements about zidovudine (AZT) are correct EXCEPT:

A. It must be converted to the nucleotide form to express its antiviral activity.
B. It is incorporated into growing viral but not mammalian nuclear DNA.
C. It is currently used to treat severe herpesvirus and respiratory syncytial virus infections as well as AIDS.
D. It is toxic to bone marrow and causes adverse hematologic effects.
E. It penetrates the CNS.

Correct choice = C. AZT is currently used only in the treatment of HIV infections. It is converted to the nucleotide (active) form by mammalian thymidine kinase. The viral reverse transcriptase then favors introduction of the drug into viral DNA; cellular DNA polymerases are more selective.

Questions 37.5 - 37.7: For each numbered phrase, select the ONE drug (A-E) that is most closely associated with it. Each drug (A-E) may be selected once, more than once, or not at all.

A. Amantadine
B. Zidovudine (AZT)
C. Ribavirin
D. Vidarabine
E. Ganciclovir

37.5 It is used solely in the treatment of influenza A infections.

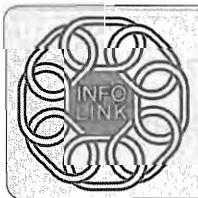
Correct answer = A (amantacine).

37.6 It is an adenosine analog that is active against all members of the herpesvirus group that infects humans.

Correct answer = D (vidarabine).

37.7 It is used in the treatment of cytomegalovirus infections in immunocompromised patients

Correct answer = E (ganciclovir).



[1]See p. 407 in **Biochemistry** (2nd ed.) for a discussion of reverse transcriptase.

Anticancer Drugs

38

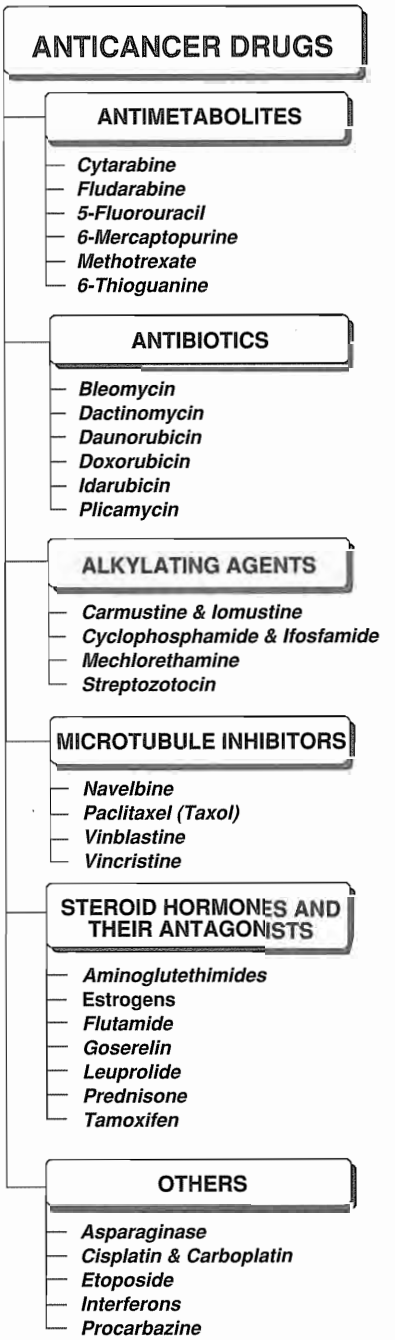


Figure 38.1
Summary of cancer chemotherapy agents.

I. OVERVIEW

It is estimated that 25% of the population of the United States will face a cancer diagnosis during their lifetime, with 1 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. (See Figure 38.1 for a summary of anticancer agents.) In a small fraction (approximately 10%) of cancer patients representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival for cancer patients is about 40%, ranking cancer second only to cardiovascular disease as a cause of mortality.

II. PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause a lethal cytotoxic lesion that can arrest a tumor's progression. The attack is generally directed against metabolic sites essential to cell replication, for example, the availability of purine and pyrimidine precursors for DNA or RNA synthesis (Figure 38.2). Ideally these drugs should interfere only with cellular processes unique to the malignant cells. However, currently available anticancer drugs do not specifically recognize neoplastic cells, but rather affect all proliferating cells—both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects; thus it is important to tailor the drug doses to the physical state of the patient.

A. Treatment strategies

1. **Goal of treatment:** The ultimate goal of chemotherapy is a cure, that is, long-term, disease-free survival. Cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity), which allows the individual to maintain a "normal" existence. In either case, the neoplastic cell burden is initially reduced (debulking) either by surgery and/or radiation, followed

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

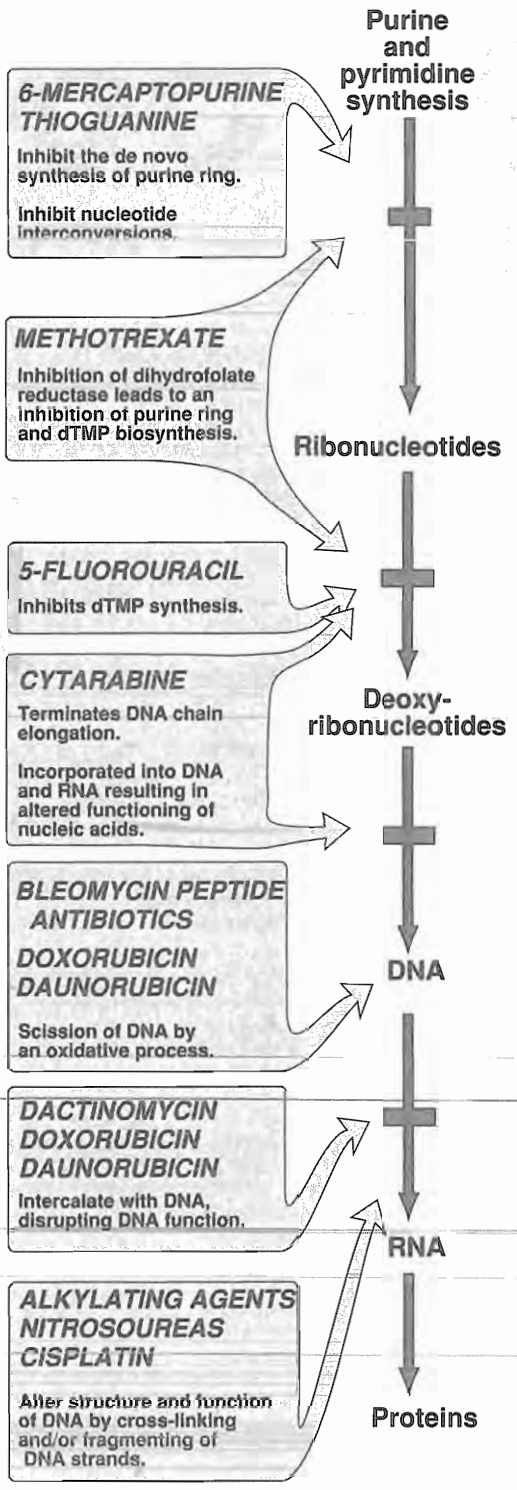


Figure 38.2
Examples of chemotherapeutic agents affecting the availability of RNA and DNA precursors.

by chemotherapy, immunotherapy, or a combination of these treatment modalities (Figure 38.3).

2. **Indications for treatment:** Chemotherapy is indicated when neoplasms are disseminated and not amenable to surgery. Chemotherapy is also used as a supplement to surgery and radiation treatment to attack micrometastases. [Note: Tumors most susceptible to current chemotherapy are undifferentiated and have high growth fractions.]

3. **Tumor susceptibility and the growth cycle:** The fraction of tumor cells that are in the replicative cycle ("growth fraction") influences their susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas nonproliferating cells (those in the G_0 phase) usually survive the toxic effects of these agents.

   a. **Cell-cycle specificity of drugs:** Both normal cells and tumor cells go through a growth cycle (Figure 38.4). However, normal and neoplastic tissue may differ in the number of cells that are in the various stages of the cycle. Chemotherapeutic agents that are effective only in replicating cells, that is those cells that are cycling, are said to be cell-cycle specific (see Figure 38.4), whereas other agents are cell-cycle nonspecific. The nonspecific drugs such as the alkylating agents, although generally more toxic in cycling cells, are also useful against tumors with a low percentage of replicating cells.

   b. **Tumor growth rate:** The growth rate of most tumors in vivo is initially rapid, but decreases as the tumor size increases because of the unavailability of nutrients and oxygen due to inadequate vascularization (see Figure 38.3). Reducing the tumor burden through surgery or radiation promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents.

B. Treatment regimens and scheduling

1. **Log kill:** Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics, that is, a given dose of drug destroys a constant fraction of cells. The term "log kill" is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 10^9 (total) leukemic cells. Consequently if treatment leads to a 99.999% kill, then 0.001% of 10^9 cells (or 10^4 cells) would remain; this is equivalent to a 5-log kill. At this point the patient appears asymptomatic, that is, the patient is in remission (see Figure 38.3). For most bacterial infections, a 5-log (100,000-fold) reduction in the number of microorganisms results in a cure, since the immune system can eradicate the residual bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.

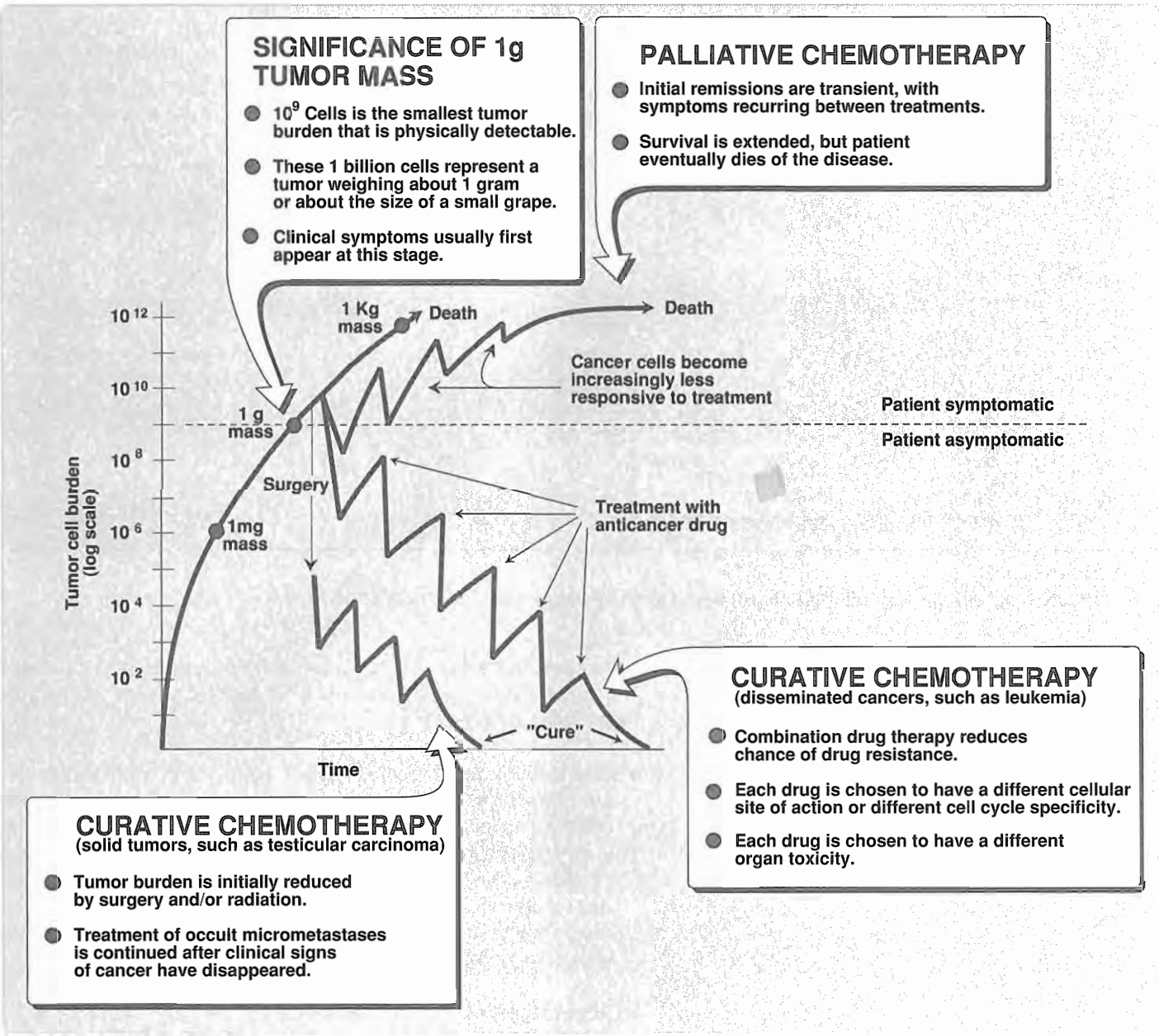


Figure 38.3
Effects of various treatments on the cancer cell burden in a hypothetical cancer patient.

2. **Pharmacologic sanctuaries:** Leukemic or other tumor cells find sanctuary in tissues, for example, the central nervous system (CNS), into which certain chemotherapeutic agents cannot enter because of transport constraints. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.

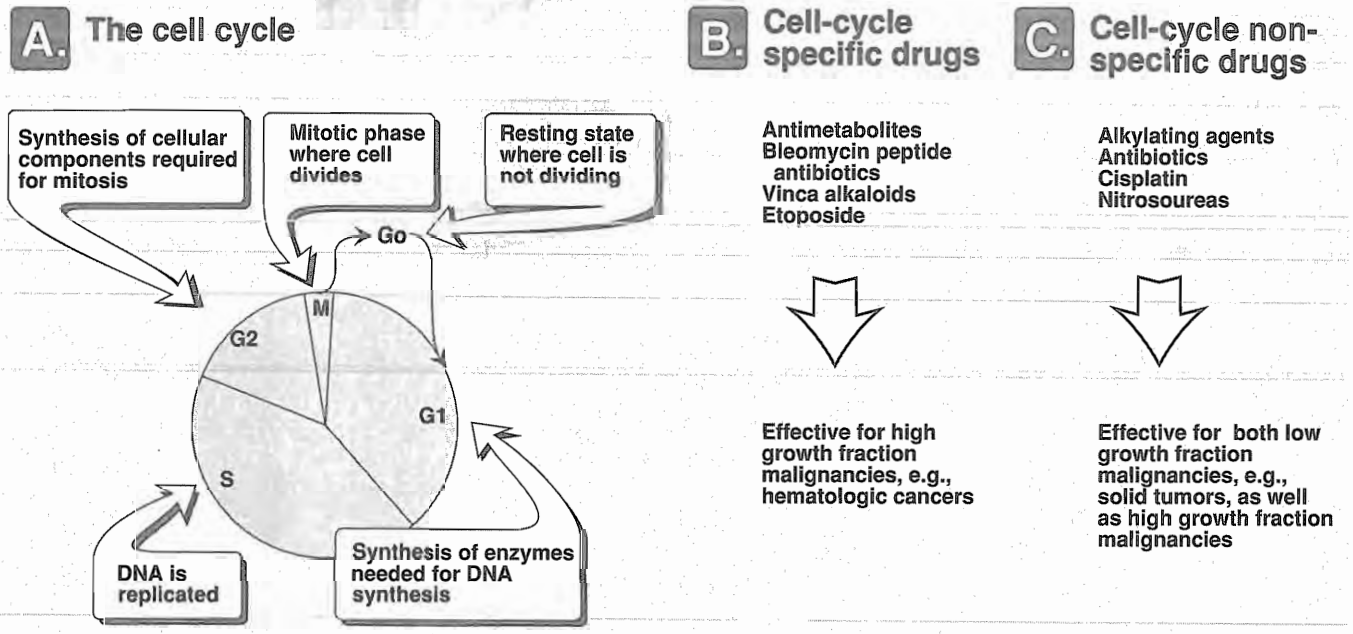


Figure 38.4
Effects of chemotherapeutic agents on the growth cycle of mammalian cells.

3. **Treatment protocols:** Combination chemotherapy is more effective than single-drug treatment in most cancers for which chemotherapy is effective.

   a. **Combinations of drugs:** Cytotoxic agents with qualitatively different toxicities and with different molecular sites and mechanisms of action are usually combined at full doses. This results in higher response rates due to both additive or potentiated cytotoxic effects and non-overlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, can be combined safely only by reducing the doses of each.

   b. **Advantages of drug combinations:** The advantages of such combinations are: 1) they provide maximal cell kill within the range of tolerated toxicity; 2) they are effective against a broader range of cell lines in the heterogeneous tumor population; and 3) they may slow or prevent the development of resistant cell lines.

   c. **Treatment protocols:** Many cancer treatment protocols have been developed; each one is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called POMP, for the treatment of acute lymphocytic leukemia (ALL) consists of **P***rednisone* (see p. 393), **O***ncovin* (*vincristine*, p. 390), **M***ethotrexate* (see p. 378) and **P***urinethol* (*mercaptopurine*, p. 381). Therapy is scheduled intermittently to allow recovery of normal tissue,

such as the patient's immune system, that has been affected by the drugs, thereby reducing the risk of serious infection.

C. Problems associated with chemotherapy

Cancer drugs are toxins that present a lethal threat to the cell. It is therefore not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1. **Resistance:** Some neoplastic cells, for example, melanoma, are inherently resistant to most anticancer drugs. Other tumor types may be selected for or acquire resistance to the cytotoxic effects of the medication, particularly after prolonged administration of low drug doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cell lines in the tumor population. A variety of mechanisms are responsible for drug resistance; each is considered separately under the particular drug.

2. **Multidrug Resistance:** Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for "permeability" glycoprotein, Figure 38.5) is responsible for multidrug resistance (MDR). The resistance is due to ATP-dependent pumping of the drug out of the cell, associated with the presence of P-glycoprotein. Cross-resistance among structurally unrelated agents occurs. For example, cells resistant to the cytotoxic effects of the vinca alkaloids (see p. 390) are also resistant to *dactinomycin* (see p. 384) and the anthracycline antibiotics (see p.385) as well as to *colchicine* (see p. 416), and vice versa. These drugs are all naturally occurring substances, have a hydrophobic aromatic ring, and carry a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that its presence may account for the intrinsic resistance to chemotherapy observed in adenocarcinomas in these tissues.] Certain drugs (for example, *verapamil*, p. 187) can inhibit the pump and thus interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacological actions of their own. Pharmacologically inert pump blockers are being sought.

3. **Toxicity:** Therapy aimed at killing rapidly proliferating cells also affects normal cells undergoing rapid proliferation—for example, buccal mucosa, bone marrow, gastrointestinal (GI) mucosa, and hair cells—contributing to the toxic manifestations of chemotherapy.

   a. **Common adverse effects:** Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting can sometimes be controlled by administration of antiemetic drugs (see p. 241). Some toxicities such as myelosuppression, which predisposes to infection, are common to many chemotherapeutic agents (Figure 38.6),

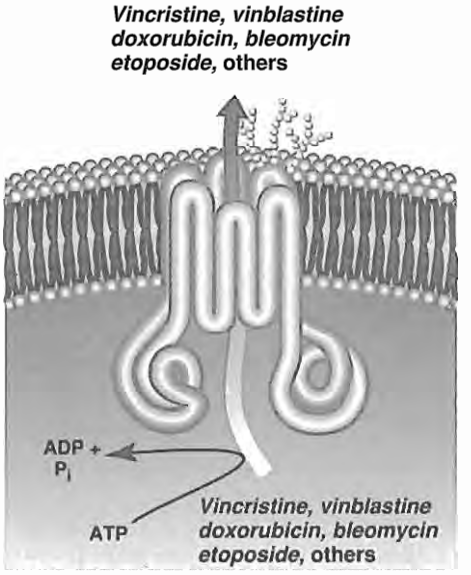


Figure 38.5
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

whereas other adverse reactions are confined to specific agents, for example, cardiotoxicity with *doxorubicin* (see p. 385) and pulmonary fibrosis with *bleomycin* (see p. 386).

b. **Duration of adverse effects:** The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.

c. **Minimizing adverse effects:** Some toxic reactions may be ameliorated by interventions, such as perfusing the tumor locally (for example, a sarcoma of the arm), removing some of the patient's marrow prior to intensive treatment then reimplanting it, or promoting intensive diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with *methotrexate* (see below) can be effectively counteracted by administering *folinic acid* (*leucovorin*, *5-formyltetrahydrofolic acid*, p. 379). With the availability of human granulocyte colony stimulating factor (*filgrastim*), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.

3. **Treatment-induced tumors:** Since most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. Treatment-induced neoplasms are especially a problem after therapy with alkylating agents (see p. 387).

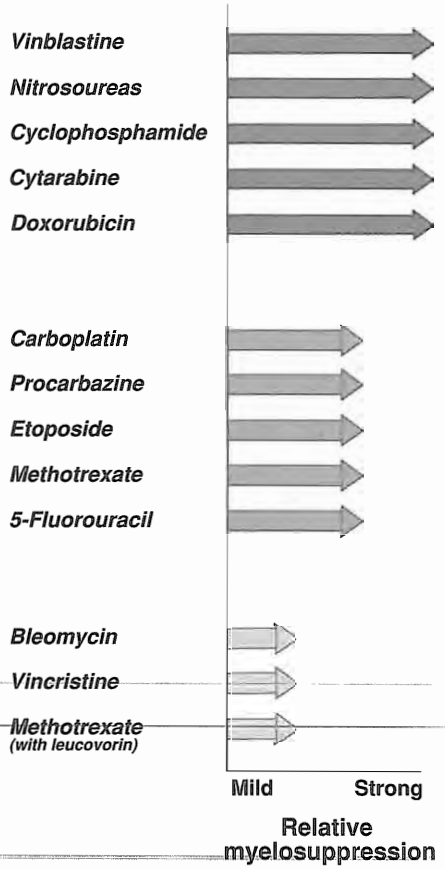


Figure 38.6
Comparison of myelosuppressive potential of anticancer drugs.

III. ANTIMETABOLITES

Antimetabolites are structurally related to normal cellular components. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are S-phase (and therefore cell-cycle) specific.

A. Methotrexate

Methotrexate [meth oh TREX ate] (*MTX*) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting dihydrofolate reductase[1], the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH_4); it therefore acts as an antagonist of that vitamin. Folate plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units. (Figure 38.7)[2].

1. Site of action

a. **Inhibition of dihydrofolate reductase:** After absorption of folic acid from dietary sources or from that produced by intestinal flora, the vitamin undergoes reduction to the tetrahydrofolate form (FH4) by the intracellular NADPH-dependent dihydrofolate reductase. *Methotrexate* enters the cell by an active transport process, which normally mediates the entry of N5-methyl FH4. At high MTX concentrations, the drug can diffuse into the

[1,2]See p. 400 for Infolink references to other books in this series.

cell. *MTX* has an unusually strong affinity for dihydrofolate reductase, and effectively inhibits the enzyme. Its inhibition can only be reversed by a thousand-fold excess of the natural substrate, dihydrofolate (FH_2, see Figure 38.7) or by administration of *leucovorin*, which bypasses the blocked enzyme and replenishes the folate pool. [Note: *Leucovorin*, or *folinic acid*, is the N^5-formyl group-carrying form of FH_4.]

b. Consequences of decreased FH4: Inhibition of dihydrofolate reductase deprives the cell of the various folate coenzymes and leads to decreased biosynthesis of thymidylic acid, methionine and serine, and the purines (adenine and guanine), and thus eventually to depressed DNA, RNA and protein synthesis and to cell death (see Figure 38.7).

c. Polyglutamated MTX: Like tetrahydrofolate itself, MTX becomes polyglutamated within the cell, a process that favors intracellular retention of the compound due to its larger size and increased negative charge (see below).

2. Resistance: Nonproliferating cells are resistant to *methotrexate*. Resistance in neoplastic cells can be due to amplification (production of additional copies) of the gene that codes for dihydrofolate reductase resulting in increased levels of this enzyme. The enzyme affinity for MTX may also be diminished. Resistance can also occur from a reduced influx of *MTX*, apparently caused by a change in the carrier-mediated transport responsible for pumping *methotrexate* into the cell.

3. Therapeutic applications: *Methotrexate,* often in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt's lymphoma in children, breast cancer, and head and neck carcinomas. High-dose *MTX* is curative for osteogenic sarcoma and choriocarcinoma; treatment is followed by administration of *leucovorin* ("citrovorum factor") to rescue the bone marrow (see Figure 38.7, and the discussion of adverse effects, p. 380). In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis. These patients require close monitoring for possible toxic sequelae.

