Antihyperlipidemic Drugs

21

I. OVERVIEW

Coronary artery disease (CAD) is the cause of about half of all deaths in the United States. CAD has been shown to be correlated with the levels of plasma cholesterol- and/or triacylglycerol-containing lipoprotein particles. These particles, which are key to the development of atherogenesis, are initially synthesized by the intestinal mucosa and the liver, and undergo extensive metabolism in the plasma. They also play an essential role in the transport of lipids between tissues. [Note: Because lipids are insoluble in aqueous solutions, they must be transported in the plasma from tissue to tissue, bound to proteins, hence the name, lipoprotein.] Their levels can be elevated by environmental causes, such as diet, or by inherited genetic defects in the appropriate synthesis or degradation of these compounds. Drugs used in the treatment of elevated serum lipids (hyperlipidemias) generally are targeted to (1) decrease production of a lipoprotein by the tissues, (2) increase catabolism of a lipoprotein in the plasma, or (3) increase removal of cholesterol from the body. Such treatments lead to a decline in the progression of coronary plaque and a possible regression of pre-existing lesions. The antihyperlipidemic drugs are listed in Figure 21.1.

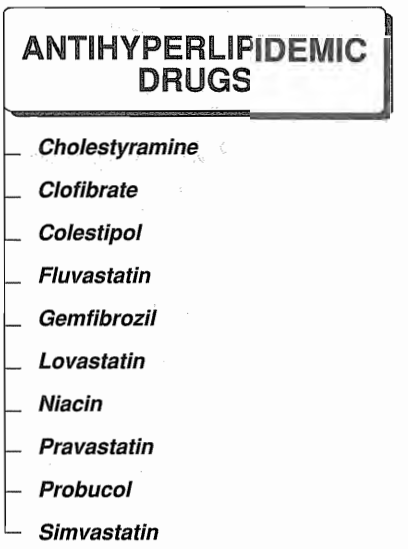

Figure 21.1
Summary of antihyperlipidemic drugs.

II. HYPERLIPIDEMIAS

The hyperlipidemias are a complex group of diseases that can be designated either primary or secondary, depending on their causes. Primary hyperlipidemias can result from a single inherited gene defect, or more commonly, are caused by a combination of genetic and environmental factors. Secondary hyperlipidemias are the result of a more generalized metabolic disorder, such as diabetes mellitus, excessive alcohol intake, hypothyroidism, or primary biliary cirrhosis. Therapeutic strategies for treating secondary hyperlipidemia caused by one of these disorders include dietary intervention plus a regimen of drugs used to treat the primary cause of the hyperlipidemia. Figure 21.2 illustrates the normal metabolism of serum lipoproteins, and the characteristics of the major genetic hyperlipidemias.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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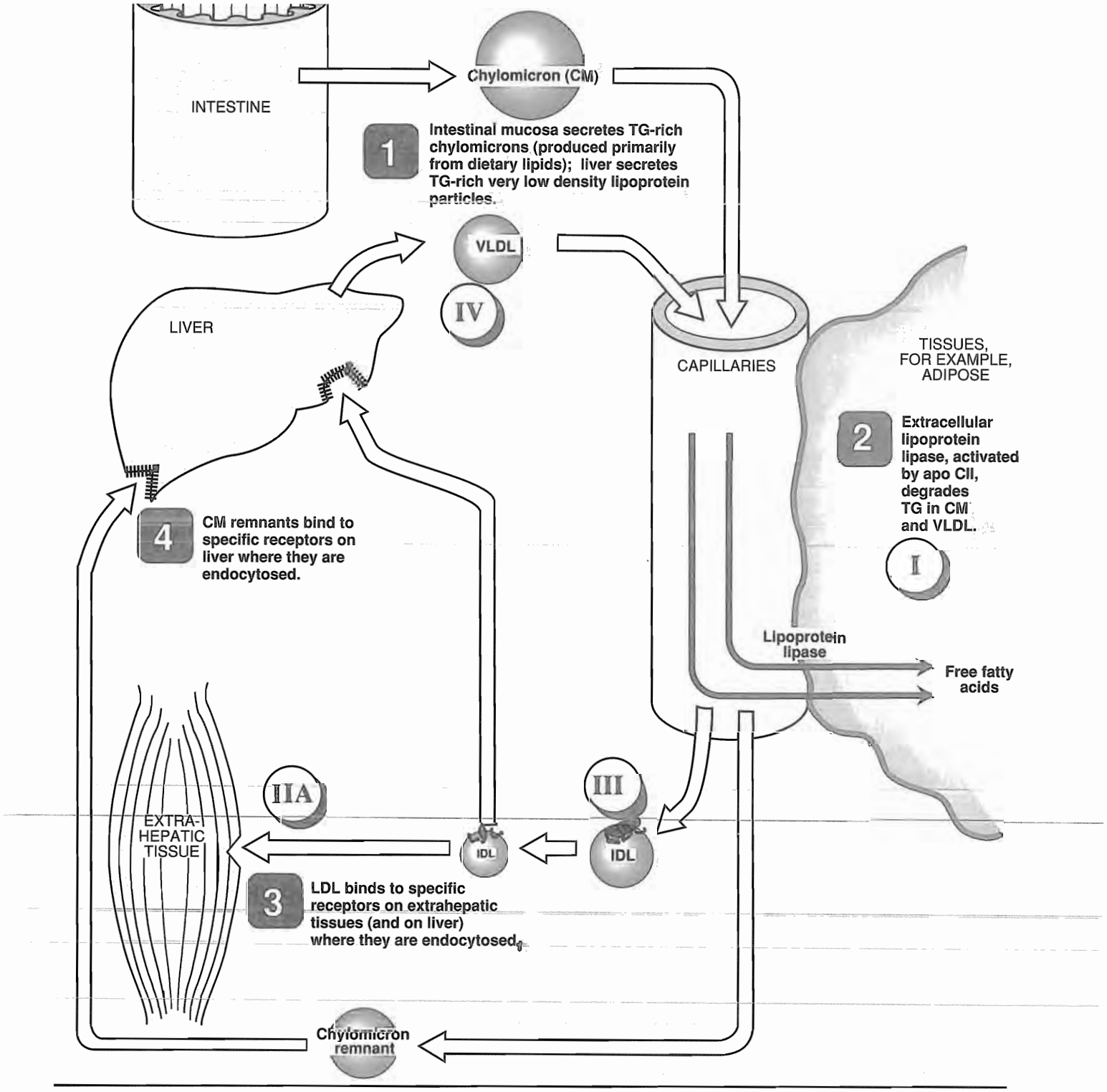

Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. CM=chylomicron, TG=triacylglycerol, VLDL=very low density lipoprotein, LDL=low density lipoprotein, IDL=intermediate density lipoprotein, apo CII=apolipoprotein CII found in chylomicrons and VLDL. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page.

Type I [FAMILIAL HYPERCHYLOMICRONEMIA]

- Massive fasting hyperchylomicronemia even following normal dietary fat intake, resulting in greatly elevated serum triacylglycerol.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low fat diet. No drug therapy is effective for Type I hyperlipidemia.

Type IIA [FAMILIAL HYPERCHOLESTEROLEMIA]

- Elevated LDL with normal VLDL levels due to block in LDL degradation, therefore increased serum cholesterol but normal triacylglycerol.
- Caused by decreased numbers of normal LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Low cholesterol and low saturated fat in the diet. Heterozygotes: Cholestyramine or colestipol, and/or lovastatin or mevastatin. Homozygotes: As above, plus niacin.

Type IIB [FAMILIAL COMBINED (MIXED) HYPERLIPIDEMIA]

- Similar to IIA except VLDL are also increased, resulting in elevated serum triacylglycerol as well as cholesterol.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Dietary restriction of cholesterol and saturated fat and alcohol. Drug therapy similar to IIA except heterozygotes also receive niacin.

Type III [FAMILIAL DYSBETALIPOPROTEINEMIA]

- Serum concentrations of IDL are increased resulting in increased triacylglycerol and cholesterol levels.
- Cause is either overproduction or underutilization of IDL, due to mutant apolipoprotein E.
- Xanthomas and accelerated coronary and peripheral vascular disease develop in patients by middle age.
- Treatment: Weight reduction (if necessary). Dietary restriction of cholesterol and alcohol. Drug therapy includes niacin and clofibrate (or gemfibrozil), or lovastatin (or mevastatin).

Type IV [FAMILIAL HYPERTRIGLYCERIDEMIA]

- VLDL levels are increased, while LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating triacylglycerol levels.
- Cause is overproduction and/or decreased removal of VLDL triacylglycerol in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic. Also seen in individuals undergoing estrogen therapy, or are in their third trimester of pregnancy, or are alcoholic.
- Treatment: Weight reduction (if necessary) is of primary importance. Dietary restriction of controlled carbohydrate, modified fat, low alcohol consumption. If necessary, drug therapy includes niacin and/or gemfibrozil (or clofibrate), or lovastatin (or mevastatin).

Type V [FAMILIAL MIXED HYPERTRIGLYCERIDEMIA]

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated triacylglycerol levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Weight reduction (if necessary) is important. Diet should include protein, low fat and controlled carbohydrate, and no alcohol. If necessary, drug therapy includes niacin, clofibrate and/or gemfibrozil, or lovastatin (or mevastatin).

Figure 21.2 (continued).

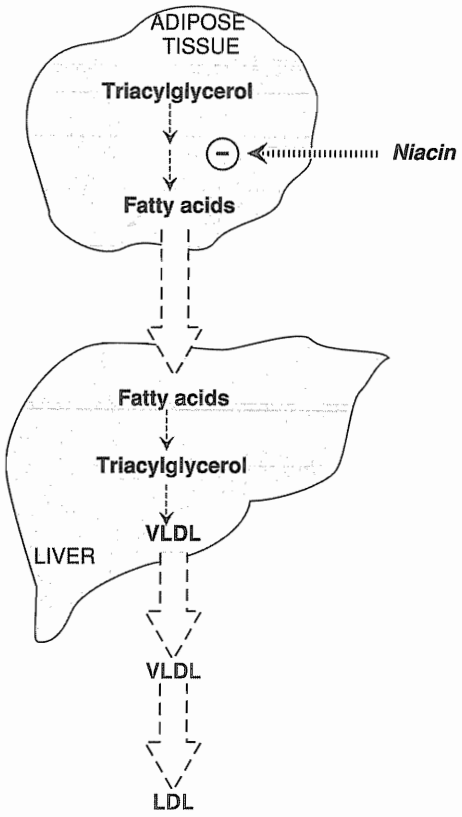

Figure 21.3
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL and LDL synthesis.

III. DRUGS THAT LOWER SERUM LIPOPROTEIN CONCENTRATION

Antihyperlipidemic drugs target the problem of elevated serum lipids (in both primary and secondary hyperlipidemias) with complementary strategies; some of these agents decrease production of the lipoprotein carriers of cholesterol and triacylglycerol, whereas others increase lipoprotein degradation. Still others directly increase cholesterol removal from the body. These drugs may be used singly or in combination, but are always accompanied by the requirement that dietary lipid intake be significantly low, especially cholesterol and saturated fats, and the caloric content of the diet must be closely monitored.

A. Niacin (nicotinic acid)

Nicotinic acid has a broad lipid-lowering ability, but its clinical use is limited due to its unpleasant side effects. Derivatives of this drug that are not available in the United States appear to have fewer adverse effects.

1. **Mechanism of Action:** At gram doses, *niacin* [NYE a sin], a water-soluble vitamin[1], strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, *niacin* causes a decrease in liver triacylglycerol synthesis, which is required for very low density lipoprotein (VLDL) production (Figure 21.3).[2] Low density lipoprotein (LDL, the cholesterol-rich lipoprotein) is derived from VLDL in the plasma. Therefore a reduction in the VLDL concentration also results in a decreased plasma LDL concentration. Thus, both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered (Figure 21.4). Furthermore, *niacin* treatment increases HDL-cholesterol levels (HDL is the "good" cholesterol carrier). Moreover, by boosting secretion of tissue plasminogen activator and lowering plasma fibrinogen, *niacin* can reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

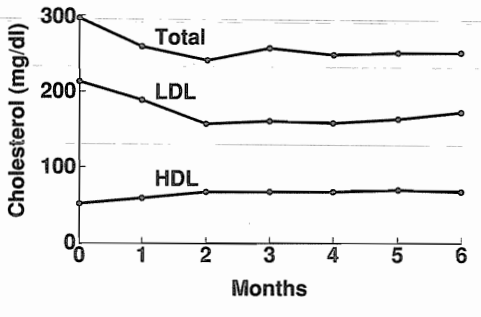

Figure 21.4
Plasma levels of cholesterol in hyperlipidemic patients during treatment with *niacin*.

2. **Therapeutic uses:** *Niacin* lowers plasma levels of both cholesterol and triacylglycerol. Therefore, it is particularly useful in the treatment of Type IIb and IV hyperlipoproteinemia, in which both VLDL and LDL are elevated. *Niacin* is also used to treat other severe hypercholesterolemias, often in combination with other antihyperlipidemic agents (see p. 215). In addition, it is the most potent antihyperlipidemic agent for raising plasma HDL levels.

3. **Pharmacokinetics:** *Niacin* is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD^+). *Niacin,* its nicotinamide derivative and other metabolites are excreted in the urine. [Note: Nicotinamide alone does not decrease plasma lipid levels.]

4. **Adverse effects:** The most common side effects of *niacin* therapy are an intense cutaneous flush (accompanied by an uncomfort-

[1,2] See p. 216 for Infolink references to other books in this series.

able feeling of warmth) and pruritus. Administration of *aspirin* prior to taking *niacin* decreases the flush, which is prostaglandin-mediated. Some patients also experience nausea and abdominal pain. Nicotinic acid inhibits tubular secretion of uric acid and thus predisposes to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

B. The fibrates—clofibrate and gemfibrozil

These agents are derivatives of fibric acid and both have the same mechanism of action. However, *gemfibrozil* [gem FYE bro zil] has largely replaced *clofibrate* [kloe FYE brate] clinically because of the higher incidence of mortality with the latter agent. The deaths were not associated with cardiovascular causes, but rather with malignancy or complications due to postcholecystectomy and pancreatitis.

1. **Mechanism of action:** Both drugs cause a decrease in plasma triacylglycerol levels by stimulating lipoprotein lipase activity, thereby hydrolyzing triacylglycerols in chylomicrons and VLDL, and thus hastening the removal of these particles from the plasma (Figure 21.5). In contrast, HDL levels rise moderately. Animal studies show that the fibrates can cause a lowering of plasma cholesterol by inhibiting cholesterol synthesis in the liver (mechanism unknown) and by increasing biliary excretion of cholesterol into the feces. The fibrates also appear to lower plasma fibrinogen levels.

2. **Therapeutic uses:** The fibrates are used in the treatment of hypertriglyceridemias, causing a significant decrease in plasma triacylglycerol levels. [Note: They are not indicated for Type I hyperlipidemia in which chylomicron levels are elevated but VLDL levels are normal.] *Clofibrate* and *gemfibrozil* are particularly useful in treating Type III hyperlipidemia (dysbetalipoproteinemia), in which intermediate density lipoproteins (IDL) particles accumulate. Patients with hypertriglyceridemia [Type IV (elevated VLDL) or Type V (elevated VLDL plus chylomicron) disease] who do not respond to diet or other drugs may also benefit from treatment with these agents.

3. **Pharmacokinetics:** Both drugs are completely absorbed after an oral dose. *Clofibrate* is deesterified to the active *clofibric acid*, which binds to albumin and distributes widely in body tissues. Likewise, *gemfibrozil* distributes extensively, bound to albumin. Both drugs undergo extensive biotransformation and are excreted in the urine as their glucuronide conjugates.

4. **Adverse effects**

   a. **GI effects:** The most common adverse effects are mild gastrointestinal disturbances. These lessen as the therapy progresses.

   b. **Lithiasis:** Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

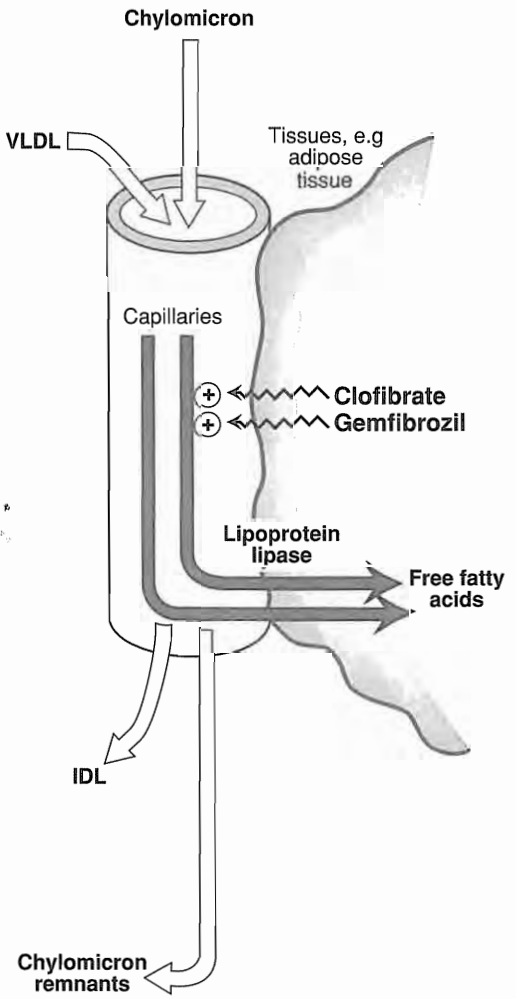

Figure 21.5
Activation of lipoprotein lipase by *clofibrate* and *gemfibrozil*.

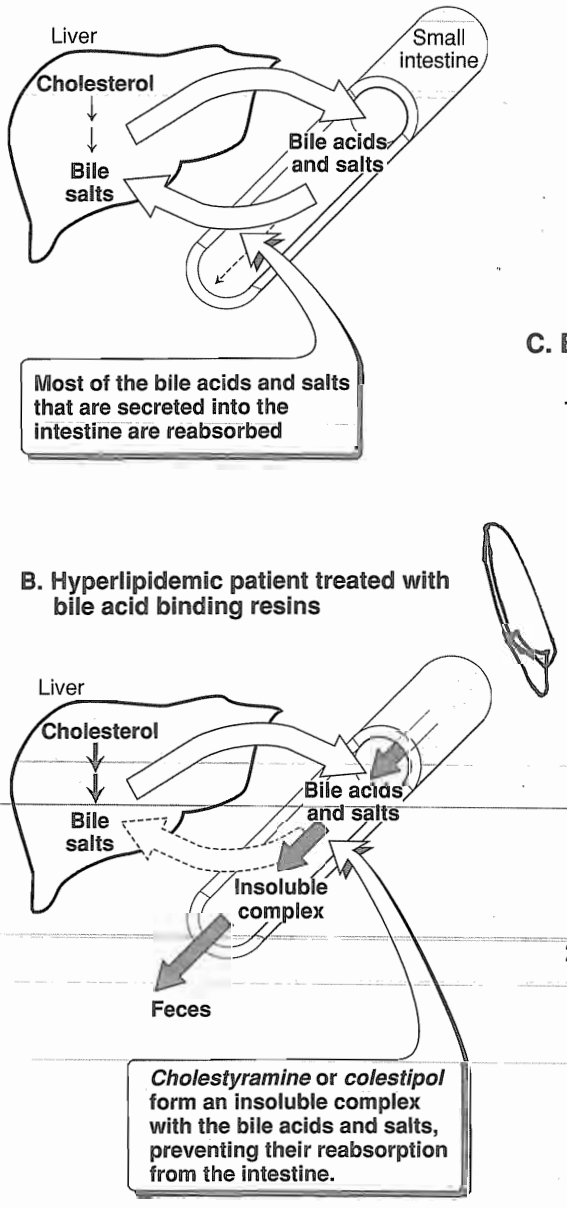

Figure 21.6
Mechanism of bile acid binding resins.

c. Malignancy: Treatment with *clofibrate* has resulted in a significant number of malignancy–related deaths.

d. Muscle: Myositis (inflammation of a voluntary muscle) can occur with both drugs, thus muscle weakness or tenderness should be evaluated. Though rare, patients with renal insufficiency are at risk. Myopathy and rhabdomyolysis have been reported in a few patients taking *gemfibrozil* and *lovastatin* together.

e. Drug interactions: Both fibrates compete with the *coumarin* anticoagulants for binding sites on plasma proteins, thus transiently potentiating anticoagulant activity. Prothrombin levels should therefore be monitored when a patient is taking both these drugs. Similarly, these drugs may transiently elevate the levels of sulfonyl ureas.

f. Contraindications: The safety of these agents in pregnant or lactating women has not been established. They should not be used in patients with severe hepatic and renal dysfunction or in patients with pre-existing gall bladder disease.