4. Pharmacokinetics:

a. Administration and distribution: *Methotrexate* is readily absorbed at low doses from the GI tract, but it can also be administered by intramuscular (IM), intravenous (IV), and intrathecal routes. [Note: Because *MTX* does not penetrate the blood-brain barrier, it is administered intrathecally to destroy neoplastic cells in the central sanctuary sites.] High concentrations of the drug are found in the intestinal epithelium, liver and kidney, as well as in ascites and pleural effusions. *MTX* is also distributed to the skin.

b. Fate: Although folates found in the blood have a single terminal glutamate, most intracellular folates are converted to polygluta-

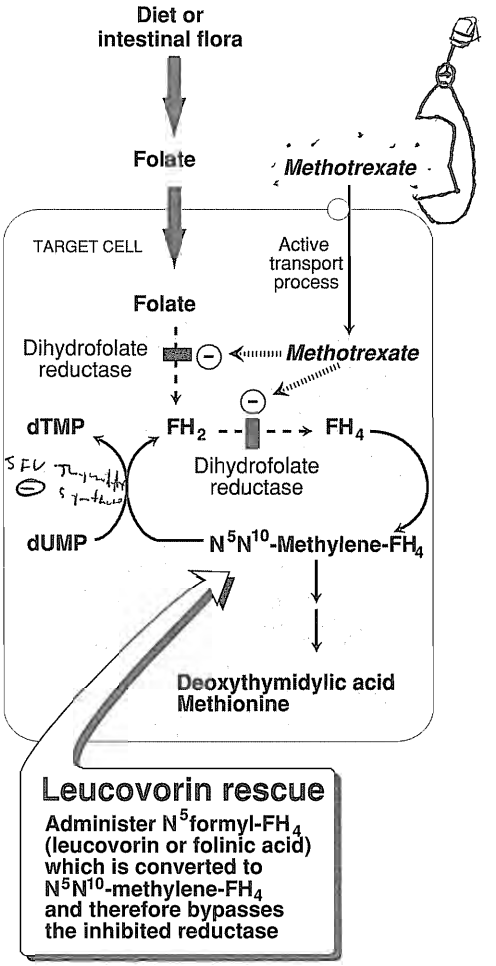
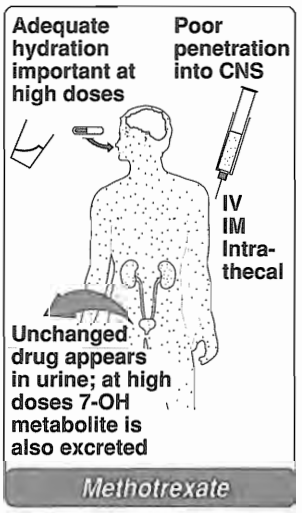


Figure 38.7
Mechanism of action of *methotrexate* and the effect of administration of leucovorin [FH_2 = dihydrofolate; FH_4 = tetrahydrofolate].

mates. These are preferentially retained inside the cells and are usually more efficient cofactors than are the monoglutamates. *Methotrexate* is also metabolized to poly-glutamate derivatives. This property is important, because the polyglutamates, which also inhibit dihydrofolate reductase, remain within the cell even in the absence of extracellular drug. This is in contrast to *MTX* per se, which rapidly leaves the cell as the extracellular drug levels fall. High doses of *methotrexate* undergo hydroxylation at the 7 position. This derivative is less water soluble, and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs via the urine.



5. Adverse effects:

a. Commonly observed toxicities: Most frequent toxicities are stomatitis, myelosuppression, erythema, rash, urticaria, alopecia, nausea, vomiting, and diarrhea. Some of these can be prevented or reversed by administering *leucovorin* (see Figure 38.7), which is taken up more readily by normal cells than by tumor cells. Doses of *leucovorin* must be kept minimal to avoid interference with the antitumor action of the *methotrexate*.

b. Renal damage: Although uncommon during conventional therapy, renal damage is a complication of high-dose *methotrexate*.

c. Hepatic function: Hepatic function should be monitored. Long-term use may lead to fibrosis.

d. Pulmonary toxicity: Children being maintained on *methotrexate* may develop cough, dyspnea, fever, and cyanosis. Infiltrates are seen on x-ray. This toxicity is reversible on suspension of the drug.

e. Neurologic toxicities: These are associated with intrathecal administration, and include subacute meningeal irritation, stiff neck, headache, and fever. Seizures, encephalopathy, or paraplegia occur rarely. Long-lasting effects, such as learning disabilities, have been seen in children who received the drug by this route.

f. Contraindications: Because *methotrexate* is teratogenic and an abortifacient it should be avoided in pregnancy. [Note: It is used with *misoprostol* (see p. 419) to induce abortion.]

B. 6-Mercaptopurine

The drug *6-mercaptopurine* [mer kap toe PYOOR een] (*6-MP*) is the thiol analog of hypoxanthine. It and *thioguanine* (*6-TG*) were the first purine analogs to prove beneficial for treating neoplastic disease. *Azathioprine*, an immunosuppressant, exerts its effects after conversion to *6-MP*.

1. **Site of action:**

   a. **Formation of nucleotide:** To exert its antileukemic effect, *6-mercaptopurine* must penetrate target cells and be converted to the corresponding nucleotide, 6-mercaptopurine ribose phosphate (6-MPRP better known as 6-thioinosinic acid, or thio-IMP, Figure 38.8). The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine-guanine phosphoribosyl transferase (HGPRT).[3]

   b. **Inhibition of purine synthesis:** Although the nature of the exact cytotoxic step is not known, the unnatural nucleotide, thio-IMP, like AMP, can feedback to inhibit the first step of de novo purine ring biosynthesis as well as formation of AMP and xanthinylic acid (XMP) from inosinic acid (IMP).[4]

   c. **Incorporation into nucleic acids:** Dysfunctional RNA and DNA result from incorporation of guanylate analogs generated from the unnatural nucleotides. Thio-IMP is dehydrogenated to thio-GMP, which after phosphorylation to di- and triphosphates, can be incorporated into RNA. The deoxyribonucleotide analogs that are also formed are incorporated into DNA.

2. **Resistance:** Resistance is associated with (1) an inability to biotransform *6-MP* to the corresponding nucleotide because of decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome in which patients lack this enzyme); (2) an increased dephosphorylation; or (3) increased metabolism of the drug to thiouric acid.

3. **Therapeutic applications:** *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia (ALL).

4. **Pharmacokinetics**

   a. **Administration and metabolism:** Absorption by the oral route is erratic. The drug is widely distributed throughout the body except for the cerebrospinal fluid. *6-MP* undergoes metabolism in the liver to the 6-methylmercaptopurine ($S\text{-}CH_3$) derivative or to thiouric acid. The latter reaction is catalyzed by xanthine oxidase. Because *allopurinol* (see p. 417), a xanthine oxidase[5] inhibitor, is frequently administered to cancer patients receiving chemotherapy to reduce hyperuricemia, it is important to decrease the dose of *6-MP* in these individuals to avoid accumulation of the drug and exacerbation of toxicities.

   b. **Excretion:** The parent drug and its metabolites are excreted by the kidney.

5. **Adverse effects:** Side effects include nausea, vomiting, and diarrhea. Bone marrow depression is the chief toxicity. Hepatotoxicity has also been reported.

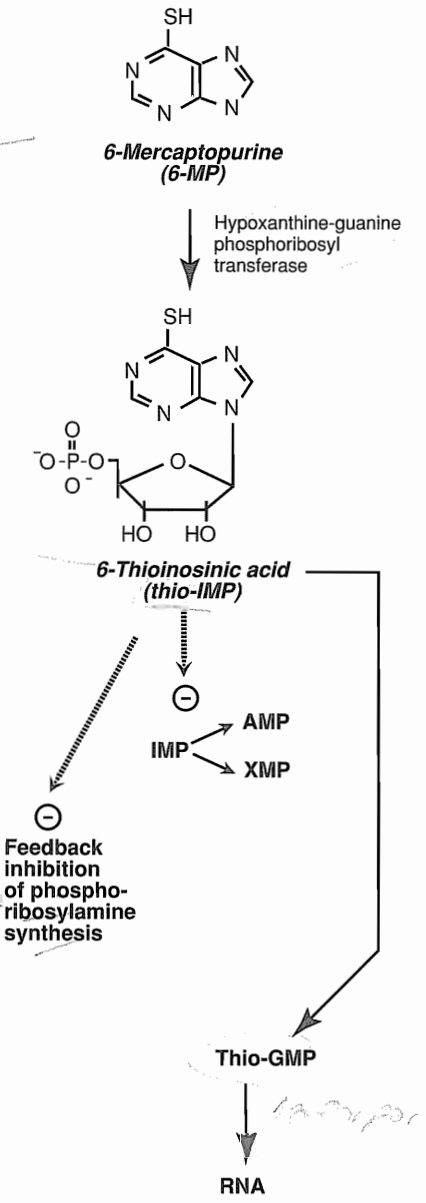
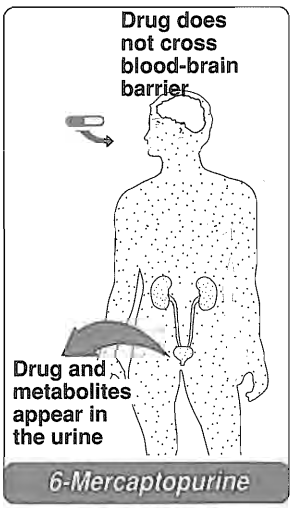


Figure 38.8
Actions of *6-mercaptopurine*.

[3,4,5]See p. 400 for Infolink references to other books in this series.



C. 6-Thioguanine

6-Thioguanine [thye oh GWAH neen] (*6-TG*), another purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with *daunorubicin* (see p. 385) and *cytarabine* (see p. 383). Like *6-MP*, *6-TG* must first be converted to the nucleotide form, which then inhibits the biosynthesis of the purine ring and the phosphorylation of GMP to GDP. *6-TG* can also be incorporated into RNA and DNA. Cross-resistance occurs between 6-MP and 6-TG. Unlike *6-MP*, *allopurinol* does not potentiate *6-TG* action because very little of the drug is metabolized to thiouric acid. Otherwise, toxicities are the same as those for *6-MP*.

D. 5-Fluorouracil

5-Fluorouracil [flure oh YOOR a sil] (*5-FU*), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of one of the essential precursors for DNA synthesis.

1. **Site of action:** *5-FU* per se is devoid of antineoplastic activity and must be converted to the corresponding deoxynucleotide (5-FdUMP, Figure 38.9), which competes with deoxyuridine monophosphate (dUMP) for thymidylate synthetase. 5-FdUMP acts as a pseudosubstrate and is entrapped with the enzyme and its N^5,N^{10}-methylene tetrahydrofolic acid coenzyme in a ternary complex that cannot proceed to products. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and cell death. [Note: *Leucovorin* is given with *5-FU* because the reduced folate coenzyme is required in the thymidylate synthetase reaction. Lack of sufficient coenzyme reduces the effectiveness of the antipyrimidine.] 5-FU is also incorporated into RNA and low levels have been detected in DNA.

2. **Resistance:** Resistant cells are encountered that have lost the ability to convert *5-FU* into its active form or have altered or increased thymidylate synthetase or have an increased rate of *5-FU* catabolism.

3. **Therapeutic applications:** *Fluorouracil* is employed primarily in the treatment of slowly growing, solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). Adjuvant therapy with *levamisole*, a veterinary anthelmintic agent, improves the survival of patients with colonic cancer. *5-FU* is also effective for the treatment of superficial basal cell carcinomas when applied topically.

4. **Pharmacokinetics:** Because of its severe toxicity to the GI tract, *5-FU* is given intravenously or, in the case of skin cancer, topically. The drug penetrates well into all tissues including the CNS. *5-FU* is metabolized in the liver, largely to CO_2, which is expired. The dose must be adjusted in the case of impaired hepatic function.

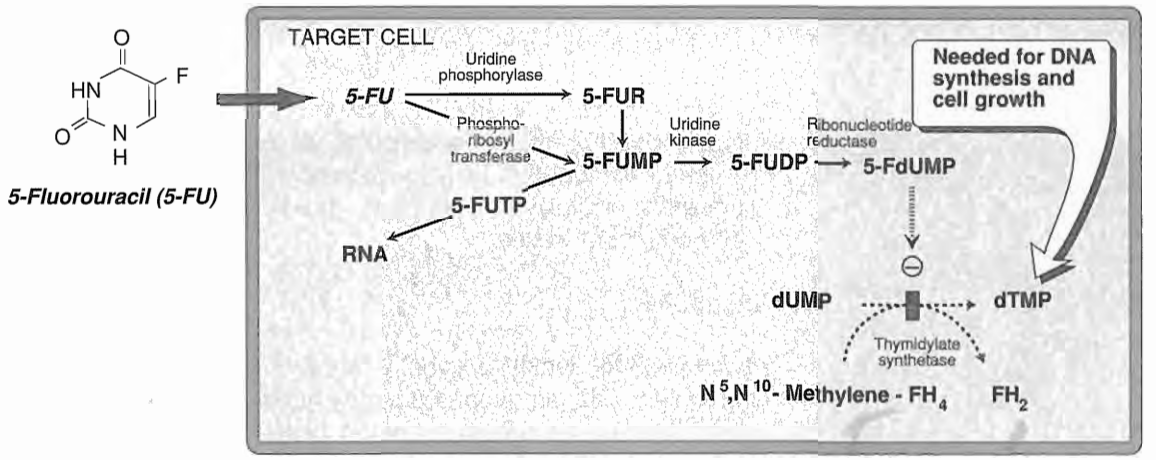
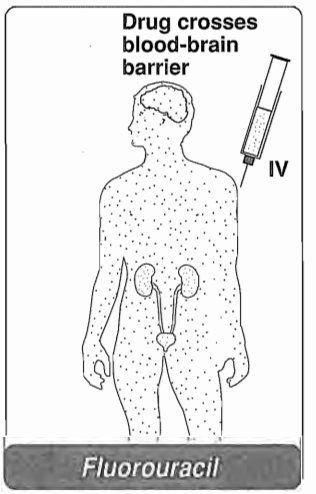


Figure 38.9
Mechanism of 5-fluorouracil's cytotoxic action. *5-Fluorouracil* is converted to 5-FdUMP, which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase.

5. **Toxicities:** In addition to nausea, vomiting, diarrhea, and alopecia, severe ulceration of the oral and GI mucosa, bone marrow depression (with bolus injection), and anorexia are frequently encountered. A dermopathy (erythematous desquamation of the palms and soles) called the "hand-foot syndrome" is seen after extended infusions.



E. Cytarabine

Cytarabine [sye TARE a been] (*cytosine arabinoside, ara-C*) is an analog of 2'-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. It acts as a pyrimidine antagonist.

1. **Site of action:** Like the other purine and pyrimidine antagonists, *ara-C* must be sequentially phosphorylated to the corresponding nucleotide, cytosine arabinoside triphosphate (ara-CTP), in order to be cytotoxic. It is S-phase (hence cell-cycle) specific. *Ara-C* is also incorporated into DNA and can terminate chain elongation. It can also inhibit the reduction of CDP to dCDP.

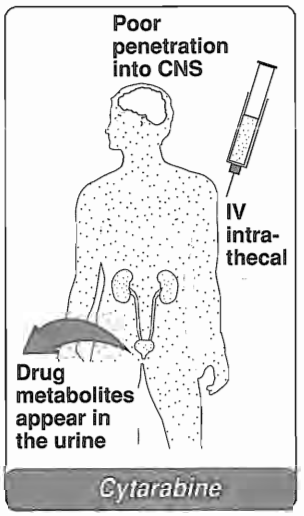
2. **Resistance:** Resistance to *ara-C* may result from a defect in the transport process, a change in phosphorylating enzymes, or an increased pool of the natural dCTP nucleotide. Increased deamination to uracil arabinoside, ara-U, a pharmacologically inactive metabolite, can also cause resistance.

3. **Therapeutic indications:** The major clinical use is in acute nonlymphocytic (myelogenous) leukemia in combination with *6-TG* (see p. 382) and *daunorubicin* (see p. 385).

4. **Pharmacokinetics:** *Ara-C* is not effective when given orally because of its deamination to the noncytotoxic uracil arabinoside (ara-U) by cytidine deaminase in the intestinal mucosa. Given IV, it distributes throughout the body, but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia. However, it may be injected intrathecally. *Ara-C* undergoes exten-

sive oxidative deamination in the body to ara-U. Both *ara-C* and ara-U are excreted by the kidney.

5. **Adverse effects:** Nausea, vomiting, diarrhea, and severe myelosuppression (primarily granulocytopenia) are the major toxicities. Hepatic dysfunction is also occasionally encountered. At high doses or intrathecal injection, *ara-C* may cause seizures or altered mental states.



F. Fludarabine

Fludarabine [flu DARE a been] is the 5' phosphate of 2-fluoro-adenine arabinoside, an unnatural purine nucleotide. Although the exact cytoxic lesion is uncertain, the triphosphate is incorporated into both DNA and RNA to decrease their synthesis and alter their function. *Fludarabine* is useful in the treatment of chronic lymphocytic leukemia. It may replace *chlorambucil*, the present drug of choice. *Fludarabine* is also effective against hairy-cell leukemia. It is administered intravenously rather than orally because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine. Urinary excretion accounts for partial elimination. In addition to nausea, vomiting and diarrhea, myelosuppression is the dose-limiting toxicity. Fever, edema, and severe neurologic toxicity also occur. At high doses, progressive encephalopathy, blindness, and death have been reported.

IV. ANTIBIOTICS

These drugs owe their cytotoxic action to their interactions with DNA, leading to disruption of DNA function. They are cell-cycle specific.

A. Dactinomycin

Dactinomycin [dak ti noe MYE sin], known to biochemists as *actinomycin D*, was the first antibiotic to find therapeutic application in tumor chemotherapy.

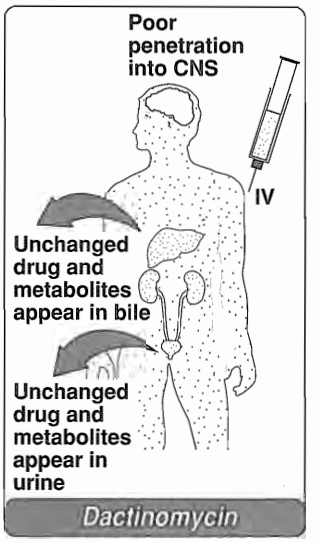
1. **Site of action:** The drug intercalates into the small groove of the double helix between guanine-cytosine base pairs of DNA, forming a stable *dactinomycin*-DNA complex. The complex interferes primarily with DNA-dependent RNA polymerase, although at high doses, *dactinomycin* also hinders DNA synthesis. The drug may also cause strand breaks. Evidence exists that *dactinomycin* stabilizes the DNA-topoisomerase II complex (see p. 397).

2. **Resistance:** Resistance is due to an increased efflux of the antibiotic from the cell via P-glycoprotein (see p. 377). DNA repair may also play a role.

3. **Therapeutic applications:** *Dactinomycin* is used in combination with surgery and *vincristine* (see p. 390) for the treatment of Wilm's tumor. With *methotrexate* (see p. 378) it is effective in the treatment of gestational choriocarcinoma. Some soft-tissue sarcomas also respond.

4. **Pharmacokinetics:** The drug, administered intravenously, is concentrated in the liver where it is partially metabolized. *Dactinomycin* does not enter the cerebrospinal fluid. Most of the parent drug and its metabolites are slowly excreted via the bile, and the remainder via the urine.

5. **Adverse effects:** The major dose-limiting toxicity is bone marrow depression, and the drug is immunosuppressive. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, and alopecia. Extravasation during injection produces serious problems. *Dactinomycin* sensitizes to radiation; inflammation at sites of prior radiation therapy may occur.



B. Doxorubicin and daunorubicin

Doxorubicin [dox oh ROO bi sin] and *daunorubicin* [daw noe ROO bi sin] are classified as anthracycline antibiotics. *Doxorubicin*, often referred to by its trade name *adriamycin*, is the hydroxylated analog of *daunorubicin*. *Idarubicin*, the 4-demethoxy analog of *daunorubicin* is also available.

1. **Site of action:** The anthracyclines have three major activities that may vary with the type of cell; all are maximal in the S and G_2 phases:

   a. **Intercalation in the DNA:** The drugs insert nonspecifically between adjacent base pairs and bind to the sugar-phosphate backbone of DNA causing a local uncoiling, thus blocking DNA and RNA synthesis. Intercalation can interfere with the topoisomerase II-catalyzed breakage-reunion reaction of DNA strands to cause unreparable breaks.

   b. **Binding to cell membranes:** This action alters the function of transport processes coupled to phosphatidylinositol activation.

   c. **Generation of oxygen radicals through lipid peroxidation:** Cytochrome P-450 reductase (present in cell nuclear membranes) catalyzes reduction of the anthracyclines to semiquinone free radicals. These in turn reduce molecular O_2, producing superoxide ions and hydrogen peroxide that mediate single strand scission of DNA (Figure 38.10). Tissues with ample superoxide dismutase (SOD) or glutathione peroxidase activity are protected.[6] Tumors and the heart are generally low in SOD. In addition, cardiac tissue lacks catalase and thus cannot dispose of hydrogen peroxide. This may explain the cardiotoxicity of anthracyclines.

2. **Resistance:** Resistance has been ascribed to increased efflux via the amplified transport P-glycoprotein (see p. 377). Cells rich in glutathione peroxidase are also resistant. Decreased cytochrome P-450 reductase, topoisomerase II and DNA repair may also play a role.

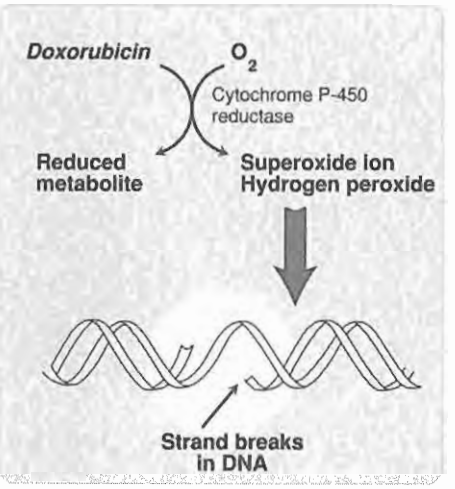
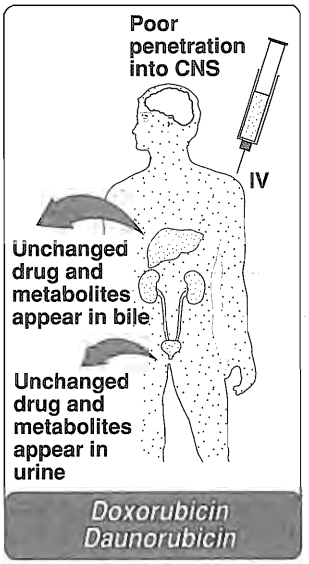


Figure 38.10
Doxorubicin interacts with molecular oxygen producing superoxide ions and hydrogen peroxide which cause single strand breaks in DNA.

[6]See p. 400 for Infolink references to other books in this series.



3. **Therapeutic applications:** Applications for these two agents differ despite their structural similarity and their apparently similar mechanisms of action. *Doxorubicin* is one of the most important and widely used anticancer drugs. It is used for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as acute lymphocytic leukemia and lymphomas. *Daunorubicin* is used in the treatment of acute lymphocytic and myelocytic leukemias.

4. **Pharmacokinetics**

   a. **Absorption and distribution:** Both drugs must be administered intravenously since they are inactivated in the gastrointestinal tract. Extravasation is a serious problem that can lead to tissue necrosis. These drugs bind to plasma proteins as well as to tissues where they are widely distributed. They do not penetrate into the central nervous system.

   b. **Fate:** Both drugs undergo extensive metabolism. The bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function. Some renal excretion also occurs, but the dose generally need not be adjusted in patients with renal failure. The drugs impart a red color to the urine.

5. **Adverse effects:** Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals, is the most serious adverse reaction. Irradiation of the thorax increases the risk of cardiotoxicity. There has been some success with the iron chelator, *dexrazone*, in protecting against the cardiotoxicity of *doxorubicin*. As with *dactinomycin*, both *doxorubicin* and *daunorubicin* also cause a transient bone marrow suppression, stomatitis, and GI tract disturbances. Alopecia is usually severe.

C. Bleomycin

Bleomycin [blee oh MYE sin] is a mixture of different copper chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process.

1. **Site of action:** A DNA-*bleomycin*-Fe(II) complex appears to undergo oxidation to *bleomycin*-Fe(III); the liberated electrons react with oxygen to form superoxide or hydroxide radicals, which in turn attack the phosphodiester bonds of the DNA, resulting in strand breakage and chromosomal aberrations (Figure 38.11). Redox recycling regenerates the Fe(II) form. *Bleomycin* is cell-cycle specific, and causes cells to accumulate in the G_2 phase.

2. **Resistance:** These mechanism(s) have not been elucidated, although experimental systems have implicated increased levels of *bleomycin* hydrolase (or deamidase), glutathione-S-transferase, and possibly increased efflux of the drug. DNA repair also may contribute.