C. Bile acid binding resins: cholestyramine and colestipol

1. Mechanism of action: *Cholestyramine* [koe less TYE ra meen] and *colestipol* [koe LES tih pole] are anion exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 21.6). The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, which are essential components of the bile. Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL. [Note: This increased uptake is mediated by an upregulation of cell-surface LDL receptors.] In some patients, a modest rise in plasma HDL levels is also observed. The final outcome of this sequence of events is a decreased total plasma cholesterol concentration.

2. Therapeutic uses: The bile acid binding resins are the drugs of choice (often in combination with diet or *niacin*) in treating Type IIa and IIb hyperlipidemias. [Note: In those rare individuals who are homozygous for Type IIa, that is, for whom functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction.

3. Pharmacokinetics: *Cholestyramine* and *colestipol* are taken orally. Because they are insoluble in water and are very large (molecular weights are greater than 10^6), they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in the feces.

4. Adverse effects

a. GI effects: The most common side effects are gastrointestinal disturbances, such as constipation, nausea, and flatulence.

b. Impaired absorptions: Absorption of the fat-soluble vitamins, A, D, E, and K can be impaired if high doses of the resin are present. Folic acid and ascorbic acid absorption may also be reduced.

c. Drug interactions: *Cholestyramine* and *colestipol* interfere with the intestinal absorption of many drugs, for example, *tetracycline*, *phenobarbital*, *digoxin*, *warfarin*, *pravastatin*, *fluvastatin*, *aspirin*, and *thiazide* diuretics. Therefore, drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid binding resins.

D. Probucol

Probucol [PROE byoo kole] was introduced in the 1970s, but because it reduced HDL levels to a greater extent than those of LDLs, it fell into disfavor. Newer information indicating that its antioxidant properties may be important in blocking atherosclerosis has resulted in renewed interest.

1. **Mechanism of action:** A number of mechanisms have been proposed to explain how *probucol* lowers serum cholesterol, but its mechanism of action remains uncertain. Recently it has been found that *probucol* inhibits the oxidation of cholesterol, resulting in the ingestion of the oxidized cholesterol-laden LDLs by macrophages (Figure 21.7). Loaded with cholesterol, these macrophages become foam cells that adhere to the vascular endothelium and are the basis for plaque formation. Thus prevention of the cholesterol oxidation reaction might slow the development of atherosclerosis.

2. **Therapeutic uses:** *Probucol* is useful in treating Type IIA and IIB hypercholesterolemia, although less so than the bile acid binding resins. Because a low HDL level is at least as great a risk for atherosclerosis as an elevated LDL level, the usefulness of this drug is limited to instances in which other antihyperlipidemic agents are ineffective. [Note: *Probucol* does not affect plasma triacylglycerol levels.]

3. **Pharmacokinetics:** *Probucol* is very lipophilic, and its absorption is highly variable. Administration with food improves absorption and reduces variability. *Probucol* is carried in the LDL particles and accumulates in adipose tissues where it may persist for months. Excretion is via the bile into the feces.

4. **Adverse effects:** Mild gastrointestinal disturbance is a common adverse effect that generally disappears with continued treatment. A more serious problem is its tendency to prolong the QT interval. Thus *probucol* is contraindicated in those patients who have an abnormally long QT interval. Care should also be taken with patients receiving drugs that prolong this interval, such as

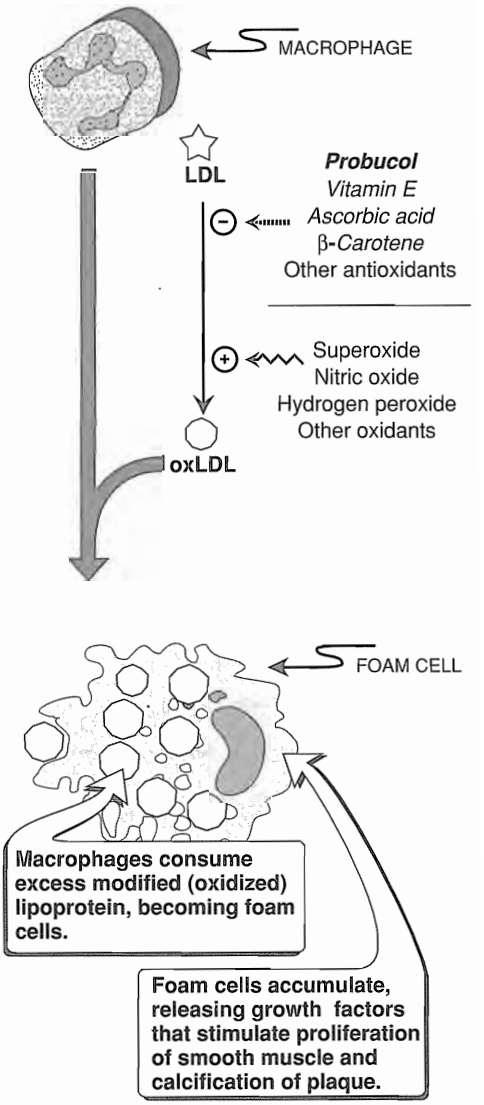

Figure 21.7
Role of *probucol* in preventing oxidation of lipoproteins.

digitalis, *quinidine*, *sotalol*, *astemizole* and *terfenadine*. Because of its long sojourn in the body, a woman should discontinue the drug at least 6 months before attempting pregnancy.

F. HMG-CoA reductase inhibitors: lovastatin, pravastatin, simvastatin and fluvastatin

This novel group of antihyperlipidemic agents inhibits the first committed enzymatic step of sterol synthesis. As structural analogs of the natural substrate, 3-hydroxy-3-methylglutaric acid (HMG), all members of this group compete to block hydroxymethylglutaryl-Coenzyme A reductase (HMG-CoA reductase).[3] Except for *fluvastatin*, the other HMG reductase inhibitors are chemical modifications of compounds occurring naturally in fungi.

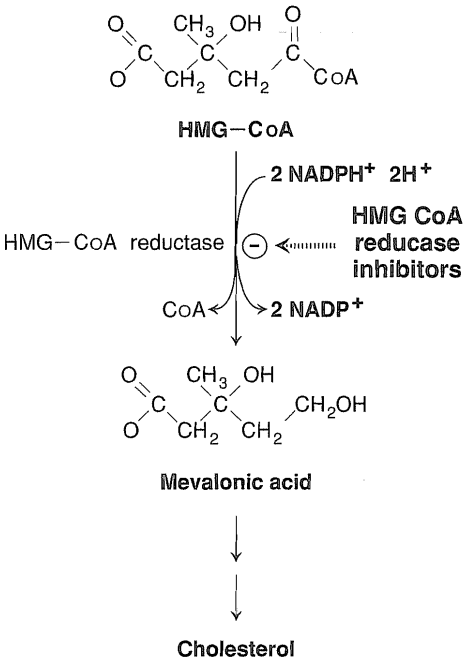

Figure 21.8
Inhibition of HMG-CoA reductase.

1. Mechanism of action

a. Inhibition of HMG-CoA reductase: *Lovastatin* [loe vah STAT in] *simvastatin* [sim vah STAT in], *pravastatin* [prah vah STAT in] and *fluvastatin* [flew vah STAT in] are analogs of 3-hydroxy-3-methylglutarate, the precursor of cholesterol. *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug. *Pravastatin* and *fluvastatin* are active as such. Because of their strong affinity for the enzyme, all compete effectively to inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 21.8).

b. Decrease in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus the end result is a reduction in plasma cholesterol both by lowered cholesterol synthesis and by increased catabolism of LDL. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG-CoA reductase inhibitors, like *cholestyramine*, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for coronary artery disease. Small decreases in triacylglycerol can also occur.

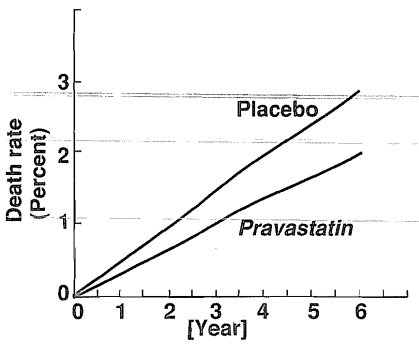

Figure 21.9
Effect of *pravastatin* therapy on deaths from all cardiovascular causes.

2. Therapeutic uses: These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias (Figure 21.9). However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and therefore benefit much less from treatment with these drugs. [Note: These drugs are often given in combination with other antihyperlipidemic drugs, see later.] It should be noted that in spite of the protection afforded by cholesterol lowering, about one fourth of the patients treated with these drugs still presented with coronary events. Thus, additional strategies such as diet, exercise, or additional agents may be warranted.

[3] See p. 216 for Infolink references to other books in this series.

3. Pharmacokinetics

Pravastatin and *fluvastatin* are almost completely absorbed after oral administration; oral doses of *lovastatin* and *simvastatin* are absorbed from 30 to 50%. Similarly, *pravastatin* and *fluvastatin* are active as such, whereas *lovastatin* and *simvastatin* must be hydrolyzed to the acid. Due to first-pass extraction, the primary action of these drugs is on the liver. All are biotransformed, with some of the products retaining activity. Excretion takes place principally through the bile and feces, but some urinary elimination also occurs. Their half-lives range from 1.5 to 2 hours.

4. **Adverse effects**: It is noteworthy that during the 5-year trials of *simvastatin* and *lovastatin*, only a few adverse effects, related to liver and muscle function, were reported (Figure 21.10).

   a. Liver: Biochemical abnormalities in liver function have occurred with the HMG-CoA reductase inhibitors. Therefore it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug. [Note: Hepatic insufficiency can cause drug accumulation.]

   b. Muscle: Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) have been rarely reported. In most of these cases, patients usually suffered from renal insufficiency or were taking drugs such as *cyclosporine, itraconazole, erythromycin, gemfibrozil,* or *niacin.* Plasma creatine kinase levels should be determined regularly.

   c. Drug interactions: The HMG-CoA reductase inhibitors also increase *coumarin* levels. Thus, it is important to evaluate prothrombin times frequently.

   d. Contraindications: These drugs are contraindicated in pregnancy and nursing mothers. They should not be used in children or teen-agers.

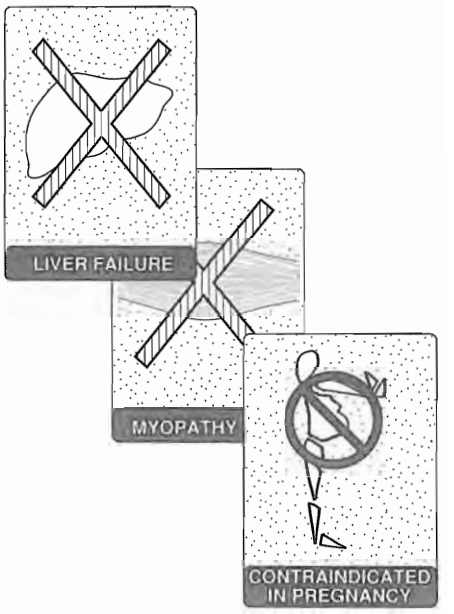

Figure 21.10
Some adverse efffects and precautionsassociated with HMG-CoA reductase inhibitors.

G. Combination Drug Therapy

It is sometimes necessary to employ two antihyperlipidemia drugs in order to achieve a significant decrease in plasma lipid levels. For example, in Type II hyperlipidemias, patients are commonly treated with a combination of *niacin* plus a bile acid binding agent, such as *cholestyramine.* [Note: Remember that *cholestyramine* causes an increase in LDL receptors that clears the plasma of circulating LDL, whereas *niacin* decreases synthesis of VLDL and therefore also the synthesis of LDL.] The combination of an HMG-CoA reductase inhibitor with a bile acid binding agent has also been shown to be useful in lowering LDL cholesterol (Figure 21.11).

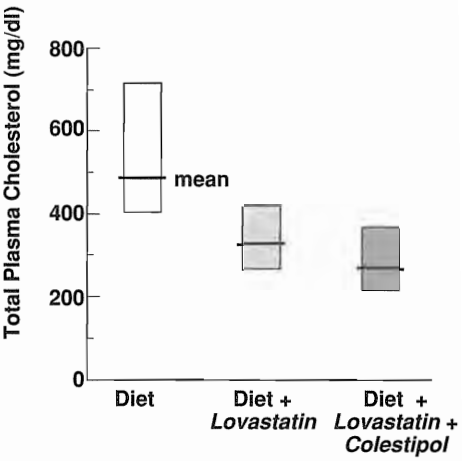

Figure 21.11
Response of total plasma cholesterol in patients with heterozygous familial hypercholesterolemia to diet (low cholesterol, low saturated fat) and hyperlipidemic drugs.

Choose the ONE best answer.

21.1 Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure
B. Gastrointestinal disturbance
C. Neurological problems
D. Heart palpitations
E. Migraine headaches

Correct answer = B. Gastrointestinal disturbances frequently occur as a side effect of antihyperlipidemic drug therapy.

21.2 Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I
B. Type II
C. Type III
D. Type IV
E. Type V

Correct answer = A. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low fat diet. No drug therapy is effective for this disorder.

21.3 Which one of the following drugs decreases de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl CoA reductase?

A. Clofibrate
B. Niacin
C. Cholestyramine
D. Lovastatin
E. Gemfibrozil

Correct answer = D. Clofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of VLDL from plasma. Niacin inhibits lipolysis in adipose tissue and thus eliminates the building blocks needed by the liver to produce triacylglycerol and therefore VLDL. Cholestyramine lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

QUESTIONS 21.4 - 21.7

DIRECTIONS: The group of questions below consists of five drugs (A–E) followed by a list of numbered statements. For each numbered statement, select the ONE drug from the list (A–E) that is most closely associated with it. Each drug may be selected once, more than once, or not at all.

Match each drug with the statement that best describes its mode of action:

A. Niacin
B. Clofibrate
C. Cholestyramine
D. Probucol
E. Lovastatin

21.4 Binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation.

Correct answer = C: Cholestyramine.

21.5 Causes a decrease in plasma triacylglycerol levels by increasing the activity of lipoprotein lipase.

Correct answer = B: Clofibrate.

21.6 Causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway.

Correct answer = A: Niacin.

21.7 Inhibits 3-hydroxy-3-methylglutaryl CoA reductase, the rate-limiting step in cholesterol synthesis.

Correct answer = E: Lovastatin.

[1]See p. 323 in **Biochemistry** (2nd ed.) for a discussion of niacin as a vitamin.

[2]See p. 213 in **Biochemistry** (2nd ed.) for a discussion of plasma lipoproteins.

[3]See p. 206 in **Biochemistry** (2nd ed.) for a discussion of the synthesis of cholesterol.

22 Drugs Affecting the Respiratory System

I. OVERVIEW

Drugs can be delivered to the lungs by inhalation, oral, or parenteral routes. Inhalation is often preferred because the drug is delivered directly to the target tissue—the airways—and is effective in doses that do not cause significant systemic side effects. Clinically useful drugs act by various mechanisms, for example, by relaxing bronchial smooth muscle, or modulating the inflammatory response. Drugs used to treat asthma, rhinitis, chronic obstructive pulmonary disease, and cough—commonly encountered respiratory disorders—are summarized in Figure 22.1.

II. DRUGS USED TO TREAT ASTHMA

Asthma is a chronic disease that affects 4 to 5% of the U.S. population, or approximately 10 million patients. The disease is characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing and rapid respirations. These acute symptoms may resolve spontaneously, or more often, require therapy such as a β_2-agonist (see p. 218). A second delayed or late-phase response may occur 4 to 12 hours later, and may require treatment with steroids. Asthma, unlike chronic bronchitis, cystic fibrosis or bronchiectasis, is usually not a progressive disease—it does not inevitably lead to crippling chronic obstructive lung disease. Rather, the clinical course of asthma is characterized by exacerbations and remissions. Deaths due to asthma are infrequent, but morbidity results in significant hospitalization and outpatient costs. The goal of therapy is to relieve symptoms and to prevent recurrence of asthmatic attacks, if possible.

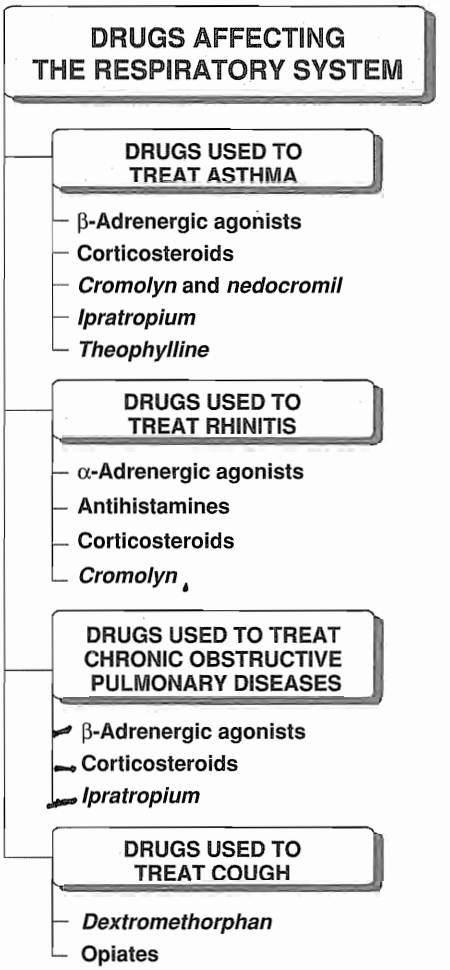

Figure 22.1
Summary of drugs affecting the respiratory system.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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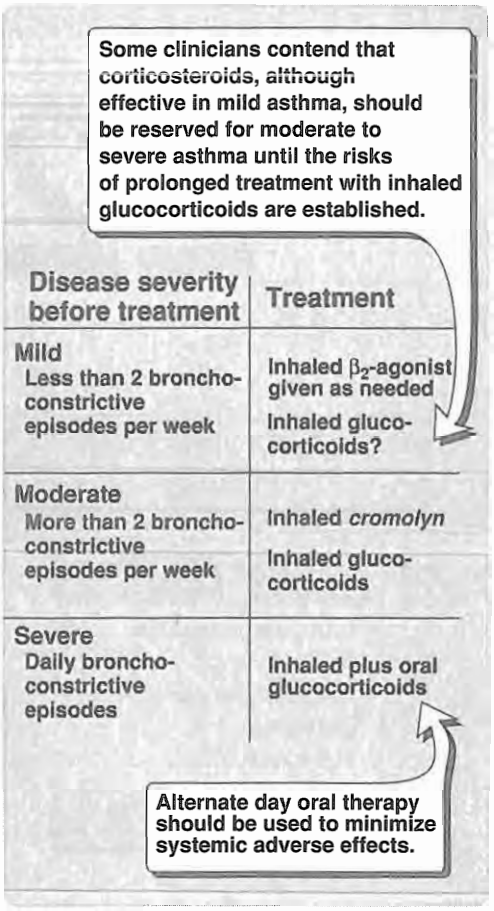

Figure 22.2
Summary of treatments for asthma of varying severity.

A. Role of inflammation in asthma

Airflow obstruction in asthma is due to bronchoconstriction resulting from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased mucous secretion. Asthmatic attacks may be related to recent exposure to allergens, inhaled irritants leading to bronchial hyperactivity and inflammation of the airway mucosa. The symptoms of asthma may be effectively treated by several drugs, but none of the agents provide a cure for this obstructive lung disease.

A. Adrenergic agonists

Inhaled adrenergic agonists with β_2 activity are the drugs of choice for mild asthma, that is, in patients showing only occasional, intermittent symptoms (Figure 22.2). β_2-Agonists are potent bronchodilators that relax airway smooth muscle directly.