3. **Therapeutic applications:** *Bleomycin* is primarily employed in the treatment of testicular tumors in combination with *vinblastine* (see p. 390) or *etoposide* (see p. 397). Response rates are close to

[8,9]See p. 400 for Infolink references to other books in this series.

100% if *cisplatin* (see p. 395) is added to the regimen. *Bleomycin* is also effective, although not curative, for squamous cell carcinomas and lymphomas.

4. **Pharmacokinetics:** *Bleomycin* is administered by a number of routes, including subcutaneous, intramuscular, intravenous, and intracavitary. The *bleomycin* inactivating enzyme (hydrolase) is high in a number of tissues (liver, spleen), but low in lung and absent in skin, accounting for its toxicity in those tissues. Most of the parent drug is excreted unchanged into the urine by glomerular filtration, necessitating dose adjustment in patients with renal failure.

5. **Adverse effects:** Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. Mucocutaneous reactions and alopecia are common. Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions. *Bleomycin* is unusual in that myelosuppression is rare.

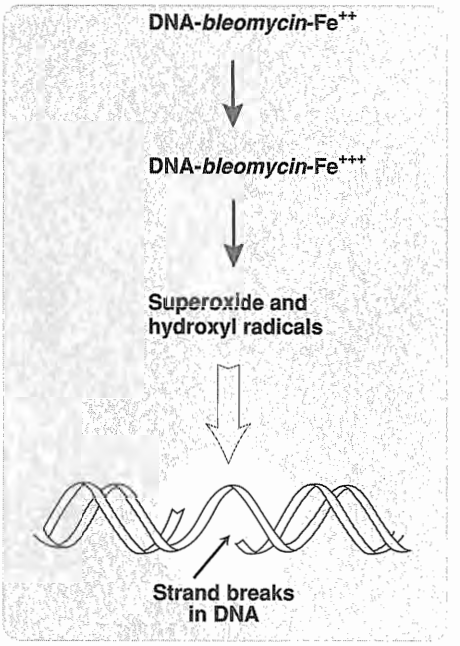


Figure 38.11
Bleomycin causes breaks in DNA by an oxidative process

D. Plicamycin

Plicamycin [plick a MYE sin] (*mithramycin*) also exerts its cytotoxicity through restriction of DNA-directed RNA synthesis. Resistance is due to P-glycoprotein efflux. *Plicamycin* has a relative toxic specificity for osteoclasts preventing their resorption, and lowers plasma calcium concentration in hypercalcemic patients—especially those with bone tumors. Toxicities include hemorrhage as well as effects on the bone marrow, liver, and kidneys.

V. ALKYLATING AGENTS

Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cell. Alkylating agents do not discriminate between cycling and resting cells, but are most toxic for rapidly dividing cells. They are used to treat a wide variety of lymphatic and solid cancers in combination with other agents. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to a second malignancy such as acute leukemia.

A. Mechlorethamine

Mechlorethamine [me klor ETH a meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers. Because it can bind and react at two separate sites, it is called a "bifunctional agent."

1. **Mechanism of action:** *Mechlorethamine* is transported into the cell by a choline uptake process. The drug loses a chloride ion and forms a reactive intermediate that alkylates the N^7 nitrogen of a

guanine residue in one or both strands of a DNA molecule (Figure 38.12). This alkylation leads to cross-linkages between guanine residues in the DNA chains, and/or depurination that facilitates DNA strand breakage. Alkylation can also cause miscoding mutations. Although alkylation can occur in both cycling and resting cells (therefore cell-cycle nonspecific), proliferating cells are more sensitive to the drug, especially those in G_1 and S phases.

2. **Resistance:** Resistance has been ascribed to decreased permeability of the drug, increased conjugation with thiols such as glutathione, and possibly increased DNA repair.

3. **Therapeutic applications:** *Mechlorethamine* is used primarily in the treatment of Hodgkin's disease as part of the **MOPP** regimen (**M**echlorethamine, **O**ncovin, **P**rednisone, **P**rocarbazine), and is also useful in the treatment of some solid tumors.

4. **Pharmacokinetics:** *Mechlorethamine* is very unstable, and solutions must be made up just prior to administration. *Mechlorethamine* is also a powerful vesicant (blistering agent), and is administered only IV, because it can cause severe tissue damage if extravasation occurs. Because of its reactivity, hardly any drug is excreted.

5. **Adverse effects:** Its adverse effects include severe nausea and vomiting (centrally mediated). [Note: These effects can be diminished by pretreatment with *cannabinoids* (see p. 243) or *phenothiazine* (see p. 242).] Severe bone marrow depression limits extensive use. Latent viral infections (for example, Herpes zoster) may appear because of immunosuppression. Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic sodium thiosulfite to inactivate the drug.

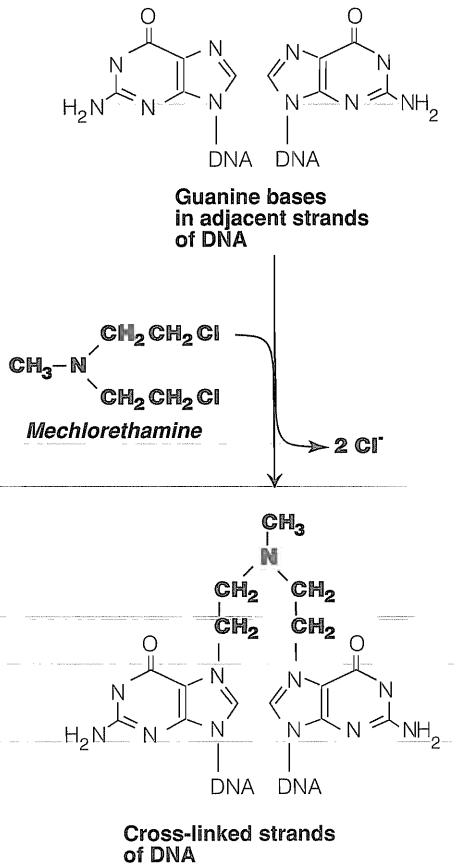


Figure 38.12
Alkylation of guanine bases in DNA is responsible for the cytotoxic effect of *mechlorethamine.*

B. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same toxicities. They are unique in that (1) they can be taken orally, and (2) they are cytotoxic only after generation of their alkylating species, following their hydroxylation by cytochrome P-450.

1. **Mechanism of action:** *Cyclophosphamide* [sye kloe FOSS fa mide] is the most commonly used alkylating agent. Both *cyclophosphamide* and *ifosfamide* [eye FOSS fa mide] are first biotransformed to hydroxylated intermediates by the cytochrome P-450 system (Figure 38.13). The hydroxylated intermediates undergo breakdown to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step. [Note: The therapeutic effect of these drugs is independent of the level of activity of the cytochrome P-450 system.]

2. **Resistance:** Resistance results from increased DNA repair, decreased drug permeability, and reaction of the drug with thiols (for example, glutathione). Cross-resistance, however, does not always occur.

3. **Therapeutic applications:** These agents have a broad clinical spectrum, being used either singly or as part of a regimen in treatment of a wide variety of neoplastic diseases, for example, Burkitt's lymphoma and breast cancer. Non-neoplastic disease entities, such as nephrotic syndrome and intractable rheumatoid arthritis, are also effectively treated with *cyclophosphamide*.

4. **Pharmacokinetics:** Unlike most of the alkylating agents, *cyclophosphamide* and *ifosfamide* are preferentially administered by the oral route. Minimal amounts of the parent drug are excreted into the feces (after biliary transport), or into the urine by glomerular filtration.

5. **Adverse effects:** The most prominent toxicities of both drugs (after alopecia, nausea, vomiting, and diarrhea) are bone marrow depression, especially leukocytosis, and hemorrhagic cystitis, which can lead to fibrosis of the bladder. The latter toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and toxic metabolites of *ifosfamide*. [Note: Adequate hydration as well as intravenous injection of *MESNA* (*sodium 2-mercaptoethane sulfonate*), which inactivates the toxic compounds, minimizes this problem. Other toxicities include effects on the germ cells resulting in amenorrhea, testicular atrophy, and sterility. A fairly high incidence of neurotoxicity has been reported in patients on high-dose *ifosfamide,* probably due to the metabolite, chloroacetaldehyde. Secondary malignancies may appear years after therapy.

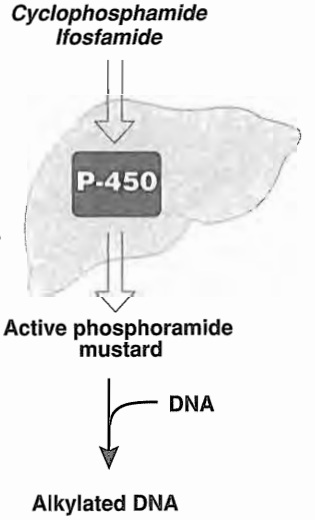


Figure 38.13
Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P-450.

C. Nitrosoureas

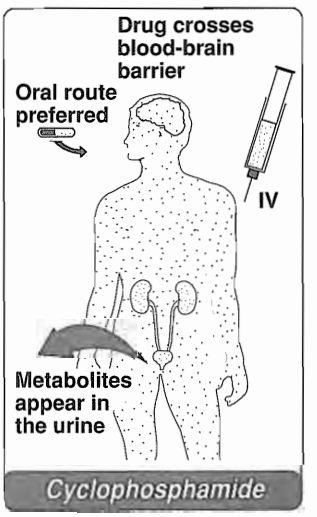
Carmustine [kar MUS teen] and *lomustine* [loe MUSteen] are closely related nitrosoureas. [Note: *Streptozotocin* [strep toe ZOE toe sin] is another nitrosourea that is specifically toxic to the β-cells of the islets of Langerhans. Its use is in the treatment of insulinomas. It is diabetogenic and can cause reversible renal damage.]

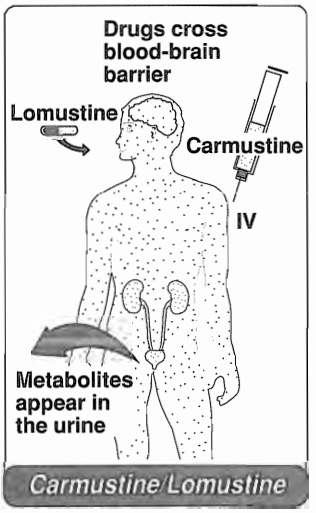
1. **Mechanism of action:** The nitrosoureas exert cytotoxic effects by an alkylation that cross-links strands of DNA to inhibit its replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed only on cell division; therefore nondividing cells can escape death if DNA repair occurs.

2. **Resistance:** Although the true nature of resistance to nitrosoureas is unknown, it probably results from DNA repair and reaction of the drugs with thiols.

3. **Therapeutic applications:** Because of their ability to penetrate into the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors. They find limited use in the treatment of other cancers.

4. **Pharmacokinetics:** In spite of the similarities in their structures, *carmustine* is administered intravenously, whereas *lomustine* is





given orally. Because of their lipophilicity, they distribute to many tissues, but their most striking property is their ability to readily penetrate into the CNS. The drugs undergo extensive metabolism. *Lomustine* is metabolized to active products. The kidney is the major excretory route for the nitrosoureas.

5. **Adverse effects:** These include delayed hematopoietic depression, which may be due to metabolic products. An aplastic marrow may develop on prolonged use. Renal toxicity and pulmonary fibrosis related to duration of therapy is also encountered.

VI. MICROTUBULE INHIBITORS

The mitotic spindle is part of a larger intracellular skeleton (cytoskeleton) that is essential for the internal movements occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin, and a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.

A. Vincristine and vinblastine

Vincristine [vin KRIS teen] and *vinblastine* [vin BLAST een] are structurally-related compounds derived from the periwinkle plant, Vinca rosea. They are therefore referred to as the vinca alkaloids. A structurally related new (and less toxic) agent, *vinorelbine* [vye NO rel been] shows promise in the treatment of advanced non-small cell lung cancer.

1. **Mechanism of action:** *Vincristine* and *vinblastine* are both cycle-specific and phase-specific, because they block mitosis in metaphase. Their binding to the microtubular protein, tubulin, is GTP-dependent and blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 38.14).

2. **Resistance:** Resistant cells have been shown to have enhanced binding of *vinblastine* to the P-glycoprotein, which is responsible for the efflux of *vincristine* and *vinblastine* and several other drugs. Alterations in tubulin structure may also affect binding of the vinca alkaloids.

3. **Therapeutic applications:** Although *vincristine* and *vinblastine* are structurally very similar, their therapeutic indications are different. They are generally administered in combination with other drugs. *Vincristine* is used in the treatment of acute lymphoblastic leukemia in children, Wilm's tumor, Ewing's soft-tissue sarcoma, and Hodgkin's and non-Hodgkin's lymphomas, as well as some

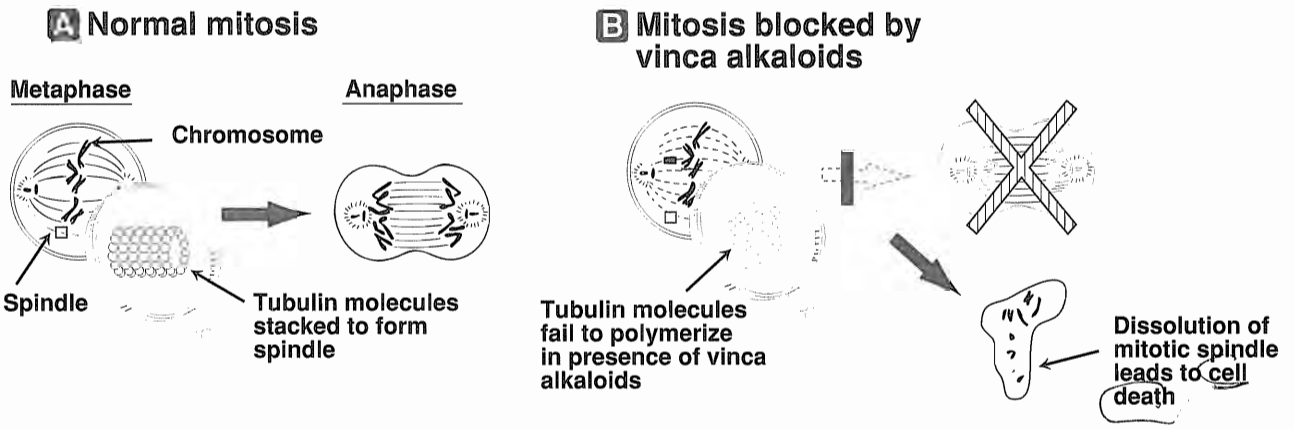


Figure 38.14
Mechanism of action of the microtubule inhibitors.

other rapidly proliferating neoplasms. [Note: *Vincristine* (trade name is ONCOVIN) is the "O" in the MOPP regimen (see p. 388) for Hodgkin's disease and a number of other protocols.] *Vinblastine* is administered with *bleomycin* (see p. 386) and *cisplatin* (see p. 395) for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin's and non-Hodgkin's lymphomas.

4. **Pharmacokinetics:** Intravenous injection of *vincristine* or *vinblastine* leads to rapid cytotoxic effects and cell destruction. This in turn can cause hyperuricemia due to the oxidation of purines to uric acid. The hyperuricemia is ameliorated by administration of the xanthine oxidase inhibitor, *allopurinol* (see p. 417). The agents are concentrated and metabolized in the liver and are excreted into bile and feces. Doses must be modified in patients with impaired hepatic function or biliary obstruction.

5. **Adverse effects:**

   a. **Shared toxicities:** *Vincristine* and *vinblastine* have certain toxicities in common. These include phlebitis or cellulitis, if the drugs extravasate during injection, as well as nausea, vomiting, diarrhea, and alopecia.

   b. **Unique toxicities:** The adverse effects of *vincristine* and *vinblastine* are not identical. *Vinblastine* is a more potent myelosuppressant, whereas peripheral neuropathy (paresthesias, loss of reflexes, footdrop, and ataxia) is associated with *vincristine*. Gastrointestinal problems are also more frequently encountered with *vincristine*.

B. Paclitaxel

Better known as *taxol*, *paclitaxel* (pak lih tax el) is the first member of the taxane family used in cancer chemotherapy. A semi-synthetic *paclitaxel* is now available through chemical modification of a precursor found in the needles of yew species.

1. **Site of action:** *Paclitaxel* binds reversibly to tubulin, but unlike the vinca alkaloids, it promotes polymerization and stabilization of the polymer rather than disassembly (Figure 38.15). Thus it shifts the depolymerization-polymerization to favor the formation of microtubules. The overly stable microtubules formed in the presence of *paclitaxel* are dysfunctional, thereby causing the death of the cell.

2. **Resistance:** Like the vinca alkaloids, resistance has been associated with the presence of amplified P-glycoprotein, or a mutation in tubulin structure.

3. **Therapeutic indications:** *Paclitaxel* has shown good activity against advanced ovarian cancer and metastatic breast cancer. Early trials indicate favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck, and several other cancers. Combination therapy with other anticancer drugs is being evaluated.

4. **Pharmacokinetics:** *Paclitaxel* is infused over 3-4 hours. Hepatic metabolism and biliary excretion are responsible for elimination of *paclitaxel*. Thus dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction.

5. **Adverse effects**

   a. **Hypersensitivity:** Because of serious hypersensitivity reactions (dyspnea, urticaria, and hypotension), the patient to be treated with *paclitaxel* is currently premedicated with *dexamethasone* (see p. 275), and *diphenhydramine* (see p. 422), as well as with an H_2 blocker (see p. 236).

   b. **Neutropenia:** The dose-limiting toxicity of *paclitaxel* is neutropenia. Treatment with granulocyte colony-stimulating factor (*filgrastim*) prevents the problems associated with this condition.

   c. **Other toxicities:** Peripheral neuropathy and a transient asymptomatic bradycardia are sometimes observed. Alopecia occurs, but vomiting and diarrhea are uncommon.

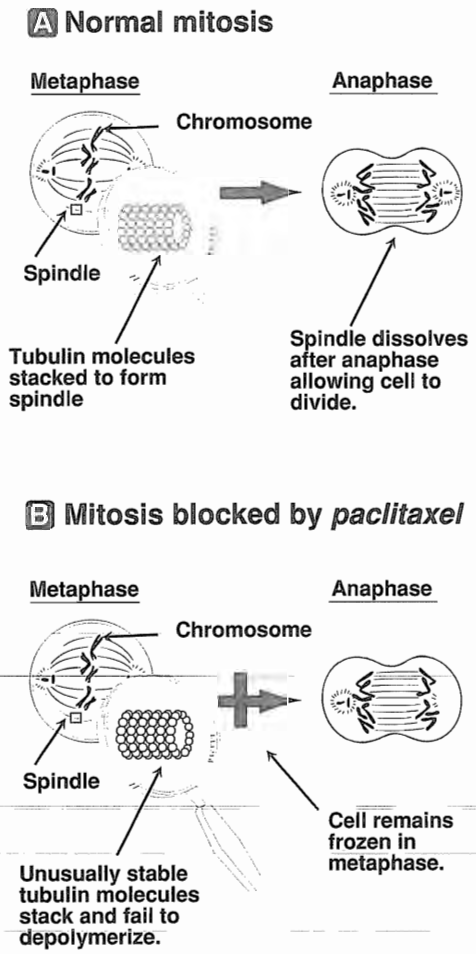


Figure 38.15
Paclitaxel stabilizes microtubules, rendering them nonfunctional.

VII. STEROID HORMONES AND THEIR ANTAGONISTS

Tumors that are steroid hormone-sensitive may be either (1) hormone-responsive, where the tumor regresses following treatment with a specific hormone; (2) hormone-dependent, where removal of a hormonal stimulus causes tumor regression; or (3) both. Hormone treatment of responsive tumors is usually only palliative, except in the case of the cytotoxic effect of glucocorticoids (for example, *prednisone*) on lymphomas. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery, for example, in the case of orchiectomy for patients with advanced prostate cancer, or by drugs, for example in the case of breast cancer, treatment with the antiestrogen

tamoxifen is used to prevent estrogen stimulation of breast cancer cells. For a steroid hormone to have an influence on a cell, that cell must have cytosolic receptors that are specific for that hormone (Figure 38.16A).

A. Prednisone

Prednisone [PRED ni sone] is a potent synthetic anti-inflammatory corticosteroid with less mineralocorticoid activity than cortisol (see p. 272). The use of this compound in the treatment of lymphomas arose when it was observed that patients with Cushing's syndrome (a syndrome associated with hypersecretion of cortisol) have lymphocytopenia and decreased lymphoid mass. These result from corticosteroid action on lymphocyte formation and distribution, that is, movement of these cells from the circulation to lymphoid tissue.

1. **Mechanism of action:** *Prednisone* itself is inactive and must first be reduced to *prednisolone* by 11-β-hydroxysteroid dehydrogenase[7]. The steroid binds to a receptor that triggers the production of specific proteins (see Figure 38.16A). The specific mechanism for its lymphocytopenic action after interaction with DNA remains to be elucidated.

2. **Resistance:** Resistance is associated with an absence of the receptor protein or a mutation that lowers receptor affinity for the hormone. However, some resistant cells appear to have functional receptors, but some subsequent step(s) is affected.

3. **Therapeutic applications:** *Prednisone* is primarily employed to induce remission in patients with acute lymphocytic leukemia, and in the treatment of both Hodgkin's and non-Hodgkin's lymphomas.

4. **Pharmacokinetics:** See p. 272 for a discussion of the pharmacologic aspects of *prednisone* and its toxic actions.

B. Tamoxifen

Tamoxifen [ta MOX i fen] is an estrogen antagonist, structurally related to the synthetic estrogen, *diethylstilbestrol*, and is active in the treatment of estrogen receptor-positive breast cancer. *Tamoxifen* has weak estrogenic activity.

1. **Mechanism of action:** *Tamoxifen* binds to the estrogen receptor but the complex is not productive, that is, the complex fails to induce estrogen-responsive genes and RNA synthesis does not ensue (Figure 38.16B). The result is a depletion of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed. [Note: Estrogen competes with *tamoxifen*; therefore, the drug is not effective in pre-menopausal women.] *Tamoxifen's* action is not related to any specific phase of the cell cycle.

2. **Resistance:** Resistance is associated either with a decreased affinity for the receptor, a decreased number of receptors, or the presence of a dysfunctional receptor.

[7] See p. 400 for Infolink references to other books in this series.

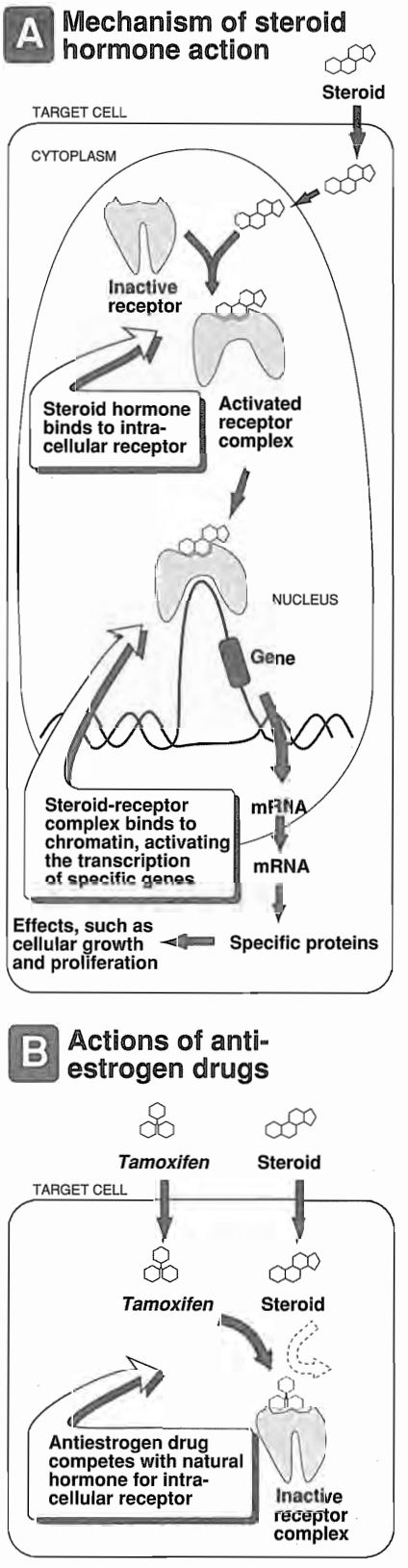


Figure 38.16
Action of steroid hormones and antiestrogen agents.

3. **Therapeutic applications:** Its clinical use is confined to the treatment of estrogen-dependent breast cancers.