1. **Short acting drugs:** Most clinically useful β-agonists have a rapid (15 to 30 minutes) onset of action and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm and as "rescue agents" to combat acute bronchoconstriction. [Note: *Epinephrine* (see p. 61) is the drug of choice for treatment of acute anaphylaxis.] β_2-Agonists have no anti-inflammatory effects and they should never be used as the sole therapeutic agents for patients with chronic asthma. The β_2-selective agents, such as *pirbuterol*, *terbutaline*, and *albuterol* (see p. 67), offer the advantage of providing maximally attainable bronchodilation with little of the undesired effect of α or β_1 stimulation. (See p. 60 for the receptor-specific actions of adrenergic agonists.) The β_2-agonists are not catecholamines and thus are not destroyed by catechol O-methyltransferase (COMT). Toxic side effects, such as tachycardia, hyperglycemia, hypokalemia and hypomagnesemia, are minimized when the drugs are delivered by inhalation rather than by systemic routes. Though tolerance to the β-agonists' effects on non-airway tissues occurs, it is uncommon with normal dosages.

2. **Long acting drugs:** *Salmeterol xinatoate* [sal MEE ter ol] is a chemical analog of *albuterol*, but differs by having a long lipophilic side chain that increases the affinity of the drug for the β-adrenoceptor. *Salmeterol* has a long duration of action, providing bronchodilation for at least 12 hours. *Salmeterol* has a slow onset of action and should not be used in acute asthmatic attacks; it should only be prescribed for administration at regular intervals and not to relieve symptoms. Like the others in this drug class, it is not a substitute for anti-inflammatory therapy.

B. Corticosteroids

Inhaled glucocorticoids are the drugs of first choice in patients with moderate to severe asthma who require inhalation of β_2-adrenergic agonists more than once daily (see Figure 22.2). Severe asthma may also require systemic glucocorticoids, usually for short term. Inhaled glucocorticoids often reduce (or eliminate) the need for oral glucocorticoids in patients with severe asthma.

To be effective in controlling inflammation, glucocorticoids must be taken continuously. (See p. 272 for a summary of the mechanism of action of corticosteroids.)

1. **Actions on lung:** Steroids have no direct effect on the airway smooth muscle. Instead, inhaled glucocorticoids decrease the number and activity of cells involved in airway inflammation—macrophages, eosinophils, and T-lymphocytes. Prolonged (several months) inhalation of steroids reduces the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise. Anti-inflammatory steroids reduce inflammation by reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes. Bronchial reactivity is greatly reduced.

2. **Pharmacokinetics**

   a. **Inhaled drugs:** The development of inhaled steroids has markedly reduced the need for systemic corticosteroid treatment. However, a few precautions are required for successful inhalation therapy. A large fraction (typically 80 to 90%) of inhaled glucocorticoids is deposited in the mouth and pharynx, or is swallowed (Figure 22.3). These glucocorticosteroids are absorbed from the gut and enter the systemic circulation through the liver. However, many of the clinically useful corticosteroids, such as *beclomethasone*, *triamcinolone*, and *flunisolide* [floo NISS oh lide], undergo extensive first-pass metabolism in the liver so that only a small amount of these drugs reaches the systemic circulation. The 10 to 20% of the metered dose of inhaled glucocorticoids that is not swallowed is deposited in the airway.

   b. **Systemic steroids:** Patients with severe exacerbation of asthma (status asthmaticus) may require intravenous administration of *methylprednisolone* or oral *prednisone* (see p. 275). Once the patient has improved, the dose of drug is gradually reduced, leading to discontinuance in 1 to 2 weeks.

   c. **Spacers:** A spacer is a large volume chamber that is attached to the metered-dose inhaler and is used to decrease the deposition of drug in the mouth (Figure 22.4). The chamber serves to reduce the velocity of the injected aerosol before it enters the mouth, and allows large drug particles to be deposited in the device. The smaller, low-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue. Spacers improve delivery of inhaled glucocorticoids and are advised in virtually all patients. [Note: Rinsing the mouth after inhalation can also decrease systemic absorption and the possibility of oropharyngeal candidiasis.]

3. **Adverse effects:** Oral or parenteral glucocorticoids have a variety of potentially serious side effects (see p. 277). However, inhaled glucocorticoids, particularly if used with a spacer, have few systemic effects. Oropharyngeal candidiasis—sometimes called thrush—may be a problem in patients who inhale glucocorticoids,

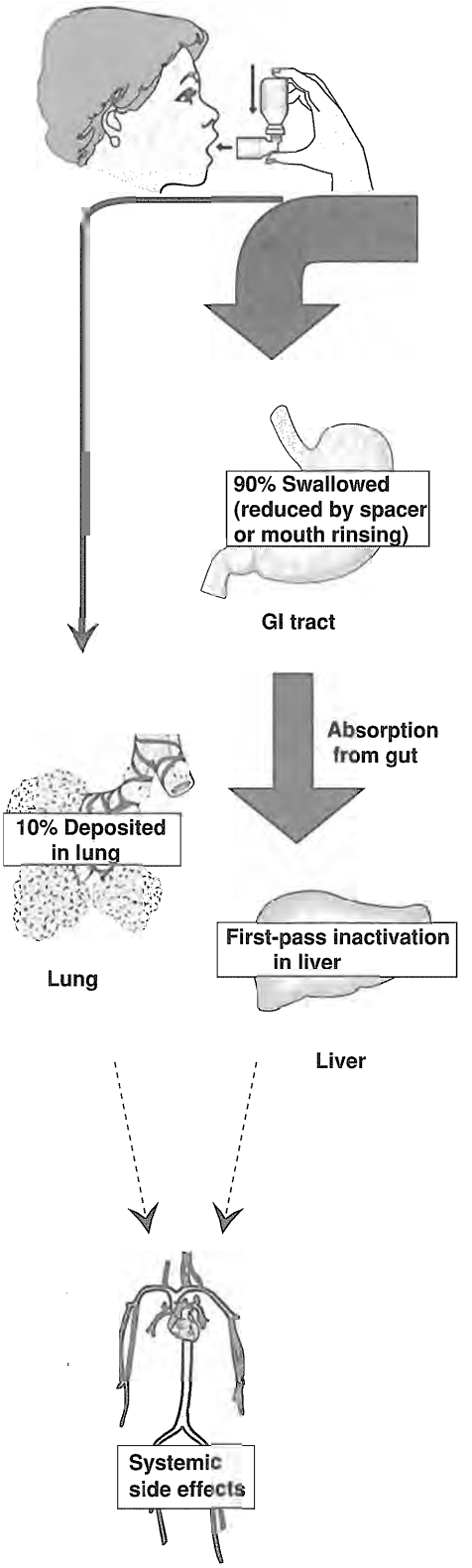

Figure 22.3
Pharmacokinetics of inhaled glucocorticoids.

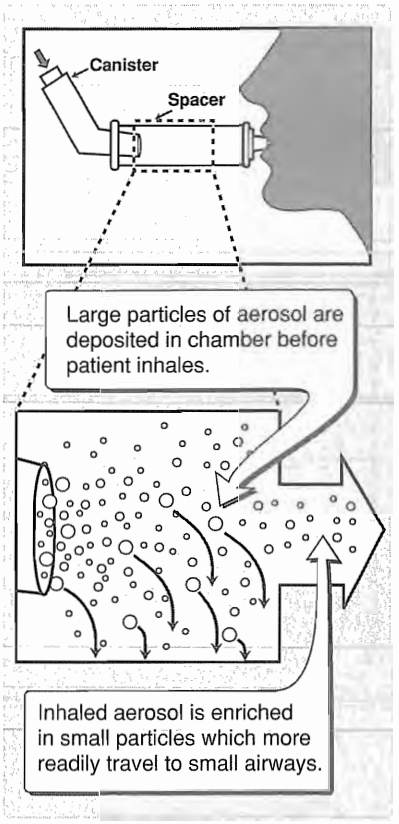

Figure 22.4
Effect of spacer on the delivery of an inhaled aerosol.

particularly immunosuppressed patients. Spacers minimize the problem of adrenal suppression by reducing the amount of glucocorticoid deposited in the oropharynx.

C. Cromolyn and nedocromil

Cromolyn [KROE moe lin] and *nedocromil* [neh DOC ro mil] are effective prophylactic anti-inflammatory agents, but are not useful in managing an acute asthmatic attack because they are not direct bronchodilators. These agents can block the precipitation of immediate and delayed asthmatic reactions. For use in asthma, *cromolyn* is administered by inhalation of a microfine powder, or as an aerosolized solution. Because it is poorly absorbed, only minor adverse effects are associated with it. Pretreatment with *cromolyn* blocks allergen-induced and exercise-induced bronchoconstriction. *Cromolyn* is also useful in reducing the symptoms of allergic rhinitis (see p. 222). A 4- to 6-week trial is required to determine efficacy. Given its safety, an initial trial of *cromolyn* is often recommended, particularly in children and pregnant women. Toxic reactions are mild; they include a bitter taste and irritation of the pharynx and larynx.

D. Cholinergic antagonists

Anticholinergic agents are generally less effective than β-adrenergic agonists. They block the vagally mediated contraction of airway smooth muscle and mucus secretion. Inhaled *ipratropium* [i pra TROE pee um], a quaternary derivative of *atropine* (Figure 22.5), is useful in patients unable to tolerate adrenergic agonists. *Ipratropium* is slow in onset, and is nearly free of side-effects.

E. Theophylline

Theophylline [the OFF i lin] is a bronchodilator that relieves airflow obstruction in chronic asthma, and decreases the symptoms of the chronic disease. Previously the main-stay of asthma therapy, *theophylline* has been largely replaced with β-agonists and corticosteroids. *Theophylline* is well absorbed by the gastrointestinal tract, and several sustained-release preparations are available. The drug has a narrow therapeutic window, and an overdose of the drug may cause seizures or potentially fatal arrhythmias. Further, *theophylline* interacts adversely with many drugs.

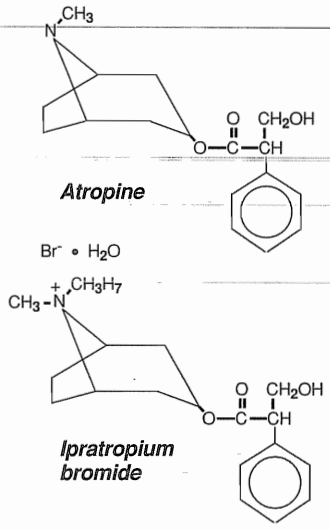

Figure 22.5
Ipratropium, a quaternary amine derivative of *atropine*.