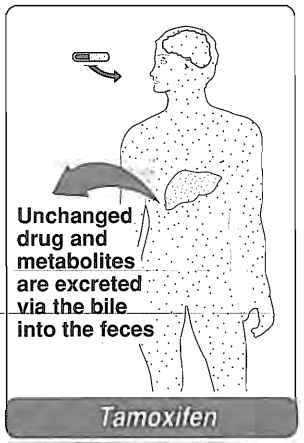
4. **Pharmacokinetics:** *Tamoxifen* is effective on oral administration. It is partially metabolized by the liver. Some metabolites possess antagonist activity while others have agonist activity. Unchanged drug and its metabolites are excreted predominantly through the bile into feces.

5. **Adverse effects:** Side effects are similar to those of natural estrogen, that is, hot flashes, nausea, vomiting, skin rash, vaginal bleeding and discharge (due to some slight estrogenic activity of the drug and some of its metabolites). Hypercalcemia requiring cessation of the drug may also occur. *Tamoxifen* can also lead to increased pain if the tumor has metastasized to bone. *Tamoxifen* has the potential to cause endometrial cancer.

6. **Potential benefits:** *Tamoxifen* is being evaluated for possible protective activity against heart disease and osteoporosis due to its ability to decrease LDL cholesterol and increase bone mineralization.

C. Estrogens

Estrogens, such as *ethinyl estradiol* or *diethylstilbestrol*, are used in the treatment of prostatic cancer. Estrogens inhibit the growth of prostatic tissue by blocking the production of luteinizing hormone and thus decreasing the synthesis of androgens in the testis. Thus, tumors dependent on androgens are affected. Estrogen treatment can cause serious complications, such as thromboemboli, myocardial infarction, strokes, and hypercalcemia. In women, loss of libido may accompany menstrual changes. Men taking estrogens may experience gynecomastia and impotence.



D. Leuprolide and goserelin

The synthetic nonapeptides, *leuprolide* [loo PROE lide] and *goserelin* [gah SER e lin] are analogs of gonadotropin-releasing hormone (GnRH, LHRH). As LHRH agonists, they occupy the LHRH receptor in the pituitary, which leads to its desensitization and consequently inhibition of release of FSH and LH. Thus, androgen and estrogen synthesis are reduced (Figure 38.17). Response to *leuprolide* in prostatic cancer is equivalent to that of orchiectomy (surgical removal of one or both testes), with 40% regression of tumor and relief of bone pain. *Leuprolide* is effective either as a daily (SC) or depot (IM) injection against metastatic carcinoma of the prostate. *Goserelin acetate* is implanted intramuscularly. [Note: Depot forms are administered monthly.] Levels of androgen may initially rise, but then fall to castration levels. The adverse effects of these drugs, including impotence, hot flashes and tumor flare, are minimal compared to those experienced with estrogen treatment.

E. Flutamide

Flutamide [FLEW tah mide] is a synthetic nonsteroidal antiandrogen used in the treatment of prostate cancer. It is metabolized to an active hydroxy derivative that binds to the androgen receptor.

Flutamide blocks the inhibitory effects of testosterone on gonadotropin secretion causing an increase in serum LH and testosterone levels. *Flutamide* is always administered in combination with *leuprolide* or *goserelin*. It is administered orally and cleared through the kidney. Side effects include gynecomastia and gastrointestinal distress.

F. Aminoglutethimide

Aminoglutethimide [ah me no glue TETH i mide] is useful in second line therapy for the treatment of metastatic breast cancer. It inhibits the adrenal synthesis of pregnenolone from cholesterol, and the extra-adrenal aromatase reaction responsible for the synthesis of estrogen from androstenedione. *Aminoglutethimide* is administered orally, and is metabolized by the hepatic cytochrome P-450 system to inactive products. Because of its ability to induce this system, its own metabolism is accelerated, and interactions that increase the metabolism of *dexamethasone* (see p. 275), *theophylline* (see p. 220) and *digoxin* (see p. 158) can occur. *Aminoglutethimide* causes transient CNS depression and a maculopapular rash.

VIII. OTHER CHEMOTHERAPEUTIC AGENTS

A. Cisplatin and carboplatin

Cisplatin [SIS pla tin] is a member of the platinum coordination complex class of anticancer drugs. Because of *cisplatin's* severe toxicity, *carboplatin* [KAR bow pla tin] was developed. The therapeutic effectiveness of the two drugs is similar but their pharmacokinetics, patterns of distribution and dose-limiting toxicities differ. *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents.

1. **Mechanism of action:** Their mechanism of action is similar to that of the alkylating agents. In the high chloride milieu of the plasma, *cisplatin* persists as the neutral species, which enters the cell and binds to the N^7 of guanine of DNA, forming inter- and intra-strand crosslinks. The resulting cytotoxic lesion inhibits both DNA and RNA synthesis. Both drugs can also bind to proteins and other compounds containing SH groups. Cytotoxicity can occur at any stage of the cell cycle, but the cell is most vulnerable to the actions of these drugs in G_1 and S.

2. **Resistance:** Sensitivity to these agents is decreased if cells have elevated glutathione levels or increased DNA repair, or if metallothionein (a protein rich in SH groups) is induced.

3. **Therapeutic applications:** *Cisplatin* has found wide application in the treatment of solid tumors such as metastatic testicular carcinoma in combination with *vinblastine* (see p. 390) and *bleomycin* (see p. 386), ovarian carcinoma in combination with *cyclophosphamide* (see p. 388), or alone for bladder carcinoma. *Carboplatin* is employed when patients cannot be vigorously hydrated as is required for *cisplatin* treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity.

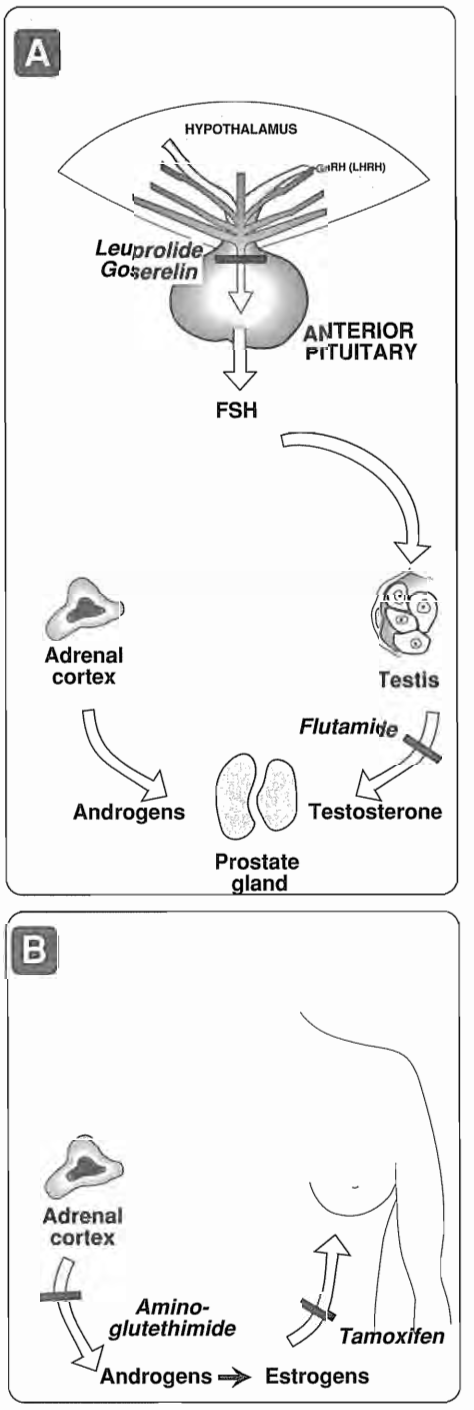
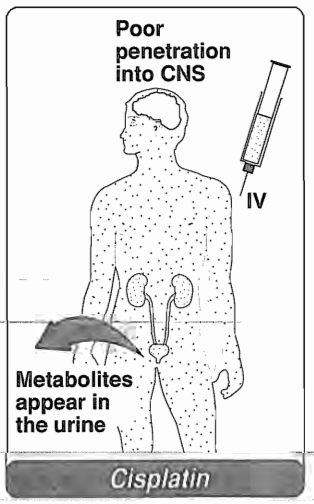


Figure 38.17
Effects of some anticancer drugs on the endocrine system. A. In therapy of prostatic cancer. B. In therapy of postmenopausal breast cancer.

4. **Pharmacokinetics:** *Cisplatin* and *carboplatin* are administered IV in saline solution; they can also be given intraperitoneally for ovarian cancer. Over 90% of *cisplatin* is bound to serum proteins. Highest concentrations are found in liver, kidney, intestinal, testicular and ovarian cells, but little penetrates into the cerebral spinal fluid (CSF). The renal route is the main avenue for excretion.

5. **Adverse effects:** Severe, persistent vomiting occurs 1 hour after administration of *cisplatin* and may continue for as long as 5 days. Premedication with antiemetic agents is usually helpful (see p. 241 for a discussion of antiemetic drugs). The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be ameliorated by aggressive hydration and diuresis. Hypomagnesemia and hypocalcemia usually occur concurrently; it is important to correct calcium levels before correcting magnesium levels. Other toxicities include ototoxicity, with high frequency hearing loss and tinnitus; mild bone marrow suppression; some neurotoxicity characterized by paresthesia and loss of proprioception; and hypersensitivity reactions, ranging from skin rashes to anaphylaxis. Patients receiving aminoglycosides (see p. 314) concomitantly are at a greater risk for nephrotoxicity and ototoxicity. Unlike *cisplatin*, *carboplatin* causes only mild nausea and vomiting and is not nephro- neuro- or ototoxic. Its dose-limiting toxicity is myelosuppression.



B. Etoposide (VP-16)

Etoposide [e toe POE side] and its analog, *teniposide* [TEN ih poe side] are semisynthetic derivatives of the plant alkaloid, podophyllotoxin. They block cells in the late S-G_2 phase of the cell cycle. Their major target is topoisomerase II[8]. Binding of the drugs to the enzyme-DNA complex results in the persistence of the transient cleavable form of the complex and thus renders it susceptible to irreversible double-strand breaks (Figure 38.18). Resistance to topoisomerase inhibitors is conferred by either the presence of the multi-drug resistant P-glycoprotein, or mutation of the enzyme. *Etoposide* finds its major clinical use in the treatment of oat cell carcinoma of the lung and refractory testicular carcinoma. It is currently being tested in other therapeutic protocols. *Etoposide* may be administered either IV or orally. It is highly bound to plasma proteins and distributes throughout the body, but it enters the CSF poorly. Metabolites are converted to glucuronide and sulfate conjugates and are excreted in the urine. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity for both drugs. Other toxicities are alopecia, anaphylactic reactions, nausea, and vomiting. Hypotension may occur if the drug is injected rapidly.

C. Procarbazine

Procarbazine [proe KAR ba zeen] inhibits DNA and RNA sythesis. *Procarbazine* is used in the treatment of Hodgkin's disease as part of the "MOPP" regimen (see p. 388), and also other cancers. *Procarbazine* rapidly equilibrates between the plasma and the CSF after oral or parenteral administration. Metabolites and the parent

[8] See p. 400 for Infolink references to other books in this series.

drug are excreted through the kidney. Bone marrow depression is the major toxicity. Nausea, vomiting, and diarrhea are common. The drug is also neurotoxic, causing symptoms ranging from drowsiness to hallucinations to paresthesias. Because it inhibits monoamine oxidase, patients should be warned against ingesting foods that contain tyramine (for example, aged cheeses, beer, and wine). Ingestion of alcohol leads to a *disulfiram*-type reaction, see p. 96). *Procarbazine* is both mutagenic and teratogenic. Nonlymphocytic leukemia has developed in patients treated with the drug.

D. L-Asparaginase

L-Asparaginase [a SPAR a gi nase] catalyzes the deamination of asparagine to aspartic acid and ammonia. The form of the enzyme used chemotherapeutically is derived from bacteria.

1. **Mechanism of action:** Some neoplastic cells require an external source of asparagine, because of their limited capacity to make sufficient L-asparagine to support growth and function. *L-Asparaginase* hydrolyzes blood asparagine and thus deprives the tumor cells of this nutrient required for protein synthesis (Figure 38.19).

2. **Resistance:** Resistance is due to increased capacity of tumor cells to synthesize asparagine.

3. **Therapeutic application:** *L-Asparaginase* is used to treat childhood acute lymphocytic leukemia in combination with *vincristine* (see p. 390) and *prednisone* (see p. 393).

4. **Pharmacokinetics:** The enzyme must be administered either IV or IM because it is destroyed by gastric enzymes. Disposition remains undefined.

5. **Adverse effects:** Toxicities include a range of hypersensitivity reactions (since it is a foreign protein), a decrease in clotting factors, and liver abnormalities, as well as pancreatitis, seizures, and coma due to ammonia toxicity.

E. Interferons

1. **Classification:** Human interferons have been classified into three type's, α, β, and γ, on the basis of their antigenicity. The α interferons are primarily leukocytic, whereas the β and γ interferons are produced by connective tissue fibroblasts and T lymphocytes, respectively. Recombinant DNA techniques in bacteria have made available large quantities of α *interferon/species A*—designated *α2(A) interferon*—which has the advantage of being purer than previous preparations derived from leukocytes. Currently the other interferons have also been obtained by recombinant techniques.

2. **Site of action:** The exact mechanism by which the interferons are cytotoxic is unknown, but they have the capacity to stimulate natural killer (NK) cells. γ Interferon is also a potent activator of tumoricidal macrophages. Interferon secreted from producing cells interacts with surface receptors on other cells, at which site they

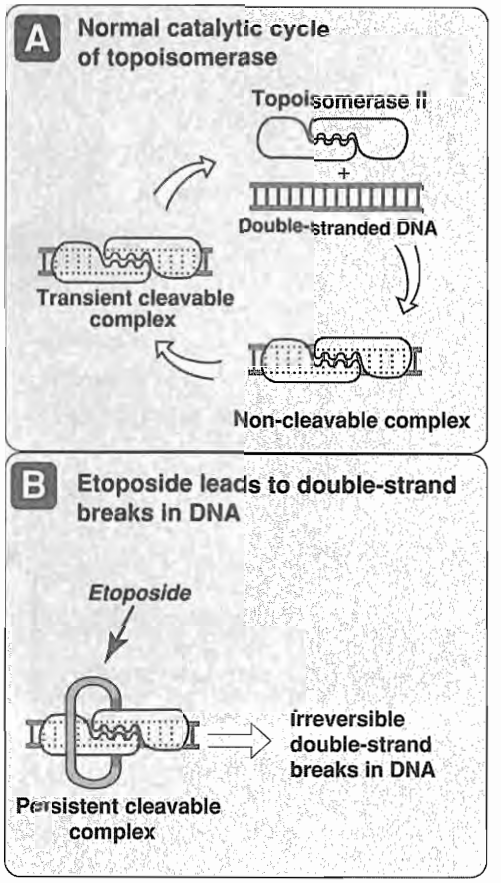


Figure 38.18
Mechanism of action of *etoposide*.

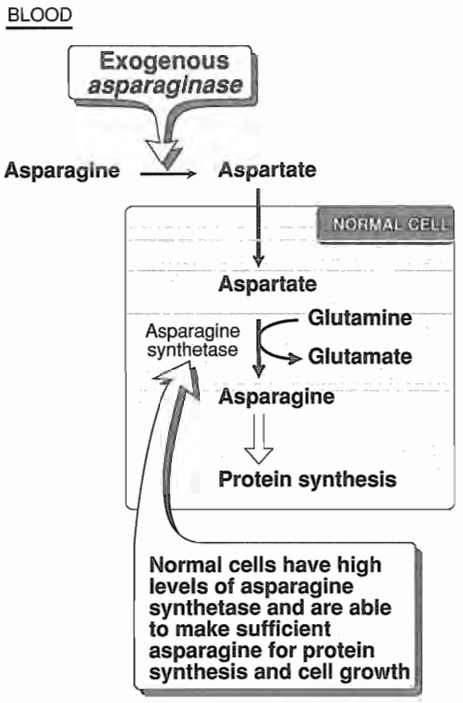
exert their effects. Bound interferons are not internalized nor degraded. The α and β interferons compete for binding and presumably bind at the same receptor or in close proximity; γ interferons bind at different receptors.

3. **Therapeutic indications:** α2(A) *Interferon* is presently approved for the management of hairy cell leukemia. More than 90% of patients treated with α *interferon* have shown resolution of cytopenia, reduction in the incidence of serious infection, and reduction in the need for transfusions. Other interferons are being tested in the treatment of various tumors, including squamous cell carcinoma, melanoma, and multiple myeloma, among others.

4. **Pharmacokinetics:** Interferons are well absorbed after intramuscular injections. Being proteins, they are probably degraded by proteases.

5. **Adverse effects:** Fever with chills occurs during the first few days of treatment. Dose-related toxicity includes leukopenia and possibly thrombocytopenia. Fatigue, malaise, anorexia, weight loss, alopecia, and transient elevation of liver enzymes have also been reported. Transient and reversible nephrotoxicity with proteinuria have been seen at high doses.

The anticancer agents are summarized in Figure 38.20



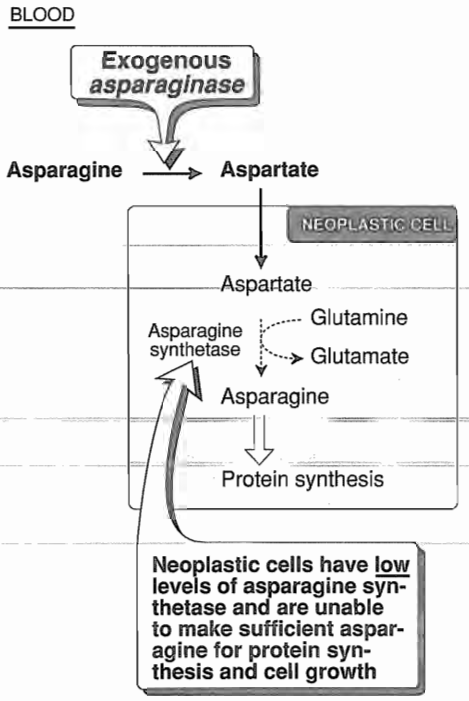


Figure 38.19
Mechanism of action of *L-asparaginase*.

Study Questions

Choose the ONE best answer.

38.1 Which one of the following agents shows cytotoxicity that is cell-cycle specific?

A. Methotrexate.
B. Dactinomycin.
C. Cisplatin.
D. Mechlorethamine.
E. Doxorubicin.

The correct answer = A. Methotrexate shows maximal cytotoxic effects in the S phase. With the exception of bleomycin, all the antibiotic anticancer agents, including dactinomycin and doxorubin, are cell-cycle nonspecific, but they tend to have a greater effect in cycling cells. Cisplatin and the alkylating agents, such as mechlorethamine, are toxic in both cycling and resting cells.

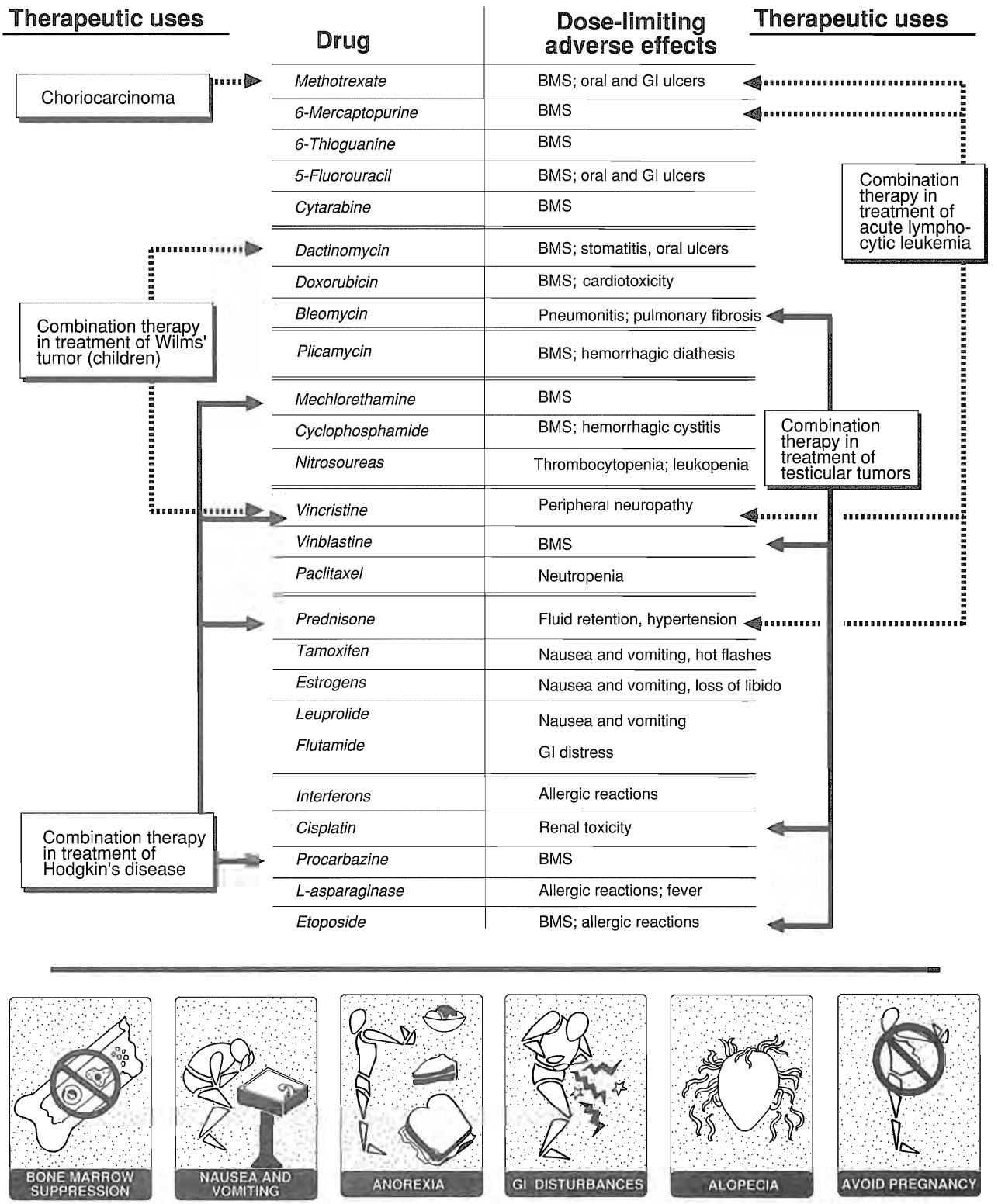


Figure 38.20
Summary of cancer chemotherapy agents. BMS= bone marrow suppression.

38.2 Which one of the following drugs is metabolized to a cytotoxic product?

A. Vincristine.
B. Dactinomycin.
C. 5-Fluorouracil.
D. Lomustine.
E. Paclitaxel.

The correct answer = C. 5-Fluorouracil is devoid of antineoplastic activity and must be converted to the corresponding deoxynucleotide. The other agents exert their cytotoxic effects directly.

38.3 All of the following agents cause their cytotoxic effects by interference in DNA transcription EXCEPT:

A. Doxorubicin.
B. Tamoxifen.
C. Cyclophosphamide.
D. Mechlorethamine.
E. Cisplatin.

The correct choice = B. Tamoxifen binds to the estrogen receptor and acts as an antagonist. Doxorubicin intercalates in DNA and thus interferes in transcription. Cyclophosphamide, mechlorethamine and cisplatin can cross-link with DNA strands to inhibit its function.

38.4 Myelosuppression is a particularly serious toxicity with all of the following EXCEPT:

A. Vinblastine.
B. Cyclophosphamide.
C. Cytarabine.
D. Mechlorethamine.
E. L-Asparaginase.

The correct choice = E. L-Asparaginase is a foreign protein and causes hypersensitivity reactions.

38.5 Cells resistant to methotrexate may

A. have higher than normal levels of dihydrofolate reductase.
B. have higher levels of formyltetrahydrofolate.
C. metabolize the drug to inactive products.
D. have a decreased metabolic need for folate.
E. show an increased uptake of methotrexate.

The correct answer = A. Resistant cells may have elevated levels of dihydrofolate reductase. Methotrexate inhibits dihydrofolate reductase and, therefore, leads to lower than normal levels of the reduced tetrahydrofolate derivatives. Methotrexate does undergo metabolism by the host, but this is not a factor in resistance. The metabolic need for folate is high in all rapidly dividing cells. A decrease in influx may be associated with resistance.

38.6 All of the following statements are true EXCEPT:

A. Patients with Hodgkin's disease being treated with procarbazine should be cautioned against ingesting food derived from fermentative sources.
B. Vincristine is effective in inducing remission in childhood acute lymphocytic leukemia.
C. X-irradiation of the cranio-spinal axis is an effective adjuvant therapy in the treatment of acute lymphocytic leukemia.
D. Treatment with alkylating agents can induce secondary tumors.
E. Tamoxifen complexes with DNA to inhibit RNA synthesis.

The correct choice = E. Tamoxifen forms a complex with the estrogen receptor. Procarbazine inhibits monoamine oxidase, an enzyme required to metabolize tyramine found in fermentative sources, such as cheese and some wines. X-irradiation is effective in eradicating leukemic cells which have found sanctuary in the CNS. Many anticancer drugs are mutagenic and carcinogenic, particularly the alkylating agents.

[1]See p. 325 in **Biochemistry** (2nd ed.)for role of methotrexate in preventing cell division.

[2]See p. 250 in **Biochemistry** (2nd ed.) for a more detailed discussion of tetrahydrofolate metabolism.

[3]See p. 349 in **Biochemistry** (2nd ed.) for a discussion of the salvage pathway of purine metabolism.

[4]See p. 247 in **Biochemistry** (2nd ed.) for a discussion of the feed-back inhibition of purine synthesis.

[5]See p. 350 in **Biochemistry** (2nd ed.) for role of xanthine oxidase in purine degradation.

[6]See p. 114 in **Biochemistry** (2nd ed.) for role of reactive oxygen intermediates.

[7]See p. 224 in **Biochemistry** (2nd ed.) for role of 11-β-hydroxysteroid dehydrogenase in steroid synthesis.

[8]See p. 365 in **Biochemistry** (2nd ed.) for role of topoisomerase in DNA synthesis.

Anti-inflammatory Drugs

39

I. OVERVIEW

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inflammation is sometimes inappropriately triggered by an innocuous agent, such as pollen, or by an autoimmune response, as in asthma or rheumatoid arthritis. In such cases, the defense reactions themselves may cause progressive tissue injury, and anti-inflammatory or immunosuppressive drugs may be required to modulate the inflammatory process. Inflammation is triggered by the release of chemical mediators from injured tissues and migrating cells. The specific chemical mediators vary with the type of inflammatory process and include amines, such as histamine and 5-hydroxytryptamine; lipids, such as the prostaglandins; small peptides, such as bradykinin; and larger peptides, such as interleukin-1. Discovery of the wide variation among chemical mediators has clarified the apparent paradox that an anti-inflammatory drug may interfere with the action of a particular mediator important in one type of inflammation but be without effect in inflammatory processes not involving the drug's target mediator. The drugs described in this chapter are summarized in Figure 39.1. [Note: The use of corticosteroids in the treatment of inflammation is discussed on p. 276.]

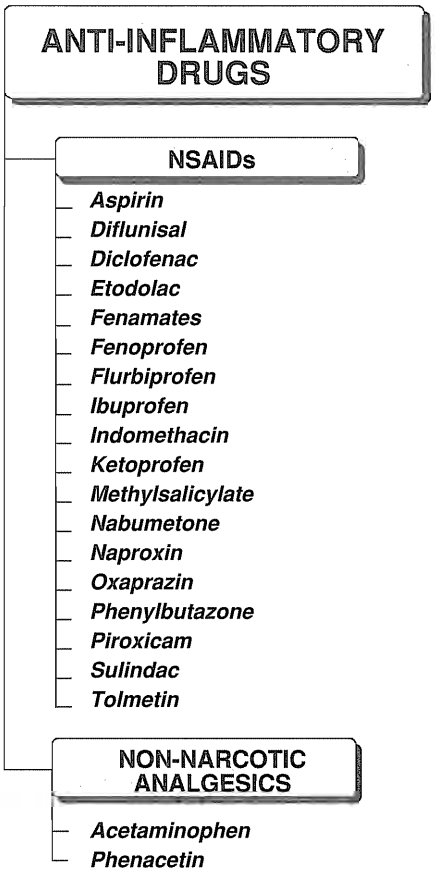


Figure 39.1
Summary of nonsteroidal anti-inflammatory drugs.
(Continued on next page.)

II. PROSTAGLANDINS

Many of the nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires a comprehension of the actions and biosynthesis of prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.] Figure 39.2 illustrates the important structural features of the prostaglandins.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

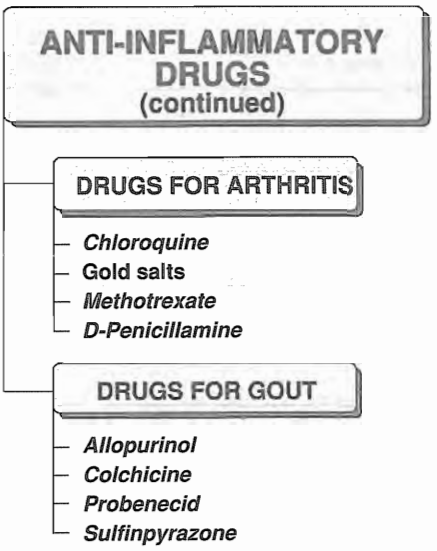


Figure 39.1 (continued)
Summary of nonsteroidal anti-inflammatory drugs.

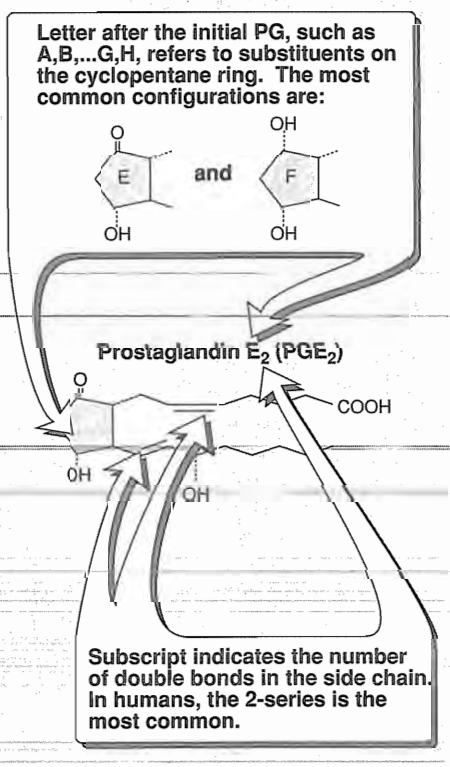


Figure 39.2
Structural features of prostaglandins.

A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes, leukotrienes, and the hydroperoxyeicosatetraenoic and hydroxyeicosatetraenoic acids (HPETEs and HETEs) are related lipids, synthesized from the same precursors as are the prostaglandins, using interrelated pathways (Figure 39.3).

B. Synthesis of prostaglandins

Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds (see Figure 39.3). Arachidonic acid is present as a component of the phospholipids of cell membranes, primarily phosphatidyl inositol and other complex lipids.[1] Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 and other acyl hydrolases, via a process controlled by hormones and other stimuli (see Figure 39.3). There are two major pathways in the synthesis of the eicosanoids from arachidonic acid (see Figure 39.3).

1. **Cyclooxygenase pathway:** All eicosanoids with ring structures, that is, the prostaglandins, thromboxanes, and prostacyclins, are synthesized via the cyclooxygenase pathway. Two cyclooxygenases have been identified: COX-1 and COX-2. The former is ubiquitous and constitutive, whereas the latter is induced in response to inflammatory stimuli. The products of these and subsequent reactions in this pathway are summarized in Figure 39.3.

2. **Lipoxygenase pathway:** Alternatively, several lipoxygenases can act on arachidonic acid to form 5-HPETE, 12-HPETE and 15-HPETE, which are unstable peroxidated derivatives that are converted to the corresponding hydroxylated derivatives (the HETES), or to leukotrienes or lipoxins, depending on the tissue (Figure 39.3).[2]

C. Actions of prostaglandins

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct membrane receptors that operate via G proteins, which subsequently activate or inhibit adenylyl cyclase or stimulate phospholipase C. This causes an enhanced formation of diacylglycerol and inositol-1,4,5-trisphosphate (IP_3). $PGF_{2\alpha}$, the leukotrienes, and thromboxane A_2 (TXA_2) mediate certain actions by activating phosphatidylinositol metabolism and causing an increase of intracellular Ca^{++}. [Note: Some prostaglandin receptor antagonists have been developed but they have no clinical use.]

D. Functions in the body

Prostaglandins and their metabolites produced endogenously in tissues act as local signals that fine-tune the response of a specific cell type. Their functions vary widely depending on the tissue. For example, the release of TXA_2 from platelets triggers the recruitment of new

[1,2]See p. 418 for Infolink references to other books in this series.

platelets for aggregation (the first step in clot formation). However, in other tissues, elevated levels of TXA_2 convey a different signal; for example, in certain smooth muscle, this compound induces contraction. Prostaglandins are one of the chemical mediators that are released in allergic and inflammatory processes (see p. 221).

III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of chemically dissimilar agents that differ in their antipyretic, analgesic and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes but not the lipoxygenase enzymes. *Aspirin* is the prototype of this group; it is the most commonly used and the drug to which all other anti-inflammatory agents are compared. However, about 15% of patients show an intolerance to *aspirin*. Therefore, these individuals may benefit from other NSAIDs. In addition, some of the newer NSAIDs are marginally superior to *aspirin* in certain patients, because they have greater anti-inflammatory activity and/or cause less gastric irritation, or can be taken less frequently. However, the newer NSAIDs are considerably more expensive than *aspirin*, and some have proved to be more toxic in other ways.

A. Aspirin and other salicylates

Aspirin [AS pir in] is a weak organic acid that is unique among the NSAIDs in irreversibly acetylating (and thus inactivating) cyclooxygenase (Figure 39.4). The other NSAIDs, including salicylate, are all reversible inhibitors of cyclooxygenase. [Note: The NSAIDs do not appear to be strictly selective for either of the cyclooxygenase isozymes. Theoretically, selective inhibition of COX-2 might be advantageous because it would be confined to inflamed tissues.] *Aspirin* is rapidly deacetylated by esterases in the body, producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects. [Note: *Diflunisal* [dye FLOO ni sal], a diflurophenyl derivative of salicylic acid, is not metabolized to salicylate and therefore cannot cause salicylate intoxication (see p. 406). *Diflunisal* is 3 to 4 times more potent than *aspirin* as an analgesic and an anti-inflammatory agent, but it has no antipyretic properties. *Diflunisal* does not enter the CNS and therefore cannot relieve fever.]

1. **Mechanism of action:** The antipyretic and anti-inflammatory effects of the salicylates are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites. Furthermore, by decreasing prostaglandin synthesis, the salicylates also prevent the sensitization of pain receptors to both mechanical and chemical stimuli. *Aspirin* may also depress pain stimuli at subcortical sites (that is, the thalamus and hypothalamus).

2. **Actions**

   The NSAIDs, including *aspirin*, have three major therapeutic actions, namely they reduce inflammation (antiinflammation), pain (analgesia), and fever (antipyrexia, see Figure 39.5). However, as described later in this section, not all of the NSAIDs are equally potent in each of these actions.

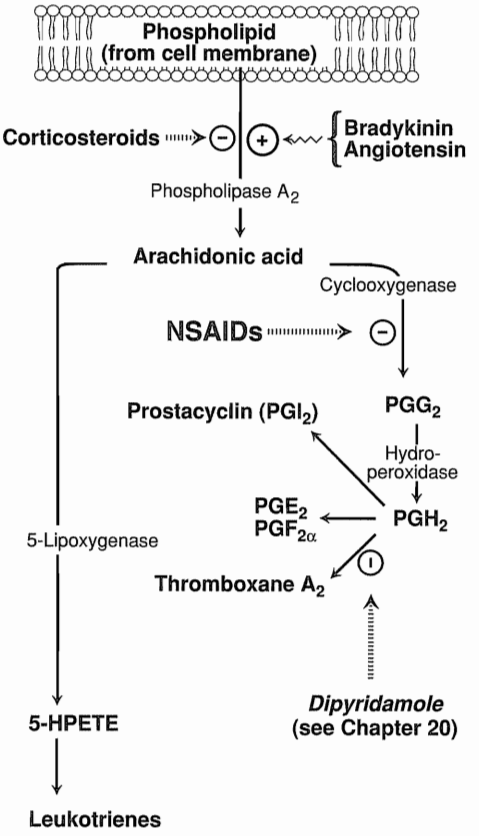


Figure 39.3
Synthesis of prostaglandins and leukotrienes.

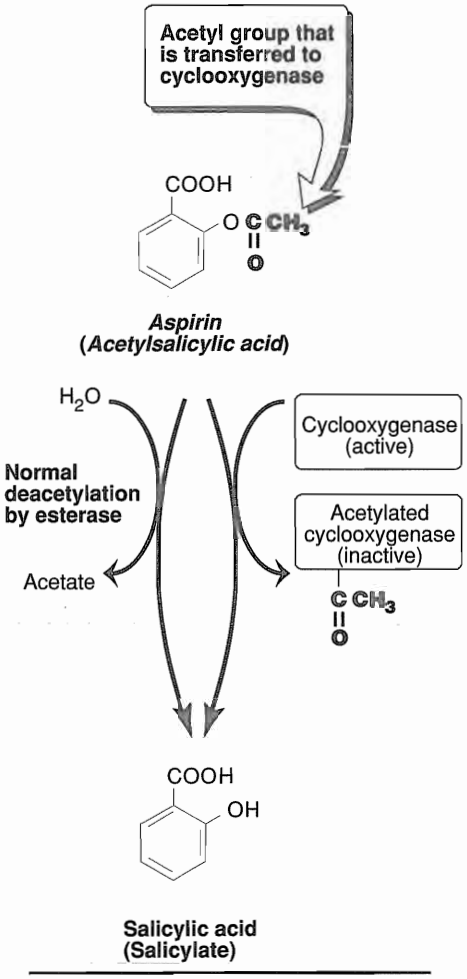


Figure 39.4
Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.

a. Anti-inflammatory actions: Because *aspirin* inhibits cyclooxygenase activity, it diminishes the formation of prostaglandins and thus modulates those aspects of inflammation in which prostaglandins act as mediators (see Figure 39.3). *Aspirin* inhibits inflammation in arthritis, but it neither arrests the progress of the disease nor does it induce remission. [Note: *Acetaminophen*, although a useful analgesic and antipyretic, has weak anti-inflammatory activity and is therefore not useful in the treatment of inflammation such as that seen with rheumatoid arthritis (see Figure 39.5). *Acetaminophen* is therefore discussed separately (see p. 412).]

b. Analgesic action: Prostaglandin E_2 (PGE_2) is thought to sensitize the nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, *aspirin* and other NSAIDs repress the sensation of pain. The salicylates are used mainly for the management of pain of low to moderate intensity arising from integumental structures rather than that arising from the viscera. NSAIDs are superior to opioids in the management of pain in which inflammation is involved; combinations of opioids and NSAIDs are effective in treating pain in malignancy.

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, stimulated when an endogenous fever-producing agent (pyrogen) such as a cytokine is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation. The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release. *Aspirin* resets the "thermostat" toward normal and rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. *Aspirin* has no effect on normal body temperature.

d. Respiratory actions: At therapeutic doses, *aspirin* increases alveolar ventilation. [Note: Salicylates uncouple oxidative phosphorylation, which leads to elevated CO_2 and increased respiration.] Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that is usually adequately compensated for by the kidney. At toxic levels, central respiratory paralysis occurs and respiratory acidosis ensues due to continued production of CO_2.

e. Gastrointestinal effects: Normally, prostacyclin (PGI_2) inhibits gastric acid secretion, whereas PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. In the presence of *aspirin*, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection. This may cause epigastric distress, ulceration, and/or hemorrhage. At ordinary *aspirin* doses, as

much as 3 to 8 ml of blood may be lost in the feces per day. [Note: Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. The PGE_1 derivative, *misoprostol*, is used in the treatment of gastric damage induced by NSAIDs (see p. 238).]

f. Effect on platelets: TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. Low doses (60 to 80 mg daily) of *aspirin* can irreversibly inhibit thromboxane production in platelets without markedly affecting TXA_2 production in the endothelial cells of the blood vessel. [Note: The acetylation of cyclooxygenase is irreversible. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days). This contrasts with the endothelial cells, which have nuclei and therefore can produce new cyclooxygenase.] As a result of the decrease in TXA_2, platelet aggregation (the first step in thrombus formation) is reduced, producing an anticoagulant effect with a prolonged bleeding time. [Note: The actions of *aspirin* as an antithrombotic drug are described on p. 197.]

g. Actions on the kidney: Cyclooxygenase inhibitors prevent the synthesis of PGE_2 and PGI_2–prostaglandins that are responsible for maintaining renal blood flow, particularly in the presence of circulating vasoconstrictors (Figure 39.6). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients. Interstitial nephritis can also occur with all of the NSAIDs except *aspirin*.

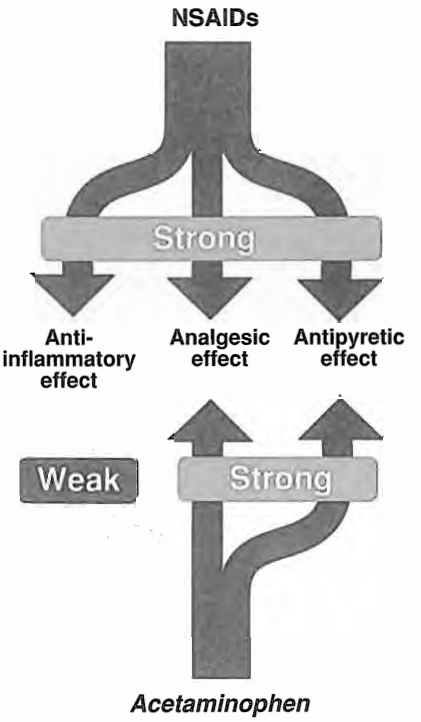


Figure 39.5
Actions of NSAIDs and *acetaminophen*.

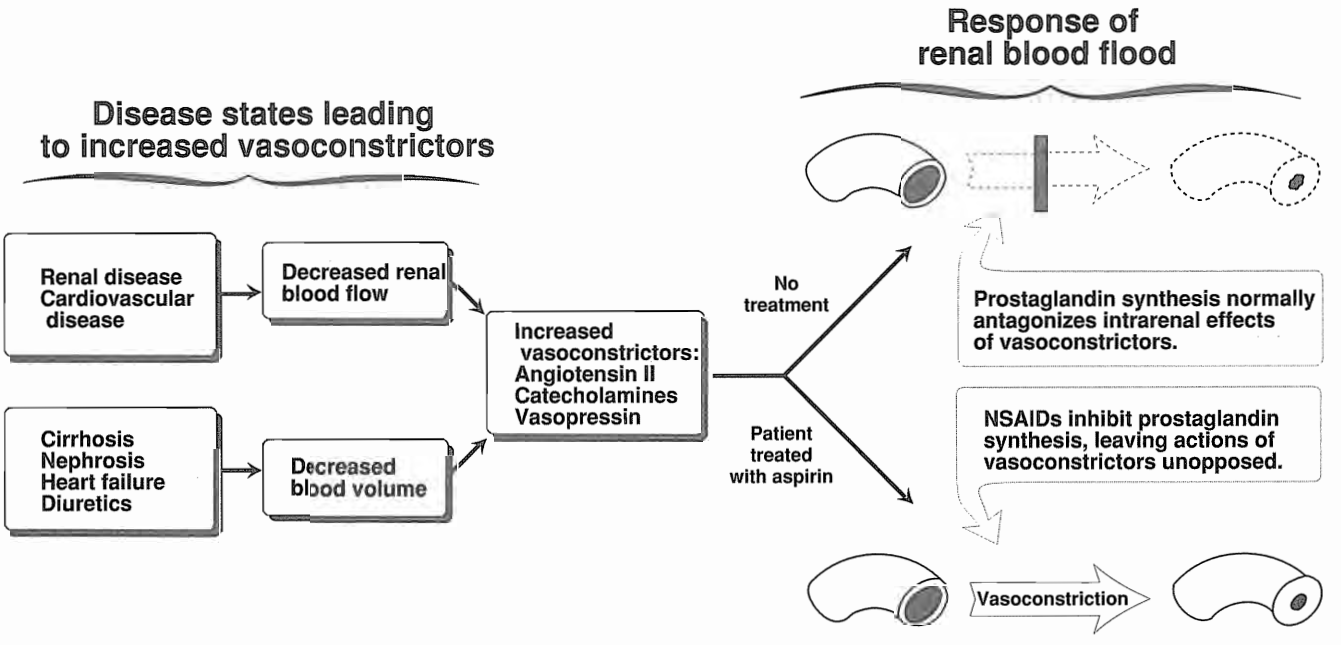


Figure 39.6
Renal effect of *aspirin* inhibition of prostaglandin synthesis.

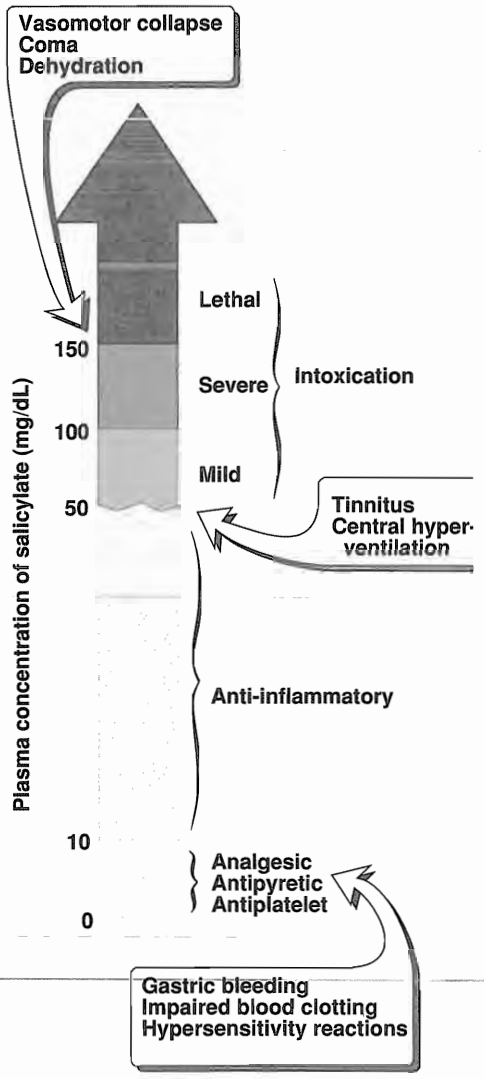


Figure 39.7
Dose-dependent effects of salicylate.

3. Therapeutic uses

a. Antipyretics and analgesics: *Sodium salicylate*, *choline salicylate* (in the liquid formulation), *choline magnesium salicylate*, and *aspirin* are used as antipyretics and analgesics in the treatment of gout, rheumatic fever, and rheumatoid arthritis. [Note: Salicylates are the drugs of choice in the treatment of rheumatoid arthritis.] Commonly treated conditions requiring analgesia include headache, arthralgia, and myalgia.

b. External applications: *Salicylic acid* is used topically to treat corns, calluses, and epidermophytosis (an eruption caused by fungi). *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments.

c. Cardiovascular applications: Salicylates are used to inhibit platelet aggregation (see above). Low doses of *aspirin* are used prophylactically to decrease the incidence of transient ischemic attack and unstable angina in men as well as that of coronary artery thrombosis. (See p. 197 for a further discussion of this phenomenon). *Aspirin* also facilitates closure of a patent ductus arteriosus (PGE_2 is responsible for keeping the ductus arteriosus open).

d. Colon cancer: There is evidence that chronic use of *aspirin* reduces the incidence of colorectal cancer.

4. Pharmacokinetics

a. Administration and distribution: Salicylates, especially *methyl salicylate*, are absorbed through intact skin. After oral administration, the unionized salicylates are passively absorbed from the stomach and the small intestine (dissolution of the tablets is favored at the higher pH of the gut). Rectal absorption of the salicylates is slow and unreliable, but it is a useful route for administration to vomiting children. Salicylates (except for *diflunisal*) cross both the blood-brain barrier and the placenta.

b. Dosage: The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity (Figure 39.7). For example, two 300 mg *aspirin* tablets administered 4 times a day produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity. Low dosages of *aspirin* (160 mg every other day) have been shown to reduce the incidence of recurrent myocardial infarction and to reduce mortality in postmyocardial infarction patients. Further, *aspirin* in a dose of 160 to 325 mg/day appears to be beneficial in the prevention of a first myocardial infarction, at least in men over the age of 50 years. Thus, prophylactic *aspirin* therapy is advocated in patients with clinical manifestations of coronary disease if no specific contraindications are present.

c. Fate: At normal low dosages (600 mg/day), *aspirin* is hydrolyzed to salicylate and acetic acid by esterases present in tissues and blood (see Figure 39.4). Salicylate is converted

by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in elimination with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dosages (>4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, with the drug having a half-life of 15 hours or more (Figure 39.8). Saturation of the hepatic enzymes requires treatment for several days to 1 week. Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion. At low doses of *aspirin,* uric acid secretion is decreased; at high doses, it is increased. [Note: Alkalinization of the urine promotes excretion.]