III. DRUGS USED TO TREAT ALLERGIC RHINITIS

Rhinitis is an inflammation of the mucous membranes of the nose, and is characterized by sneezing, nasal itching, watery rhinorrhea and congestion. An attack may be precipitated by inhalation of allergen (such as dust, pollen, or animal dander), which interacts with mast cells coated with IgE, generated in response to a previous exposure to the allergen (Figure 22.6). The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors, which promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Combinations of oral antihistamines with decongestants are the first-line therapy for allergic rhinitis. However, the systemic

effects sometimes associated with these oral preparations (sedation, insomnia, and rarely cardiac arrhythmias) have prompted interest in topical intranasal delivery of drugs for the treatment of allergic rhinitis.

A. Antihistamines (H_1 receptor blockers)

Antihistamines are the most frequently used agents in the treatment of sneezing and watery rhinorrhea associated with allergic rhinitis. H_1-Histamine receptor blockers, such as *diphenhydramine, chlorpheniramine, loratadine, terfenadine* and *astemizole* (see p. 422), are useful in treating the symptoms of allergic rhinitis caused by histamine release. Combinations of antihistamines with decongestants (see below) are effective when congestion is a feature of rhinitis. They differ in their ability to cause sedation, and their duration of action.

B. α-Adrenergic agonists

α-Adrenergic agonists ("nasal decongestants") such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Long-acting *oxymetazoline* [ox i met AZ oh leen] is also available. When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Oral administration results in longer duration of action but increased systemic effects. Combinations of these agents with antihistamines are frequently used. However, they should be used no longer than several days because rebound nasal congestion often occurs upon discontinuance of these drugs. Therefore, α-adrenergic agents have no place in the long-term treatment of allergic rhinitis.

C. Corticosteroids

Corticosteroids, such as *beclomethasone, fluticasone, flunisolide* and *triamcinolone* (see p. 275), are effective when administered as nasal sprays. [Note: Systemic absorption is minimal and side effects of intranasal corticosteroid treatment are localized—nasal irritation, nosebleed, sore throat and, rarely candidiasis.] Topical steroids may be more effective than systemic antihistamines in relieving the nasal symptoms of both allergic and nonallergic rhinitis. The effects of long-term usage are unknown, although they are considered to be generally safe. Periodic assessment of the patient is advised. Treatment of chronic rhinitis may not result in improvement until 1 to 2 weeks after starting therapy.

D. Cromolyn

Intranasal *cromolyn* may be useful, particularly when administered before contact with an allergen.

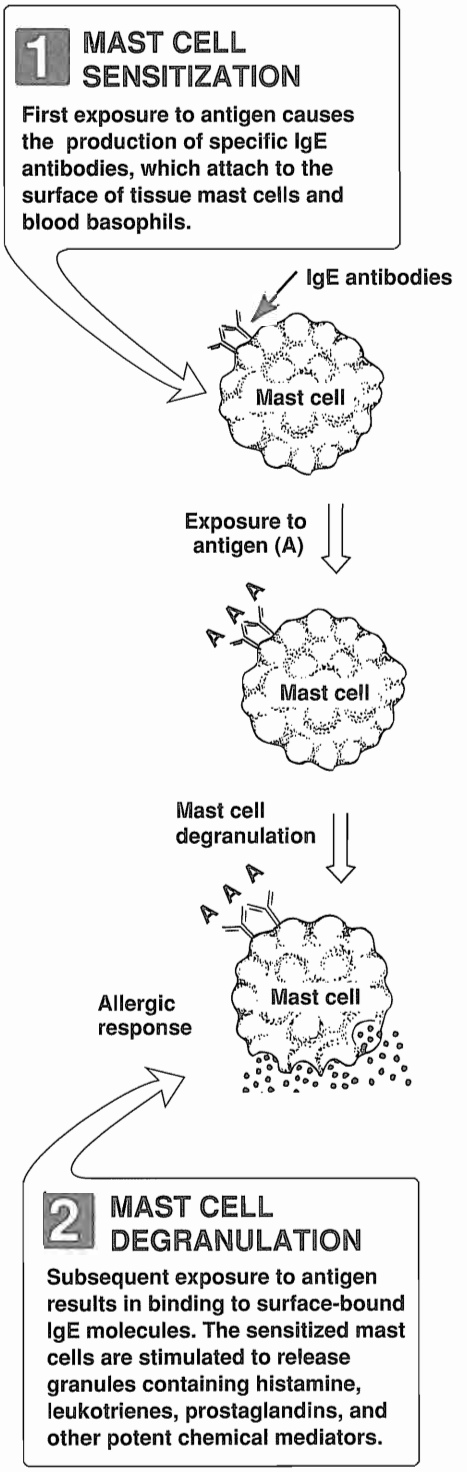

Figure 22.6
Hypersensitivity reactions mediated by IgE molecules can cause rhinitis.

IV. DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) affects approximately 30 million people in the U.S., and is the fifth most common cause of

death. It is a chronic, irreversible obstruction of air flow. Smoking is the greatest risk factor for COPD. The disease may respond to bronchodilators, such as anticholinergic agents, β-adrenergic agents and *theophylline*. Therapy does not cure the disease or even significantly slow its progress. Treatment consists of a trial of β_2-agonist or *ipratropium* to assess any reversible component of the disease, and is a reasonable first-line initial therapy for all patients. Glucocorticoids may be helpful in the treatment of acute exacerbations in some patients.

V. DRUGS USED TO TREAT COUGH

Codeine, *hydrocodone*, and *hydromorphone* decrease the sensitivity of CNS cough centers to peripheral stimuli, and decrease mucosal secretion. These actions occur at doses lower than required for analgesia (see p. 135 for a more complete discussion of the opiates). *Dextromethorphan* [dex troe meth OR fan], a synthetic derivative of morphine, suppresses the response of the cough center. It has no analgesic or addictive potential, and is less constipating than codeine.

Study Questions

Questions 22.1 to 22.4:

A 12-year-old girl with a childhood history of asthma complained of cough, dyspnia, and wheezing after visiting a riding stable. Her symptoms became so severe that her parent brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 132/65 mm Hg.

For each of the statements below choose the most appropriate drug from the following list:

A. Inhaled cromolyn
B. Inhaled beclomethasone
C. Oral or IV methylprednisolone
D. Inhaled ipratropium
E. Inhaled albuterol
F. Intravenous propranolol
G. Diphenhydramine
H. Inhaled salmeterol
I. Oxymetazoline

22.1 The most appropriate drug to rapidly reverse bronchoconstriction.

22.1 Correct answer = E. Inhalation of a rapid acting β_2 agonist, such as albuterol, usually provides immediate bronchodilation.

22.2 The drug most likely to provide sustained resolution of the patient's symptoms.

22.2 Correct answer = C. An acute asthmatic crisis often requires IV corticosteroids, often methylprednisolone. Inhaled beclomethasone will not deliver enough steroid to fully combat airway inflammation.

22.3 A drug contraindicated in this patient.

22. 3. Correct answer = F. Propranolol is a β-blocker and would aggravate the patient's bronchoconstriction

22.4 A drug likely to be ineffective in this patient.

22. 4. Correct answer = A. Cromolyn can be used prophylactically to reduce the inflammatory response, but is ineffective in relieving acute symptoms.

Diuretic Drugs

23

I. OVERVIEW

Drugs inducing a state of increased urine flow are called diuretics. These agents are ion transport inhibitors that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions such as Cl^- enter the urine in greater amounts than normal along with water, which is carried passively to maintain osmotic equilibrium. Diuretics thus increase the volume of the urine and often change its pH as well as the ionic composition of the urine and blood. The efficacy of the different classes of diuretics varies considerably, with the increase in secretion of Na^+ varying from less than 2% for the weak, potassium-sparing diuretics, to over 20% for the potent loop diuretics. Their major clinical uses are in managing disorders involving abnormal fluid retention (edema) or in treating hypertension in which their diuretic action causes a decreased blood volume, leading to a reduction in blood pressure. In this chapter, the diuretic drugs (Figure 23.1) are discussed in the order of their site of action along the nephron (Figure 23.2).

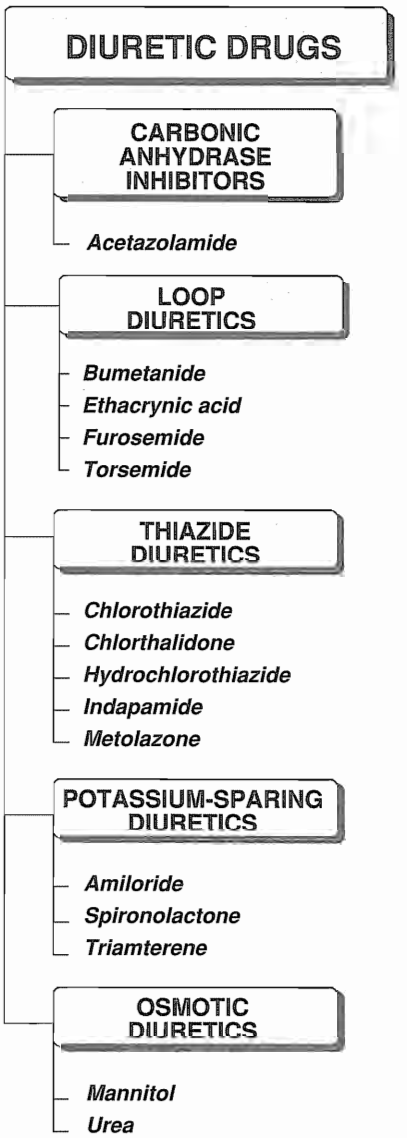

Figure 23.1
Summary of diuretic drugs.

II. NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16–20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, does contain most low molecular weight plasma components in approximately the same concentrations as are found in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, plus electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of urine by the reabsorption or secretion of ions and/or water at five functional zones along the nephron, namely the proximal convoluted tubule, the descending loop of Henle, the ascending loop of Henle, the distal convoluted tubule, and the collecting duct (Figure 23.2).

A. Proximal convoluted tubule

In the extensively convoluted proximal tubule located in the cortex of the kidney, almost all of the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two thirds of the Na^+ is also reabsorbed in the proximal tubule; chloride and water

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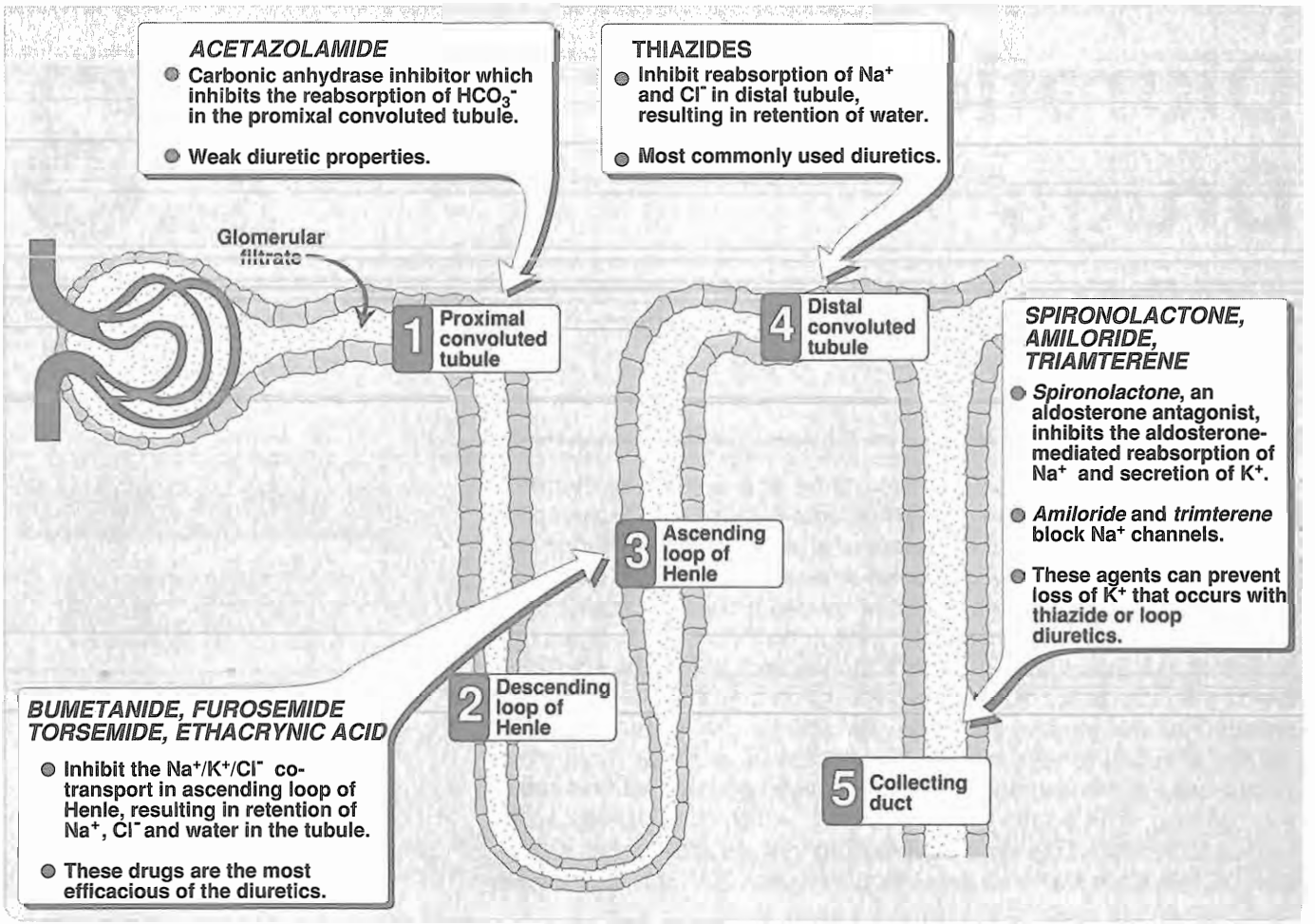


Figure 23.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

follow passively to maintain electrical and osmolar equality. If it were not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and lose its normal osmolarity.

1. **Acid secretory system:** The proximal tubule is the site of the organic acid and base secretory systems (Figure 23.3). The organic acid secretory system secretes a variety of organic acids (such as uric acid, some antibiotics, diuretics) from the bloodstream into the proximal tubule's lumen. Most diuretic drugs are delivered to the tubular fluid via this system. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids, such as uric acid. This explains the hyperuricemia seen with certain of the diuretic drugs, such as *furosemide* or *chlorothiazide*.

B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney.

The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism. This results in a tubular fluid with a three-fold increase in salt concentration.

C. Ascending loop of Henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+ and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Mg^{++} and Ca^{++} enter the interstitial fluid via the paracellular pathway. The ascending loop is thus a diluting region of the nephron. Approximately 25–30% of the tubular sodium chloride returns to the interstitial fluid, thus helping to maintain the fluid's high osmolarity. Since the loop of Henle is a major site for salt reabsorption, drugs affecting this site, such as loop diuretics, are the most efficacious of all the diuretic classes.

D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 10% of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter, which is sensitive to thiazide diuretics. Additionally, Ca^{++} excretion is regulated by parathyroid hormone in this portion of the tubule.

E. Collecting tubule and duct

The principal and intercalated cells of the collecting tubule are responsible for Na^+– K^+ exchange and for H^+ secretion and K^+ reabsorption, respectively. Stimulation of aldosterone receptors in the principal cells results in Na^+ reabsorption and K^+ secretion. Antidiuretic hormone (ADH, vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts (Figure 23.3). This action is mediated by cAMP.

III. KIDNEY FUNCTION IN DISEASE

In many diseases the amount of sodium chloride reabsorbed by the kidney tubules is abnormally high. This leads to the retention of water, an increase in blood volume, and expansion of the extravascular fluid compartment, resulting in edema of the tissues. Several commonly encountered causes of edema include:

A. Congestive heart failure

The decreased ability of the failing heart to sustain adequate cardiac output causes the kidney to respond as if there were a decrease in blood volume. The kidney, as part of the normal compensatory mechanism, retains more salt and water as a means of raising blood volume and increasing the amount of blood that is returned to the heart. However, the diseased heart cannot increase its output, and the increased vascular volume results in edema (see p. 151 for causes and treatment of congestive heart failure).

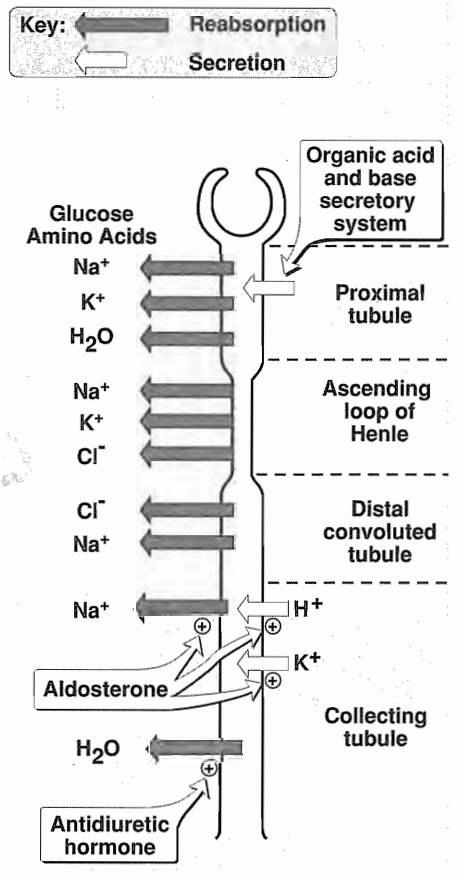


Figure 23.3
Sites of transport of solutes and water along the nephron.

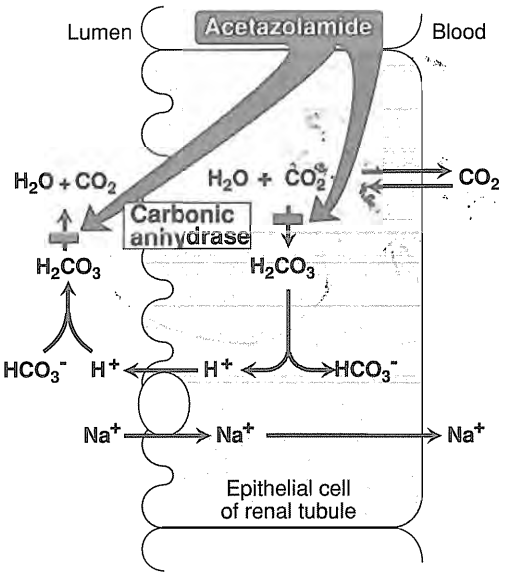


Figure 23.4
Role of carbonic anhydrase in sodium retention by epithelial cells of renal tubule.

B. Hepatic ascites

Ascites, the accumulation of fluid in the abdominal cavity, is a common complication of cirrhosis of the liver.

1. **Increased portal blood pressure:** Blood flow in the portal system is often obstructed in cirrhosis, resulting in an increased portal blood pressure. Further, colloidal osmotic pressure of the blood is decreased as a result of impaired synthesis of plasma proteins by the diseased liver. Increased portal blood pressure and low osmolarity of the blood cause fluid to escape from the portal vascular system and collect in the abdomen.

2. **Secondary hyperaldosteronism:** Fluid retention is also promoted by elevated levels of circulating aldosterone. This secondary hyperaldosteronism results from the decreased ability of the liver to inactivate the steroid hormone and leads to increased Na^+ and water reabsorption, increased vascular volume, and exacerbation of fluid accumulation (see Figure 23.3).

C. Nephrotic syndrome

When damaged by disease, the glomerular membranes allow plasma proteins to enter the glomerular ultrafiltrate. The loss of protein from the plasma reduces the colloidal osmotic pressure resulting in edema. The low plasma volume stimulates aldosterone secretion through the renin-angiotensin-aldosterone system (see p. 180). This leads to retention of Na^+ and fluid, further aggravating the edema.

D. Premenstrual edema

Edema associated with menstruation is the result of imbalances in hormones such as estrogen excess, which facilitates the loss of fluid into the extracellular space. Diuretics can reduce the edema.