5. Adverse effects

a. GI: The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Microscopic GI bleeding is almost universal in patients treated with salicylates. [Note: *Aspirin* is an acid. At stomach pH, *aspirin* is uncharged; consequently it readily crosses into the mucosal cells where it ionizes (becomes negatively charged) and becomes trapped (see p. 23 for discussion of ion trapping), thus potentially causing direct damage to the cells. *Aspirin* should be taken with food and large volumes of fluids to diminish GI disturbances. Alternatively, *misoprostol* (see p. 238) may be taken concurrently.]

b. Blood: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA_2, resulting in inhibition of platelet aggregation and a prolonged bleeding time. For this reason *aspirin* should not be taken for at least 1 week prior to surgery. When salicylates are administered, anticoagulants may have to be given in reduced dosage.

c. Respiration: In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

d. Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation. The energy normally used for the production of ATP is dissipated as heat, which explains the hyperthermia caused by salicylates when taken in toxic quantities.

e. Hypersensitivity: Approximately 15% of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, or angioneurotic edema. Fatal anaphylactic shock is rare.

f. Reye's syndrome: *Aspirin* given during viral infections has been associated with an increased incidence of Reye's syndrome, an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who therefore should be given *acetaminophen* instead of *aspirin* when such medication is required.

g. Drug interactions: Concomitant administration of salicylates with many classes of drugs may produce undesirable side effects (Figure 39.9).

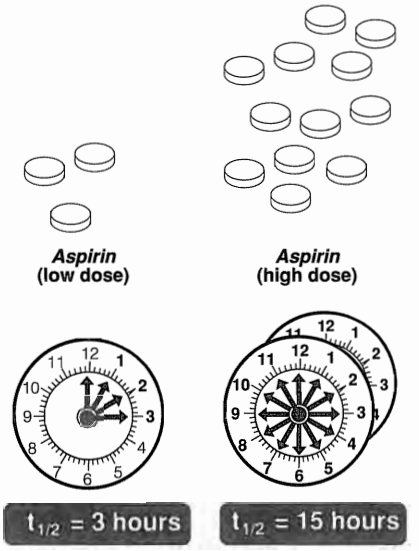


Figure 39.8
Effect of dose on the half-life of *aspirin.*

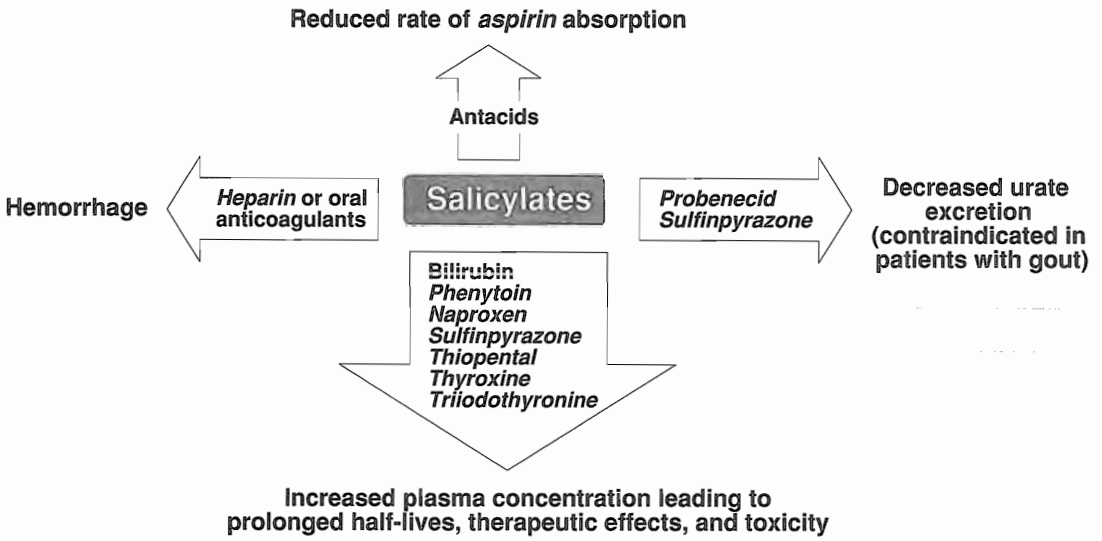


Figure 39.9
Drugs interacting with salicylates.

6. **Toxicity:** Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result (see Figure 39.7). The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *aspirin* (or 5 g of *methyl salicylate*, the latter being used as a counterirritant in liniments) can cause death in children. Treatment of salicylism should include measurement of serum salicylate concentrations and of pH to determine the best form of therapy. In mild cases, symptomatic treatment is usually sufficient. Increasing the urinary pH enhances the elimination of salicylate. In serious cases, mandatory measures include the intravenous administration of fluid, dialysis (hemodialysis or peritoneal dialysis), and the frequent assessment and correction of acid-base and electrolyte balances. [Note: *Diflunisal* does not cause salicylism.]

B. Propionic acid derivatives.

Ibuprofen [eye byoo proe fen] was the first in this class of agents to become available in the United States. It has been joined by *naproxen* [nah PROX en], *fenoprofen* [fen oh proe fen], *ketoprofen* [key toe proe fen], *flurbiprofen* [flur bye proe fen]. and *oxaprozin* [ox ah PROE zin]. All of these drugs possess anti-inflammatory, analgesic and antipyretic activity and have gained wide acceptance in the chronic treatment of rheumatoid and osteoarthritis because their gastrointestinal effects are generally less intense than that of *aspirin*. These drugs are reversible inhibitors of the cyclooxygenases and thus, like *aspirin*, inhibit the synthesis of prostaglandins but not that of leukotrienes. All are well absorbed on oral administra-

tion and are almost totally bound to serum albumin. [Note: *Oxaprozin* has the longest half-life and is administered once daily.] They undergo hepatic metabolism and are excreted by the kidney. The most common adverse effect is gastrointestinal, ranging from dyspepsia to bleeding. Side effects involving the CNS, such as headache, tinnitus and dizziness, have also been reported.

C. Indoleacetic acids

This group of drugs includes *indomethacin* [in doe METH a sin], *sulindac* [sul IN dak] and *etodolac* [eh TOE doh lak]. All have anti-inflammatory, analgesic and antipyretic activity. They act by reversibly inhibiting cyclooxygenase. They are generally not used to lower fever.

1. **Indomethacin:** This NSAID is more potent than *aspirin* as an anti-inflammatory agent, but it is inferior to the salicylates at doses tolerated by rheumatoid arthritic patients. In certain instances, however (for example, with acute gouty arthritis, ankylosing spondylitis, and osteoarthritis of the hip), *indomethacin* is more effective in relieving inflammation than is *aspirin* or any of the other NSAIDs.

   a. **Therapeutic uses:** Despite its potency as an anti-inflammatory agent, *indomethacin's* toxicity limits its use to the treatment of the conditions described above. *Indomethacin* is also beneficial in the control of pain associated with uveitis and postoperative ophthalmic procedures, and as an antipyretic for Hodgkin's disease, when the fever is refractory to other agents. Like *aspirin*, *indomethacin* can delay labor by suppressing uterine contractions. It is also effective in treating patent ductus arteriosus.

   b. **Pharmacokinetics:** *Indomethacin* is rapidly and almost completely absorbed from the upper GI tract after oral administration. It is metabolized by the liver. Unchanged drug and metabolites are excreted in bile and urine.

   c. **Adverse effects:** Adverse effects with *indomethacin* occur in up to 50% of patients treated; approximately 20% find the adverse effects to be intolerable (Figure 39.10) and discontinue use of the drug. Most adverse effects are dose-related. GI complaints consist of nausea, vomiting, anorexia, diarrhea, and abdominal pain. Ulceration of the upper GI tract can occur, sometimes with perforation and hemorrhage. The most severe and frequent CNS effect is frontal headache, which occurs in 25 to 50% of patients who chronically use *indomethacin*. Other frequent CNS effects are dizziness, vertigo, light-headedness, and mental confusion. Acute pancreatitis has been known to occur. Hepatic effects are rare, but some fatal cases of hepatitis and jaundice have been reported. Hematopoietic reactions reported with *indomethacin* include neutropenia, thrombocytopenia, and (rarely) aplastic anemia. Hypersensitivity reactions include rashes, urticaria, itching, acute attacks of asthma, and 100% cross-reactivity with *aspirin*. Concurrent administration of *indomethacin* may decrease the antihypertensive effects of *furosemide*, the thiazide diuretics, β-blocking drugs and ACE inhibitors.

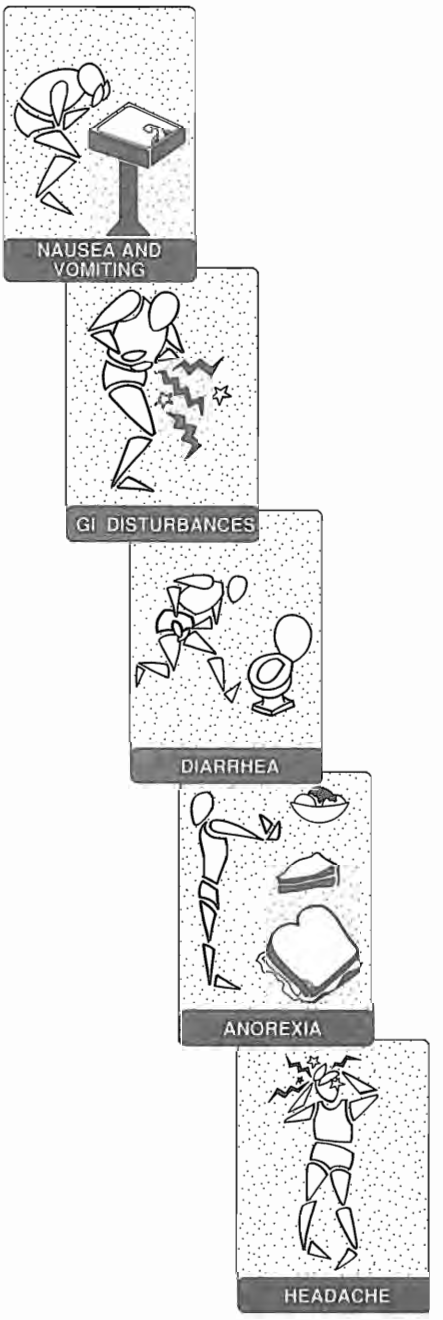


Figure 39.10
Some adverse effects of *indomethacin*.

2. **Sulindac:** This inactive pro-drug is closely related to *indomethacin*. Metabolism by hepatic microsomal enzymes produces the active form (a sulfide) of the drug, which has a long duration of action. Although the drug is less potent than *indomethacin*, it is useful in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout. The adverse reactions are similar to but less severe than those of the other NSAIDs, including *indomethacin*.

3. **Etodolac:** This drug has effects similar to those of the other NSAIDs. Gastrointestinal problems may be less common. However, other adverse effects such as fluid retention and abnormal kidney and liver function have been reported. *Etodolac* may increase the serum levels and thus raise the risk of adverse reactions caused by *digoxin, lithium*, *methotrexate*, and enhance the nephrotoxicity of *cyclosporine*.

D. Oxicam derivatives

Presently, only *piroxicam* [peer OX i kam] is available in the United States. Other members of this group are being tested and may become available. Its mechanism of action has not been established, but *piroxicam* is used to treat rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. Its mean half-life of 50 hours permits administration once a day. GI disturbances are encountered in approximately 20% of patients. The drug and its metabolites are excreted in the urine. *Piroxicam* can interfere with the renal excretion of *lithium*.

E. Fenamates

Mefenamic acid [meh FEN a mick] and *meclofenamate* [meh KLO fen a mate] have no advantages over the other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be severe and associated with inflammation of the bowel. Cases of hemolytic anemia have been reported.

F. Phenylbutazone

Phenylbutazone [fen ill BYOO ta zone] has powerful anti-inflammatory effects but weak analgesic and antipyretic activities. It is not a first line drug.

1. **Therapeutic uses:** *Phenylbutazone* is prescribed chiefly in short-term therapy of acute gout and in acute rheumatoid arthritis when other NSAID agents have failed. The usefulness of *phenylbutazone* is limited by its toxicity. *Aspirin* and newer NSAIDs are superior to *phenylbutazone* in most applications.

2. **Pharmacokinetics:** *Phenylbutazone* is rapidly and completely absorbed after oral or rectal administration. Oxyphenbutazone is an active metabolite and contributes to the activity of the parent drug. Like most of the other NSAIDs, *phenylbutazone* is extensively bound to plasma proteins. This property causes displace-

ment of *warfarin*, oral hypoglycemics and sulfonamides from binding sites on plasma proteins, causing transient elevations in the free fraction of these drugs.

3. **Adverse effects:** *Phenylbutazone* is poorly tolerated by many patients; adverse effects occur in nearly one half of those treated. The most serious adverse effects are agranulocytosis and aplastic anemia. However, the most common adverse effects of *phenylbutazone* are nausea, vomiting, skin rashes, and epigastric discomfort (Figure 39.11). Other side effects include fluid and electrolyte (sodium and chloride) retention, with resulting edema and decreased urine volume. Also, diarrhea, vertigo, insomnia, blurred vision, euphoria, nervousness, and hematuria may occur. *Phenylbutazone* reduces the uptake of iodine by the thyroid gland, sometimes resulting in goiter and myxedema. *Phenylbutazone* can also displace other drugs from plasma proteins, resulting in serious consequences (see above). Because of all these potential side-effects, the drug should be given for short periods of time—up to 1 week only. Patients should be observed closely, and frequent blood tests should be taken.

G. Other agents

1. **Diclofenac:** A cyclooxygenase inhibitor, *diclofenac* [dye KLO fe nak] is approved for long-term use in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondilitis. It is more potent than *indomethacin* or *naproxen*. An ophthalmic preparation is also available. *Diclofenac* accumulates in synovial fluid. The urine is the primary route of excretion for the drug and its metabolites. Its toxicities are similar to those of the other NSAIDs, for example, gastrointestinal problems are common, and the drug can also give rise to elevated hepatic enzyme levels.

2. **Ketorolac:** This drug acts like the other NSAIDs. In addition to the oral route, *ketorolac* [key TOE row lak] can be administered intramuscularly in the treatment of postoperative pain, and topically for allergic conjunctivitis. *Ketorolac* undergoes hepatic metabolism; the drug and its metabolites are eliminated via the urine. It causes the same side effects as the other NSAIDs.

3. **Tolmetin and nabumetone:** *Tolmetin* [TOLL me tin] and *nabumetone* [na BYOO me tone] are as potent as *aspirin* in treating adult or juvenile rheumatoid arthritis or osteoarthritis, but may have fewer adverse effects.

(See Figure 39.12 for a summary of the therapeutic advantages and disadvantages of members of the NSAID family.)

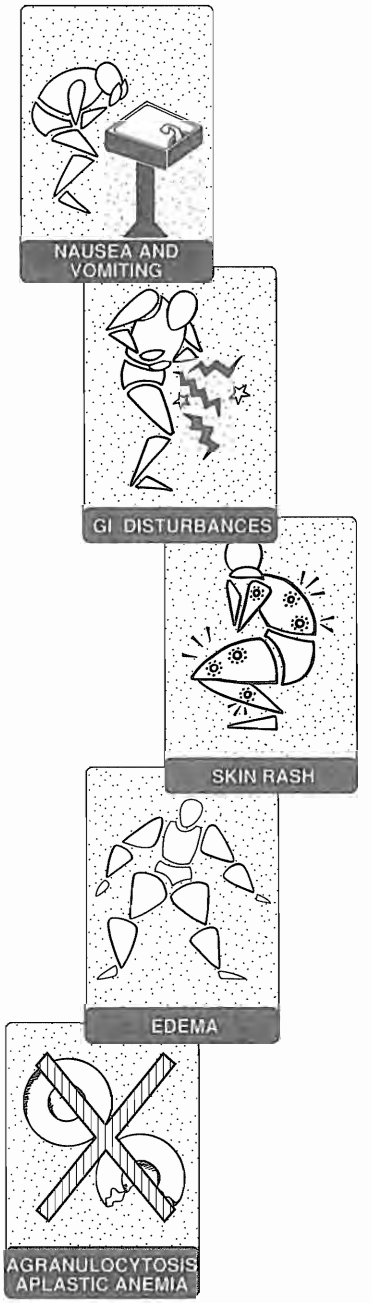


Figure 39.11
Some adverse effects of *phenylbutazone*.

IV. NON-NARCOTIC ANALGESICS

Non-narcotic analgesics, unlike the NSAIDs, have little or no anti-inflammatory activity. They have a therapeutic advantage over narcotic analgesics in that they do not cause physical dependence or tolerance.

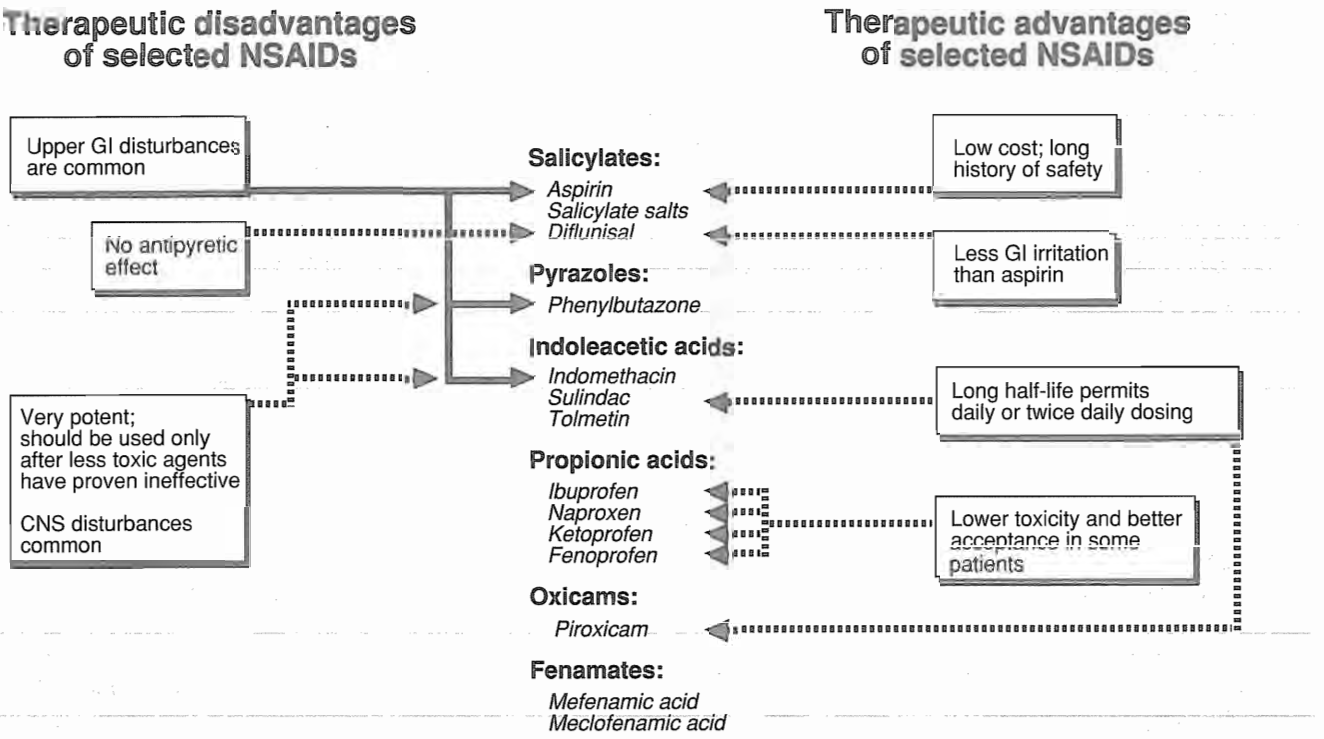


Figure 39.12
Summary of nonsteroidal anti-inflammatory agents (NSAIDs).

A. Acetaminophen and phenacetin

Acetaminophen [a seat a MIN oh fen] and *phenacetin* [fe NASS e tin] act by inhibiting prostaglandin synthesis in the CNS. This explains their antipyretic and analgesic properties. They have less effect on cyclooxygenase in peripheral tissues, which accounts for their weak anti-inflammatory activity. *Acetaminophen* and *phenacetin* do not affect platelet function or increase blood clotting time, and they lack many of the side-effects of *aspirin*. [Note: *Phenacetin* can no longer be prescribed in the United States because of its potential for renal toxicity. However, it is present in some proprietary preparations.]

1. **Therapeutic uses:** *Acetaminophen* is a suitable substitute for the analgesic and antipyretic effects of *aspirin* in those patients with gastric complaints and in those for whom prolongation of bleeding time would be a disadvantage or who do not require the anti-inflammatory action of *aspirin*. [Note: Because of its lower toxicity, *acetaminophen* has replaced *phenacetin* in virtually all headache products.] *Acetaminophen* is the analgesic-antipyretic of choice for children with viral infections or chicken pox (recall that *aspirin* increases the risk of Reye's syndrome, see p. 407). *Acetaminophen* does not antagonize the uricosuric agent *probenecid* and therefore may be used in patients with gout taking that drug.

2. **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. *Phenacetin* is largely converted to *acetaminophen* within 3 hours of administration. 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-benzoquinoneimine—a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of *acetaminophen*, the N-acetyl-benzoquinoneimine reacts with the sulfhydryl group of glutathione, forming a nontoxic substance (see Figure 39.13). *Acetaminophen* and its metabolites are excreted in the urine.

3. **Adverse effects:** With normal therapeutic doses, *acetaminophen* is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. There may be minor alterations in leukocyte count, but these are generally transient. Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged large-dose therapy. With large doses of *acetaminophen,* the available glutathione in the liver becomes depleted and N-acetyl-benzoquinoneimine reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (Figure 39.13). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Renal tubular necrosis may also occur. [Note: Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be life-saving if administered within 10 hours of the overdose.]

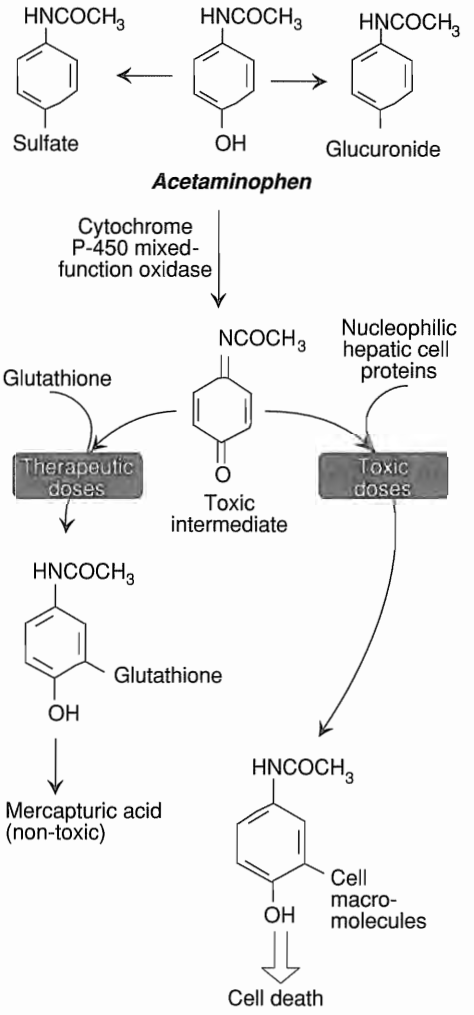


Figure 39.13
Metabolism of *acetaminophen*.

V. SLOW-ACTING, ANTI-INFLAMMATORY AGENTS

In contrast to the NSAID drugs described earlier, remittive (remission-inducing) arthritis drugs are slow-acting. They do not act by inhibiting cyclooxygenase and have no analgesic or primary anti-inflammatory activity. These drugs are used primarily for rheumatic disorders, especially in cases where the inflammation does not respond to cyclooxygenase inhibitors. They slow the course of the disease and may also induce a remission, preventing further destruction of the joints and involved tissues. They have a slow onset of action, sometimes taking 3 to 4 months.

A. Gold salts

Gold compounds, like the other drugs in this group, cannot repair existing damage. Rather, they can only prevent further injury. The currently available gold preparations are *gold sodium thiomalate*, *auroth-ioglucose*, and *auranofin*. It is believed that gold salts are taken up by macrophages and suppress phagocytosis and lysosomal enzyme activity. This mechanism retards the progression of bone and articular destruction. Other mechanisms have also been proposed.

1. **Therapeutic uses:** The major use of gold salts is in the treatment of rheumatoid arthritis that does not respond to salicylates or

other nonsteroidal anti-inflammatory therapy. They are the most effective agents for the rapidly progressive types of the disease, particularly if given in its early stages.

2. **Pharmacokinetics:** *Gold sodium thiomalate* and *aurothioglucose* are water-soluble salts that are administered intramuscularly. *Auranofin* is taken by mouth. If a favorable response is achieved without serious toxic reaction, the drug can be continued indefinitely. The half-life of the drug lengthens with continued use. The gold concentrates in synovial fluid and in macrophages in a number of tissues including liver, kidney, spleen and adrenal cortex. Elimination is largely through the urine but some is also excreted in the feces. Sulfhydryl compounds such as *dimercaprol*, *penicillamine* or *N-acetylcysteine* hasten excretion.

3. **Adverse effects:** *Auranofin* is better tolerated than the injectable compounds. About one third of those patients receiving treatment with gold salts experience some adverse effects, the most common of which is dermatitis of the skin or of the mucous membranes (especially in the mouth), occuring in up to 20% of patients. Other possible adverse effects include proteinuria and nephrosis (5 to 8% of patients) and rare, severe blood disorders, such as agranulocytosis and aplastic anemia. Gold salts should be avoided in patients suffering from hepatic or renal disease, who have a history of toxicity to these agents, are pregnant, or are taking other drugs with a potential for blood dyscrasias. In the event of a serious toxicity, *dimercaprol* is administered.

B. Chloroquine and hydroxychloroquine

The pharmacology of these drugs, which are also used in the treatment of malaria, is presented on p. 351. The mechanism of their anti-inflammatory activity is uncertain. Besides inhibiting nucleic acid synthesis, they are known to stabilize lysosomal membranes and trap free radicals. In treating inflammatory disorders, they are reserved for rheumatoid arthritis that has been unresponsive to the NSAIDs or else they are used in conjunction with an NSAID, which allows a lower dose of *chloroquine* or *hydroxychloroquine* to be administered. These drugs have been shown to slow progression of erosive bone lesions and may induce remission. They do cause serious adverse effects (see p. 351).

C. D-Penicillamine

D-Penicillamine [pen i SILL a meen], an analog of the amino acid cysteine, slows the progress of bone destruction and rheumatoid arthritis. Its mechanism of action is unknown, but rheumatoid factor levels fall with administration. Prolonged treatment with *penicillamine* has serious side effects ranging from dermatologic problems to nephritis and aplastic anemia; therefore it is used primarily in the treatment of rheumatoid arthritis after use of gold salts has failed but before use of corticosteroids has been attempted. [Note: *Penicillamine* is used as a chelating agent in the treatment of poisoning by heavy metals. It is also of benefit in treating cystinuria.]

D. Methotrexate

Methotrexate [meth oh TREX ate] is used for the treatment of patients with severe rheumatoid arthritis who have not responded adequately to NSAIDs and at least one other slow-acting agent. Response to *methotrexate* occurs sooner than is usual for other slow-acting agents—often within 3 to 6 weeks of starting treatment. It is an immunosuppressant, and this may account for its effectiveness in arthritis–an autoimmune disease. Doses of *methotrexate* required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week; therefore the adverse effects (see p. 380) are minimized. The most common side effects observed after *methotrexate* treatment of rheumatoid arthritis are mucosal ulceration and nausea. Cytopenias (particularly depression of the white blood cell count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur on chronic administration. [Note: Taking *leucovorin* a day after *methotrexate* reduces the severity of the adverse effects (see p. 379).] Other immunosuppressants such as *azathioprine* and *cyclosporine* are being investigated as possible anti-inflammatory agents.

VI. DRUGS EMPLOYED IN THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood. This hyperuricemia results in the deposition of crystals of sodium urate in tissues, especially the kidney and joints. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. In humans, sodium urate is the endproduct of purine metabolism.[3] The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals. This process generates oxygen metabolites, which damage tissue, resulting in the release of lysosomal enzymes that evoke an inflammatory response. In addition, lactate production in the synovial tissues increases. The resulting local decrease in pH fosters further deposition of urate crystals. (See Figure 39.14 for a summary of this process.) The cause of hyperuricemia is an overproduction of uric acid relative to the patient's ability to excrete it. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point, thus preventing the deposition of urate crystals. This can be accomplished by (1) interfering with uric acid synthesis with *allopurinol*, (2) increasing uric acid excretion with *probenecid* or *sulfinpyrazone*, (3) inhibiting leukocyte entry into the affected joint with *colchicine*, or (4) administration of NSAIDs.

A. Treating acute gout

Acute gouty attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, or kidney disease. Acute attacks are treated with *colchicine* to decrease movement of granulocytes into the affected area, and with NSAIDs to decrease pain and inflammation. [Note: *Aspirin* is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.]

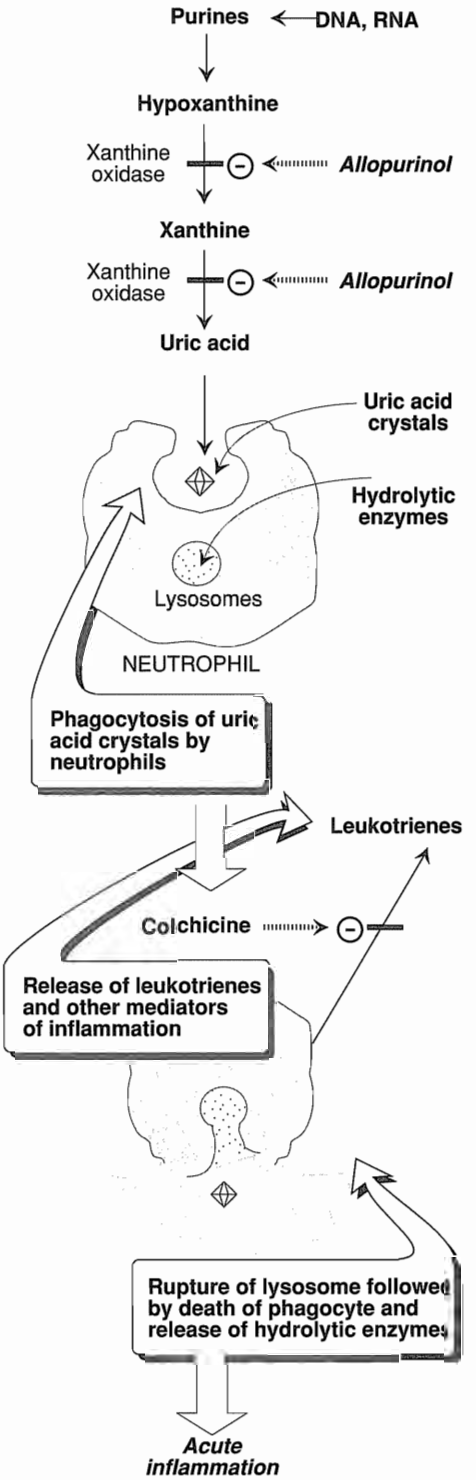


Figure 39.14
Role of uric acid in the inflammation of gout.

[3]See p. 418 for Infolink references to other books in this series.

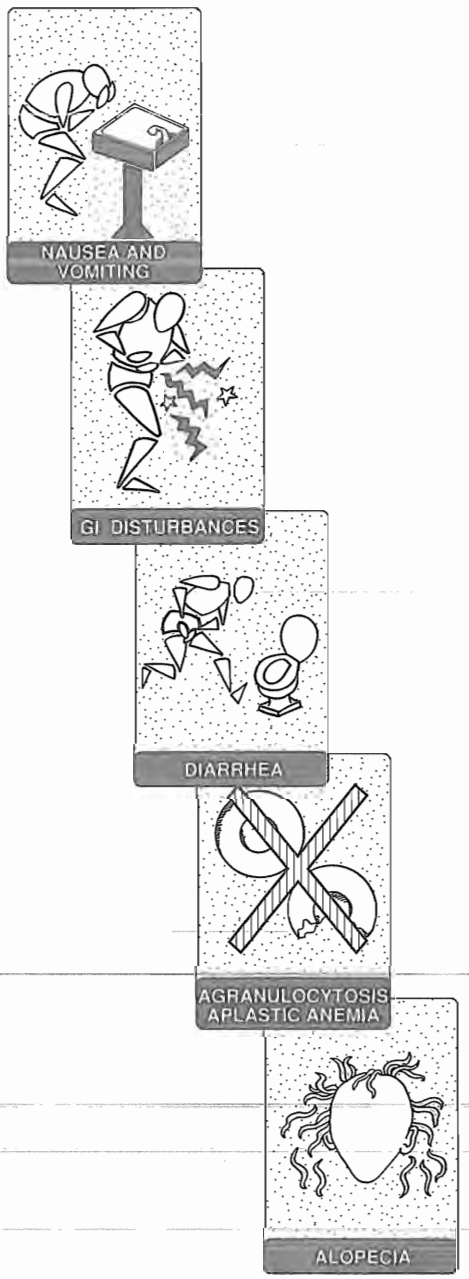


Figure 39.15
Some adverse effects of *colchicine*.

B. Treating chronic gout

Chronic gout can be caused by (1) a genetic defect, for example, one resulting in an increase in the rate of purine synthesis, (2) renal deficiency, (3) Lesch-Nyhan Syndrome,[4] or (4) excessive synthesis of uric acid associated with cancer chemotherapy. Treatment strategies for chronic gout include the use of uricosuric drugs that increase the excretion of uric acid, thereby reducing its concentration in plasma, and the use of *allopurinol*, which is a selective inhibitor of the terminal steps in the biosynthesis of uric acid.

C. Colchicine

Colchicine [KOL chi seen], a plant alkaloid, is reserved for the treatment of acute gouty attacks when they occur. It is not a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout. *Colchicine* does not prevent the progression of gout to acute gouty arthritis, but it does have a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain.

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. *Colchicine* also inhibits the synthesis and release of the leukotrienes (see Figure 39.14).

2. **Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. It is only rarely effective in other kinds of arthritis.

3. **Pharmacokinetics:** *Colchicine* is administered orally, followed by rapid absorption from the GI tract. It is also available combined with *probenecid* (see below). *Colchicine* is recycled in the bile and is excreted unchanged in the feces or urine.

4. **Adverse effects:** *Colchicine* treatment may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 39.15). Chronic administration may lead to myopathy, agranulocytosis, aplastic anemia, and alopecia. The drug should not be used in pregnancy, and should be used with caution in patients with hepatic, renal or cardiovascular disease.

D. Allopurinol

Allopurinol [al oh PURE i nole] is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis, which are catalyzed by xanthine oxidase (see Figure 39.14). [Note: Uric acid is less water-soluble than its precursors. When xanthine oxidase is inhibited, the circulating purine derivatives (xanthine and hypoxanthine) are more soluble and therefore are less likely to precipitate].

[4] See p. 418 for Infolink references to other books in this series.

1. **Therapeutic uses:** *Allopurinol* is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced) 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. The pharmacologic effect of administered *allopurinol* results from the combined activity of these two compounds. The plasma half-life of *allopurinol* is short (2 hours), whereas the half-life of oxypurinol is long (15 hours). Thus, effective inhibition of xanthine oxidase can be maintained with once daily dosage. The drug and its metabolite are excreted in the feces and urine.

3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions, occurring among approximately 3% of patients. The reactions may occur even after months or years of chronic administration. Acute attacks of gout may occur more frequently during the first several weeks of therapy; therefore *colchicine* and NSAIDs should be administered concurrently. Gastrointestinal side effects such as nausea and diarrhea are common. *Allopurinol* interferes with the metabolism of the anticancer agent, *6-mercaptopurine* (see p. 381) and the immunosuppressant, *azathioprine*, requiring a reduction in dosage of these drugs.

E. Uricosuric agents: probenecid and sulfinpyrazone

Probenecid [proe BEN e sid], a general inhibitor of the tubular secretion of organic acids, and *sulfinpyrazone* [sul fin PEER a zone], a derivative of *phenylbutazone* (see p. 411), are the two most commonly used uricosuric agents. At therapeutic doses, they block proximal tubular resorption of uric acid. [Note: At low dosage, these agents block proximal tubular secretion of uric acid.] These drugs have few adverse effects although gastric distress may force discontinuance of *sulfinpyrazone*. *Probenecid* blocks the tubular secretion of *penicillin* and is sometimes used to increase levels of the antibiotic. It also inhibits excretion of *naproxen*, *ketoprofen,* and *indomethacin*.

Choose the ONE best answer.

39.1 In which one of the following conditions would aspirin be contraindicated?

A. Myalgia
B. Fever
C. Peptic ulcer
D. Rheumatoid arthritis
E. Unstable angina

Correct answer = C. Among the NSAIDs, aspirin is among the worst for causing gastric irritation. Aspirin is an effective analgesic and is used to reduce muscle pain. It also has antipyretic actions so that it can be used to treat fever. Because of its anti-inflammatory properties, aspirin is used to treat pain related to the inflammatory process, for example, in the treatment of rheumatoid arthritis. Low doses of aspirin also decrease the incidence of transient ischemic attacks.

39.2 Overdoses of salicylates lead to all of the following EXCEPT:

A. Nausea and vomiting.
B. Tinnitus (ringing or roaring in the ears).
C. Marked hyperventilation.
D. Increased metabolic rate.
E. Increase in blood pH.

Correct choice = E. An overdose of salicylates causes acidosis.

39.3 Acetaminophen has all of the following properties EXCEPT:

A. It is a weaker anti-inflammatory agent than aspirin.
B. It reduces fever of viral infections in children.
C. It is an aspirin substitute in patients with peptic ulcer.
D. It exacerbates gout.
E. It causes hepatotoxic effects at high doses.

Correct choice = D. Acetaminophen does not antagonize the uricosuric agent probenecid and therefore may be used in patients with gout. Acetaminophen has little anti-inflammatory effect, but has analgesic and antipyretic activities equal to those of aspirin. It is the analgesic-antipyretic of choice for children with viral infections; aspirin can increase the risk for Reye's syndrome in children. Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin in those patients with gastric complaints.

39.4 Which of the following statements concerning gold salts is CORRECT?

A. They may provide immediate relief of arthritic pain.
B. They act by inhibiting prostaglandin synthesis.
C. They frequently cause dermatitis of the skin or mucous membranes.
D. They are drugs of first choice in treating arthritis.
E. They must all be given intramuscularly.

Correct answer = C. Gold salts may not provide clinical improvement until after several weeks of administration. They are thought to suppress phagocytosis and lysosomal enzyme activity in macrophages. Gold salts are used in rheumatoid arthritis that does not respond to NSAIDs. Auranofin can be taken by mouth.

39.5 Which of the following is INCORRECTLY paired?

A. Indomethacin:	Causes frontal headaches
B. Sulindac:	Long half-life permits daily or twice daily dosing
C. Naproxen:	Better tolerated than aspirin in some patients
D. Phenylbutazone:	Less toxic than aspirin
E. Aspirin:	Can cause GI symptoms

Correct choice = D. Phenylbutazone is more toxic than aspirin and should be used only after less toxic agents have proven ineffective.

[1]See p. 172 in **Biochemistry** (2nd ed.) for a discussion of the chemistry of arachidonic acid.

[2]See p. 185 in **Biochemistry** (2nd ed.) for a discussion of prostaglandin synthesis.

[3]See p. 350 in **Biochemistry** (2nd ed.) for a discussion of purine metabolism.

[4]See p. 348 in **Biochemistry** (2nd ed.) for a discussion Lesch-Nyhan syndrome.

Autacoids and Autacoid Antagonists

40

I. OVERVIEW

Prostaglandins, histamine, and serotonin belong to a group of compounds called autacoids. These heterogenous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act; thus, they function as local hormones. [Note: The word autacoid comes from the Greek: autos (self) and akos (medicinal agent, or remedy).] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter (Figure 40.1) are either autacoids (both naturally occurring and synthetic analogs) or autacoid antagonists (that is, compounds that inhibit the synthesis of certain autacoids, or interfere with their interactions with receptors).

II. PROSTAGLANDINS

Prostaglandins are unsaturated fatty acid derivatives that act on the tissues in which they are synthesized and are rapidly metabolized to inactive products at the site of action. The biosynthesis and actions of the prostaglandins are presented on p. 402 and Figure 39.3.

A. Therapeutic uses of prostaglandins

Systemic administration of prostaglandins evokes a bewildering array of effects, a fact that limits the therapeutic usefulness of these agents.

1. **Abortion:** Several of the naturally occurring prostaglandins, such as *dinoprost* [DYE noe prost], *dinoprostone* [dye noe PROST one], and *carboprost* [KAR boe prost], find use as abortifacients (that is, agents causing abortions, Figure 40.2). *Misoprostol* in combination with *methotrexate* is particularly effective in terminating pregancy in the first trimester.

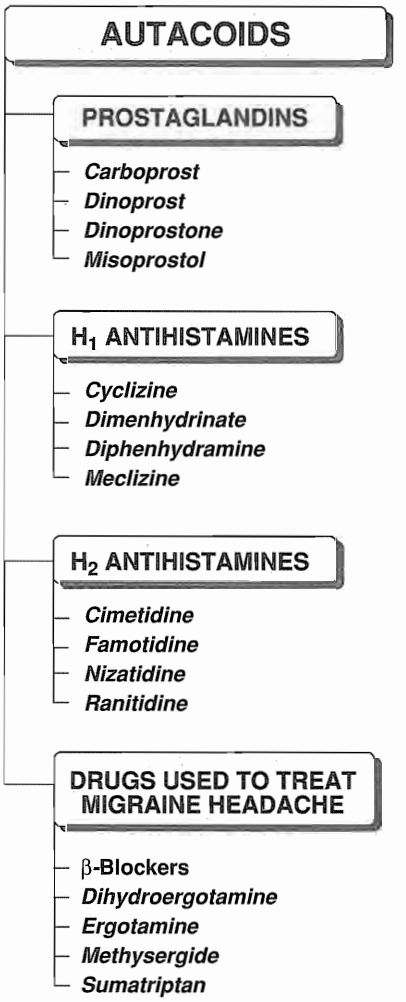


Figure 40.1
Summary of drugs affecting the autacoids.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

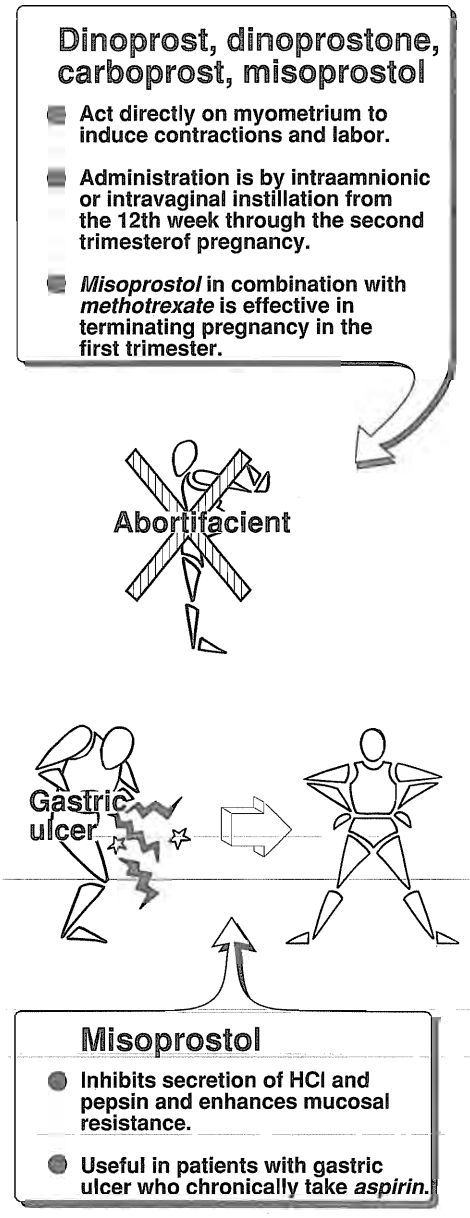


Figure 40.2
Therapeutic applications of prostaglandin derivatives.

2. **Peptic ulcers:** *Misoprostol* [MIZ o prost ol] is a synthetic prostaglandin E_1 analog used to inhibit the secretion of hydrochloric acid in the stomach. It produces inhibition of gastric acid and pepsin secretion and enhances mucosal resistance to injury. *Misoprostol* is particularly useful in patients with gastric ulcer who are chronically taking nonsteroidal anti-inflammatory agents (see p. 238 for a more complete discussion of this drug).

3. **Erectile dysfunction:** *Alprostadil* injected into the corpus cavernosum of the penis provides effective treatment of some forms of male impotence. The drug increases arterial inflow through vasodilation and decreases venous outflow by causing relaxation of the corporal smooth muscle that occludes draining venules. Possible side effects include pain at the site of injection and, rarely, prolonged erection.

III. ANTIHISTAMINES

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and possibly neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications.

A. Location, synthesis, and release of histamine

1. **Location:** Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract (sites where the "inside" of the body meets the "outside"). It is found in high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings.

2. **Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine (Figure 40.3). This process occurs primarily in the mast cells, basophils, and in the lungs, skin, and gastrointestinal mucosa—the same tissues in which histamine is stored. In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated anion, heparin, along with an anionic protein. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

3. **Release of histamine:** The release of histamine may be the primary response to some stimuli, but most often, histamine is just one of several chemical mediators released. Stimuli causing the release of histamine from tissues include the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. Allergies and anaphylaxis can also trigger release of histamine.

B. Mechanism of action of histamine

Histamine released in response to the stimuli just described exerts its effects by binding to two types of receptors, designated H_1 and

H_2, located on the surfaces of cells. Some of histamine's wide range of pharmacologic effects are mediated by both H_1 and H_2 receptors, whereas others are mediated by only one class (Figure 40.4). For example, the H_1 receptors are important in producing smooth muscle contraction and increasing capillary permeability. Histamine promotes vasodilation by causing vascular endothelium to release nitric oxide; this chemical signal diffuses to the vascular smooth muscle where it stimulates cGMP production, causing vasodilation. Histamine H_2 receptors mediate gastric acid secretion. The two histamine receptors exert their effects by different second messenger pathways; for example, binding of an agonist to the H_1 receptor stimulates the intracellular activity of the polyphosphatidylinositol pathway, whereas stimulation of H_2 receptors enhances the production of cAMP by adenylyl cyclase (see p. 33).

C. Role of histamine in allergy and anaphylaxis

There is a similarity between the symptoms resulting from intravenous (IV) injection of histamine and those associated with anaphylactic shock and allergic reactions. These include contraction of smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

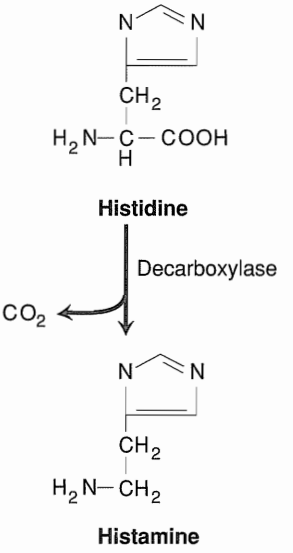


Figure 40.3
Biosynthesis of histamine.

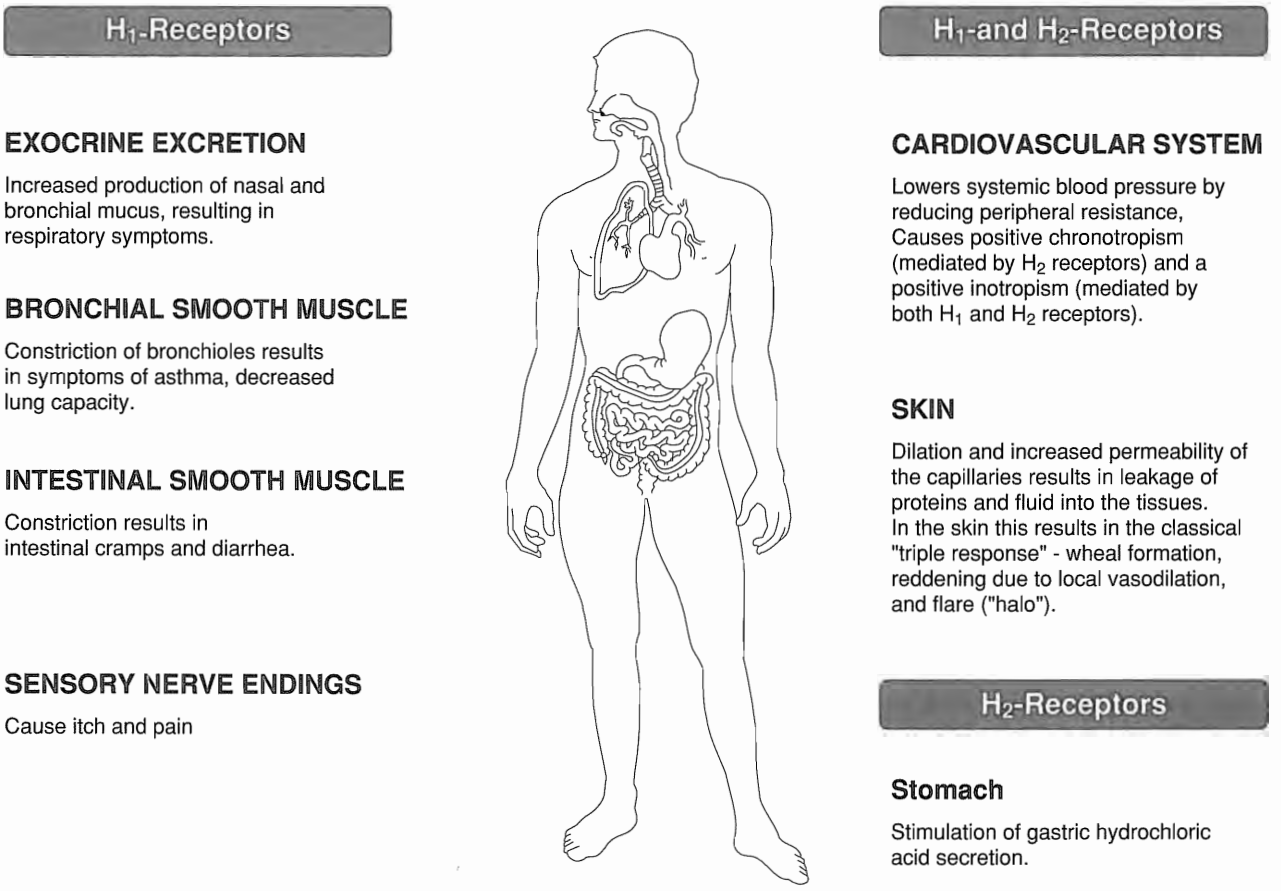


Figure 40.4
Actions of histamine.

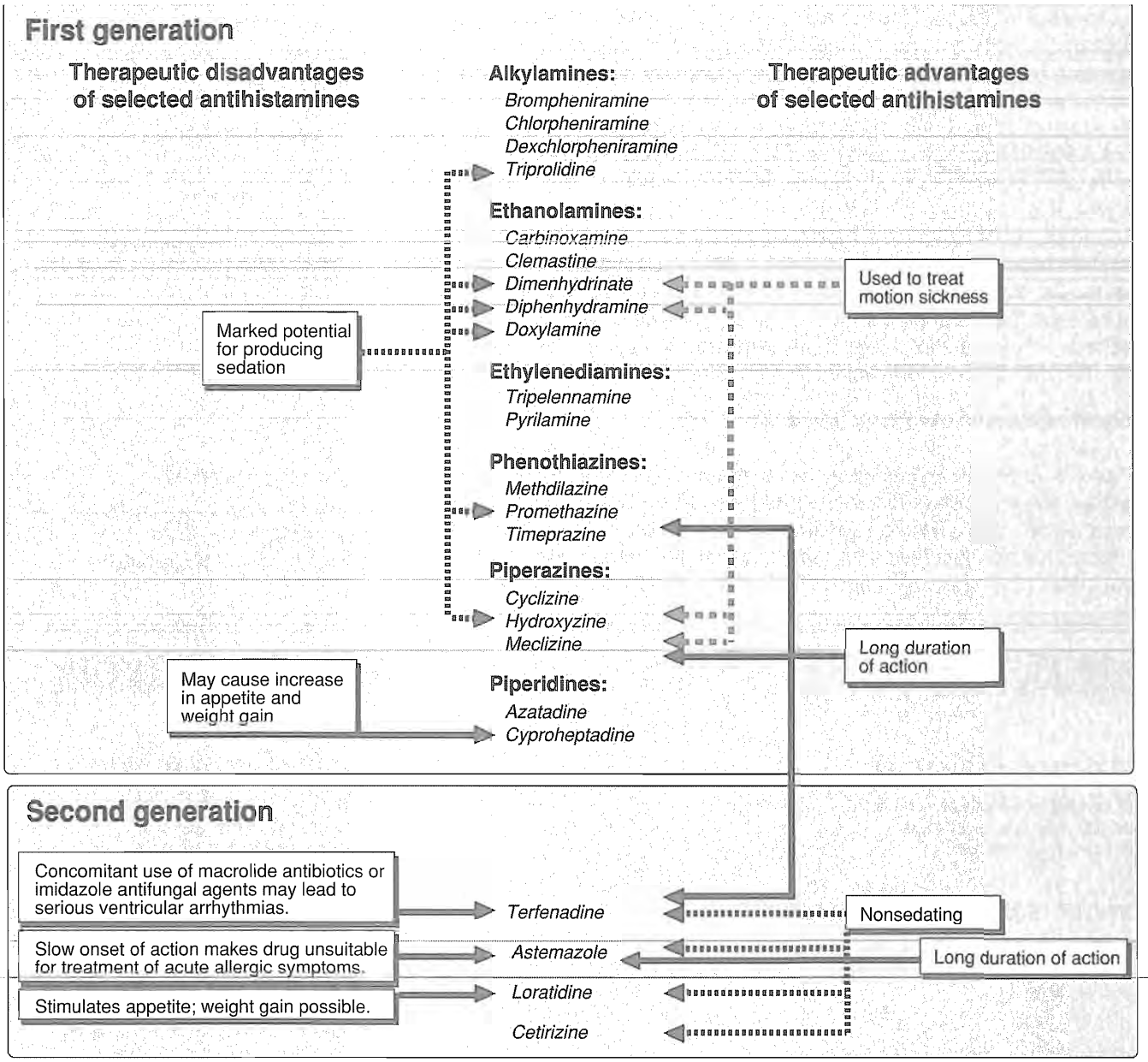


Figure 40.5
Summary of therapeutic advantages and disadvantages of the H_1-histamine receptor blocking agents.

1. **Role of mediators:** Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin leukotrienes and the eosinophil chemotactic factor of anaphylaxis. In some cases, these cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results.

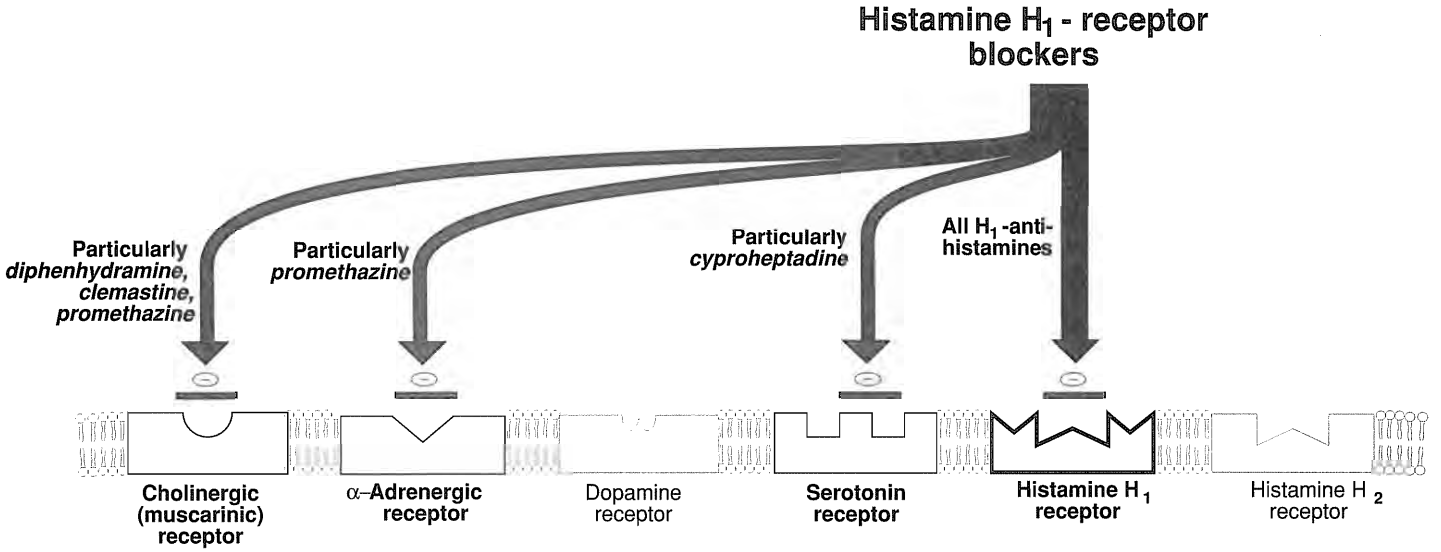


Figure 40.6
H_1-antihistamines block at histamine receptors as well as at adrenergic, cholinergic, and serotonin-binding receptors.

However, if histamine release is too fast for inactivation to be efficient, a full-blown anaphylactic reaction occurs. (See p. 221 for a more complete discussion of allergic reactions.)

D. Histamine H_1 receptor blockers

The term "antihistamine," without a modifying adjective, refers to the classic H_1 receptor blockers. These compounds do not influence the formation or release of histamine, but rather they competitively block the receptor-mediated response of a target tissue. [Note: This contrasts with the action of *cromolyn* (see p. 220), which inhibits the release of histamine from mast cells and is useful in the treatment of asthma.] The H_1 receptor blockers can be divided into first- and second generation drugs.(Figure 40.5). The first generation drugs are still widely used because they are effective and inexpensive. However, the second generation agents, because they do not penetrate the blood-brain barrier, show less CNS toxicity than the older drugs. [Note: The histamine receptors are distinct from those that bind serotonin, acetylcholine, and the catecholamines.]

1. **Actions:** H_1 antihistamines antagonize all actions of histamine except for those mediated solely by H_2 receptors. The action of all of the H_1 receptor blockers is qualitatively similar. However, most of these blockers have additional effects unrelated to their blocking of H_1 receptors; these effects probably reflect binding of the H_1 antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 40.6). Some H_1 blockers, such as *diphenhydramine*, have good local anesthetic activity.

2. **Therapeutic uses**

   a. **Allergic conditions:** H_1 Blockers are useful in treating allergies caused by antigens acting on IgE-antibody sensitized mast

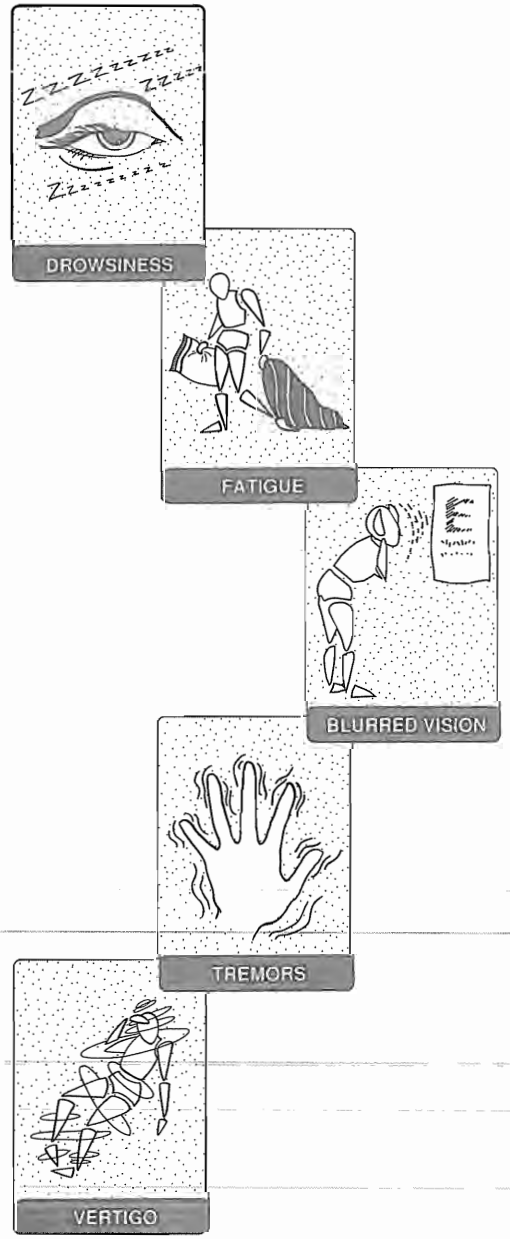


Figure 40.7
Some adverse effect observed with first generation H_1-histamine blockers.

cells. For example, antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator. However, the H_1 receptor blockers are ineffective in treating bronchial asthma (see p. 217), because histamine is only one of several mediators. [Note: *Epinephrine* (see p. 61) has actions on smooth muscle that are opposite to those of histamine and it acts at different receptors. Therefore, *epinephrine* is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.]

b. Motion sickness and nausea: Along with the antimuscarinic agent *scopolamine* (see p. 48), certain H_1 receptor blockers, such as *diphenhydramine* [dye fen HYE dra meen], *dimenhydrinate* [dye men HYE dri nate], *cyclizine* [SYE kli zeen], and *meclizine* [MEK li zeen] (see Figure 40.5), are the most effective agents for the prevention of the symptoms of motion sickness. The antihistamines prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these substances seems to be independent of their antihistaminic and other actions. (Other antiemetic agents are summarized in Figure 24.6, p. 243.).

c. Somnifacients: Some of the antihistamines, such as *diphenhydramine*, have strong sedative properties and are used in the treatment of insomnia.

3. **Pharmacokinetics:** H_1 receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for *meclizine*, which has a half-life of 12 to 24 hours. H_1 receptor blockers have high bioavailability; they are distributed in all tissues, including the CNS.The major site of biotransformation is the liver. Minute amounts of unchanged drug and most of the metabolites are excreted in the urine.

4. **Adverse effects:** H_1 receptor blockers have a low specificity, that is, they interact not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors (see Figure 40.6). The extent of interaction with these receptors and, as a result, the nature of the side effects, vary with the structure of the drug. Some side effects may be undesirable, and others may have therapeutic value. Furthermore, the incidence and severity of adverse reactions varies between individual subjects.

a. Sedation: The most frequently observed adverse reaction is sedation (Figure 40.7). Other central actions include tinnitus, fatigue, dizziness, lassitude, incoordination, blurred vision, and tremors. Sedation is less common with the second generation drugs that do not readily enter the CNS.

b. Dry mouth: Oral antihistamines also exert weak anticholinergic effects, leading not only to a drying of the nasal passage but also to a tendency to dry the oral cavity. Blurred vision can also occur with some drugs.

c. Drug interactions: Interaction of H_1 receptor blockers with other drugs can cause serious consequences, such as the potentiation of the effects of all other CNS depressants, including alcohol. Persons taking MAO inhibitors (see p. 123) should not take antihistamines, since the MAO inhibitors can exacerbate the anticholinergic effects of the antihistamines. *Erythromycin* and *clarithromycin* interfere in the metabolism of *terfenadine* and *astemizole* and may cause serious cardiac arrhythmias.

d. Overdoses: Although the margin of safety of H_1 receptor blockers is relatively high and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

E. Histamine H_2 receptor blockers

Histamine H_2 receptor blockers have little if any affinity for H_1 receptors. Although antagonists of the histamine H_2 receptor (H_2 antagonists) block the actions of histamine at all H_2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers. (see p. 236). By competitively blocking the binding of histamine to H_2 receptors, these agents reduce intracellular concentrations of cyclic AMP and thereby, secretion of gastric acid. The four drugs used in the United States, *cimetidine, ranitidine, famotidine* and *nizatidine*, are discussed in Chapter 24.

IV. DRUGS USED TO TREAT MIGRAINE HEADACHE

It has been estimated that 18 million women and 6 million men in the United States suffer from severe migraine headaches. Migraine can usu-

	Migraine	Cluster	Tension type
Family history	**Yes**	**No**	**Yes**
Sex	**Females more often than males**	**Males more often than females**	**Females more than males**
Onset	**Variable**	**During sleep**	**Under stress**
Location	**Usually unilateral**	**Behind or around one eye**	**Bilateral in band around head**
Character, severity	**Pulsating, throbbing**	**Excruciating, sharp, steady**	**Dull, persistent, tightening/pressing**
Duration	**Two to 72 hours per episode;**	**15 to 90 minutes per attack**	**30 minutes to 7 days per episode**
Associated symptoms	**Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting**	**Unilateral or bilateral sweating, facial flushing, nasal congestion, ptosis, lacrimation, pupillary changes**	**Mild intolerance to light and noise, anorexia**

Figure 40.8
Characteristics of migraine, cluster and tension-type headaches.

ally be distinguished clinically from the two other common types of headaches—the cluster headache and tension-type headache—by its characteristics (Figure 40.8). For example, migraines present as a pulsatile, throbbing pain; cluster headaches as excruciating, sharp, steady pain; whereas tension-type headaches show dull pain with a persistent tightening feeling in the head. Migraine headaches typically affect patients for a major part of their lives, and result in considerable health costs.

A. Types of migraine

There are two main types of migraine headaches. The first, migraine without aura (previously called common migraine), is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). Approximately 85% of patients with migraine do not have aura. In the second type, migraine with aura (previously called classic migraine), the headache is preceded by neurologic symptoms called aura, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly these prodromal symptoms are visual, occurring 20 to 40 minutes before headache pain begins. In the 15% of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache itself in migraine with or without aura is similar. For both types of migraines, women are three times more likely to experience either type of migraine than are men.

B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes, for example, the hypoperfused regions show an abnormal response to changes in arterial pCO_2. The hypoperfusion persists throughout the aura and well into the headache phase, after which hyperperfusion occurs. Patients with migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial dilation leading to release of neuroactive molecules such as substance P.

C. Symptomatic treatment of acute migraine

A migraine can usually be aborted if therapy is initiated at the onset of symptoms—either during the aura or at the first hint of migraine pain without aura. The most useful drugs for averting an acute attack are *sumatriptan*, *ergotamine*, and nonsteroidal antiinflammatory drugs .

1. **Sumatriptan:** *Sumatriptan* [sew mah TRIP tan] rapidly and effectively aborts or markedly reduces the severity of migraine headaches in about 80 % of patients. *Sumatriptan* is a serotonin agonist, acting at 5-HT_{1D} receptors, a subgroup of serotonin receptors found on small, peripheral nerves that innervate the

intracranial vasculature. Their activation probably suppresses release of sensory neuropeptides, such as substance P. The nausea that occurs with *dihydroergotamine* and the vasoconstriction caused by *ergotamine* (see next sections) are much less pronounced with *sumatriptan. Sumatriptan* is given subcutaneously or orally. The onset of the parenteral drug is about 20 minutes compared to 1 to 2 hours for drug adminisatered orally. The drug has a short duration of action, with an elimination half-life of two hours. Headache commonly recurs within 24 to 48 hours after a single dose of *sumatriptan*; in most patients a second dose is effective in aborting the headache. Because of its high cost, *sumitriptan* should be reserved for patients for whom other drugs have been ineffective, or were not well-tolerated.

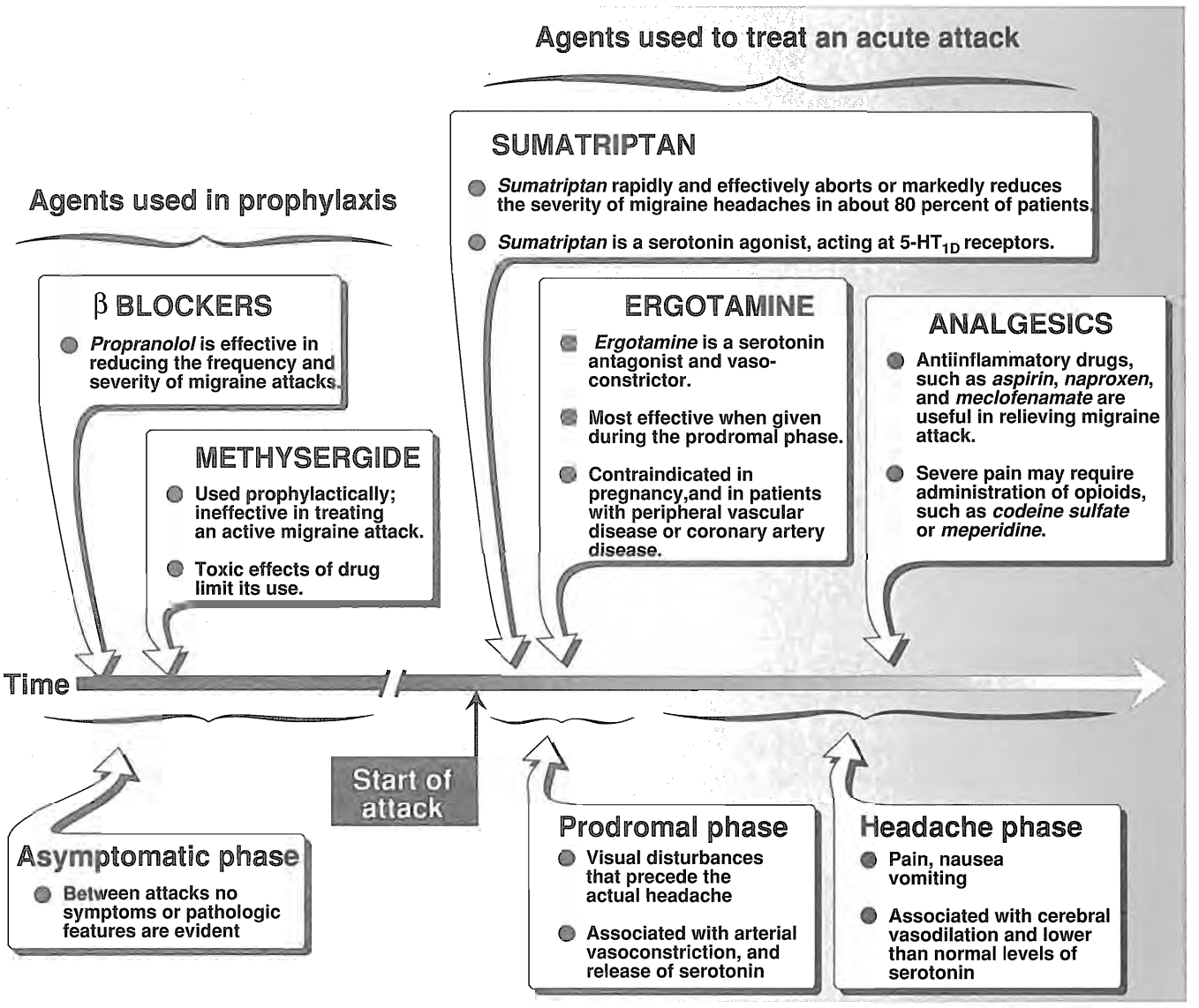


Figure 40.9
Drugs useful in the treatment and prophylaxis of migraine headaches.

2. **Ergotamine:** *Ergotamine* [er GOT a meen] has in the past been the drug of choice for treatment of moderate-to-severe migraine. *Ergotamine* and *dihydroergotamine* (see below) have similar actions to *sumatriptan*, but they have less selectivity for the 5-HT receptors. *Ergotamine* can be given orally, sublingually, rectally or nasally, and is effective in about 50% of patients. The gastrointestinal absorption of the ergot alkaloids is variable, but it can be increased by *caffeine* (that is, coffee increases effectiveness of ergot alkaloids). The drug is most effective when administered during the early phase of an attack. The most common side effects are diarrhea, nausea, and vomiting.

3. **Dihydroergotamine:** *Dihydroergotamine* [dye hye droe er GOT a meen], a derivative of *ergotamine*, is administered intravenously and has an efficacy similar to that of *sumatriptan*, but nausea is a common adverse effect.

4. **Analgesics:** Analgesics or nonsteroidal anti-inflammatory drugs are often effective in mild-to-moderate migraine. *Aspirin*, *acetaminophen*, *naproxen*, *propoxyphene*, *acetaminophen* with *butalbital*, and *caffeine* are all effective in treating a migraine attack.

D. Prophylaxis

Therapy to prevent migraine is indicated if the attacks occur two times or more a month, and if the headaches are severe or complicated by serious neurologic signs. *Propranolol* (see p. 74) is the drug of choice, but other β-blockers, particularly *nadolol* (see p. 76), have been shown to be effective. *Methysergide* [meth i SER jide], another ergot alkaloid, is effective for prevention of recurrent, refractory, severe migraine (Figure 40.9).

Study Questions

Choose the ONE best answer.

40.1 Ergot alkaloids:

A. cause vasodilation.
B. exert their actions by binding to specific ergotamine receptors.
C. are useful in treating acute migraine headache.
D. are useful to maintain uterine muscle tone during pregnancy.
E. have actions similar to those of nitroprusside.

Correct answer = C. Ergotamine acts to counteract cerebral vasodilation that plays a role in migraine headaches. Vasoconstriction leading to tissue ischemia is one of the toxic complications associated with an overdose of these drugs. The ergot alkaloids interact with adrenergic, dopaminergic, and serotonin receptors. They are contraindicated in pregnancy because of their ability to cause uterine contraction and abortion. Nitroprusside is a powerful vasodilator used to treat vasoconstriction that is characteristic of an overdose with ergot alkaloids.

40.2 Histamine H_1 receptor blockers are useful in the treatment of all of the following EXCEPT:

A. urticaria.
B. seasonal rhinitis.
C. drug reactions.
D. bronchial asthma.
E. insomnia.

Correct choice = D. H_1 histamine receptor blockers are not effective in bronchial asthma.