IV. CARBONIC ANHYDRASE INHIBITORS

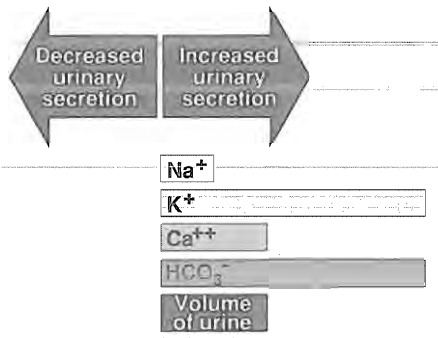


Figure 23.5
Relative changes in the composition of urine induced by *acetazolamide*.

Acetazolamide [a set a ZOLE a mide] is a sulfonamide without antibacterial activity. Its main action is to inhibit the enzyme carbonic anhydrase in the proximal tubular epithelial cells. However, carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect, because these agents are much less efficacious than the thiazides or loop diuretics.

A. Acetazolamide

1. **Mechanism of action:** *Acetazolamide* inhibits carbonic anhydrase, located intracellularly and on the apical membrane of the proximal tubular epithelium (Figure 23.4). [Note: Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O leading to H^+ and HCO_3^- (bicarbonate)]. The decreased ability to exchange Na^+ for H^+ in the presence of *acetazolamide* results in a mild diuresis. Additionally, HCO_3^- is retained in the lumen with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic

metabolic acidosis and decreased diuretic efficacy following several days of therapy. Changes in the composition of urinary electrolytes induced by *acetazolamide* are summarized in Figure 23.5.

2. **Therapeutic uses:**

   a. **Treatment of glaucoma:** The most common use of *acetazolamide* is to reduce the elevated intraocular pressure of open-angle glaucoma. *Acetazolamide* decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary body of the eye. It is useful in the chronic treatment of glaucoma but should not be used for an acute attack; *pilocarpine* (see p. 41) is preferred for an acute attack because of its immediate action.

   b. **Epilepsy:** *Acetazolamide* is sometimes used in the treatment of epilepsy—both generalized and partial. It reduces the severity and magnitude of the seizures. Often *acetazolamide* is used chronically in conjunction with antiepileptic medication to enhance the action of these other drugs.

   c. **Mountain sickness:** Less commonly *acetazolamide* can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet. *Acetazolamide* given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral and pulmonary edema characteristic of the syndrome.

3. **Pharmacokinetics:** *Acetazolamide* is given orally once a day.

4. **Adverse effects:** Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur.

V. LOOP OR HIGH-CEILING DIURETICS

Bumetanide [byoo MET a nide], *furosemide* [fur OH se mide], *torsemide* [TOR se myde] and *ethacrynic acid* [eth a KRIN ik] are four diuretics that have their major action on the ascending limb of the loop of Henle (Figure 23.2). Compared to all other classes of diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body. *Ethacrynic acid* has a steeper dose-response curve (see p. 21) than *furosemide*; it shows greater side effects than those seen with the other loop diuretics and is not as widely used. *Bumetanide* is much more potent than *furosemide*, and its use is increasing.

A. Bumetanide, furosemide, torsemide, ethacrynic acid

1. **Mechanism of action:** Loop diuretics inhibit the $Na^+/K^+/Cl^-$ cotransport of the luminal membrane in the ascending limb of the loop of Henle. Therefore reabsorption of Na^+, K^+, and Cl^- is decreased (Figure 23.6). The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25–30% of filtered NaCl and downstream sites are not able to compensate for this increased Na^+ load.

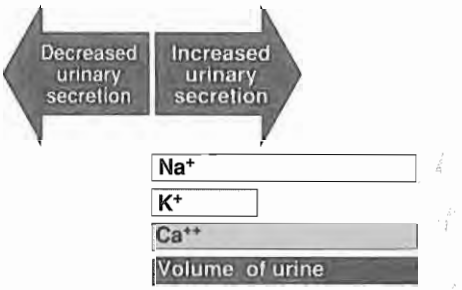


Figure 23.6
Relative changes in the composition of urine induced by loop diuretics.

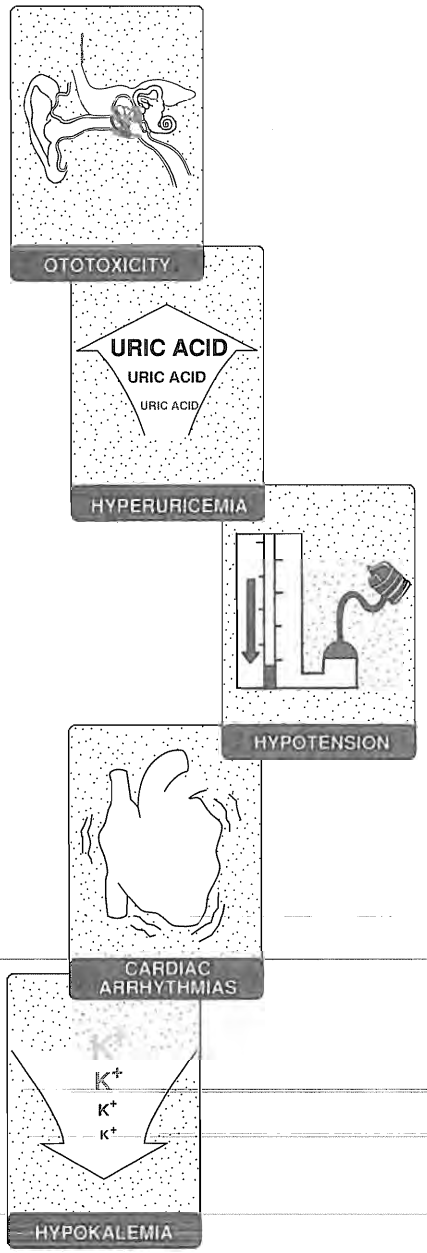


Figure 23.7
Summary of adverse effects commonly observed with loop diuretics.

2. **Actions:** The loop diuretics act promptly, even among patients who have poor renal function or who have not responded to thiazides or other diuretics. Changes in the composition of the urine induced by loop diuretics are shown in Figure 23.6. [Note: Loop diuretics increase the Ca^{++} content of urine, while thiazide diuretics (see p. 229) decrease the Ca^{++} concentration of the urine.] The loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

3. **Therapeutic uses:** The loop diuretics are the drugs of choice for reducing the acute pulmonary edema of congestive heart failure. Because of their rapid onset of action, the drugs are useful in emergency situations, such as acute pulmonary edema, which calls for a rapid, intense diuresis. Loop diuretics (along with hydration) are also useful in treating hypercalcemia because they stimulate tubular Ca^{++} secretion.

4. **Pharmacokinetics:** Loop diuretics are administered orally or parenterally. Their duration of action is relatively brief, 1 to 4 hours.

5. **Adverse effects:**

   a. **Ototoxicity:** Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics (see p. 314). Permanent damage may result with continued treatment. Vestibular function is less likely to be disturbed, but it too may be affected by combined treatment.

   b. **Hyperuricemia:** *Furosemide* and *ethacrynic acid* compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and thereby causing or exacerbating gouty attacks.

   c. **Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

   d. **Potassium depletion:** The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, with the possibility of inducing hypokalemia. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Potassium depletion can be averted by use of potassium-sparing diuretics or dietary supplementation with K^+. The adverse effects of the loop diuretic are summarized in Figure 23.7.

VI. THIAZIDES AND RELATED AGENTS

The thiazides are the most widely used of the diuretic drugs. They are sulfonamide derivatives and are related in structure to the carbonic anhydrase inhibitors. The thiazides have significantly greater diuretic activity than *acetazolamide*, and they act on the kidney by different mechanisms. All thiazides affect the distal tubule, and all have equal maximum diuretic effect, differing only in potency, expressed on a per - milligram basis.

A. Chlorothiazide

Chlorothiazide [klor oh THYE a zide], the prototype thiazide diuretic, was the first modern diuretic that was active orally and was capable of affecting the severe edema of cirrhosis and congestive heart failure with a minimum of side effects. Its properties are representative of the thiazide group, although newer derivatives such as *hydrochlorothiazide* or *chlorthalidone* are now used more commonly.

1. **Mechanism of action:** The thiazide derivatives act mainly in the distal tubule to decrease the reabsorption of Na^+ by inhibition of a Na^+/Cl^- cotransporter on the luminal membrane (see Figure 23.2). They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. The acid-base balance is not usually affected. [Note: Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.]

2. **Actions:**

   a. **Increased excretion of Na^+ and Cl^-:** *Chlorothiazide* causes diuresis with increased Na^+ and Cl^- excretion, which can result in the excretion of a very hyperosmolar urine. This latter effect is unique among the other diuretic classes, which are unlikely to produce a hyperosmolar urine. The diuretic action is not affected by the acid-base status of the body, nor does *chlorothiazide* use change the acid-base status of the blood. The relative changes in the ionic composition of the urine during therapy with thiazide diuretics is given in Figure 23.8.

   b. **Loss of K^+:** Because thiazides increase the Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+. Thus, prolonged use of these drugs results in continual loss of K^+ from the body. Therefore, it is imperative to measure serum K^+ once per month (more frequently at the beginning of therapy) to assure that hypokalemia does not develop. Often, K^+ can be supplemented by diet alone, such as by increasing the intake of citrus fruits, bananas, and prunes. In some cases, K^+ salt supplementation may be necessary.

   c. **Decreased urinary calcium excretion:** Thiazide diuretics decrease the Ca^{++} content of urine by promoting the reabsorption of Ca^{++}. This contrasts with the loop diuretics (see p. 227), which increase the Ca^{++} concentration of the urine.

   d. **Reduced peripheral vascular resistance:** An initial reduction in blood pressure results from a decrease in blood volume and therefore a decrease in cardiac output (see p. 180). With continued therapy, volume recovery occurs. However, there are continued hypotensive effects, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle. This usually occurs prior to the diuretic effect.

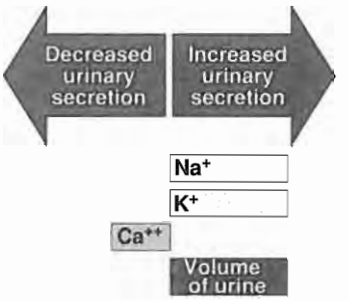


Figure 23.8
Relative changes in the composition of urine induced by thiazide diuretics.

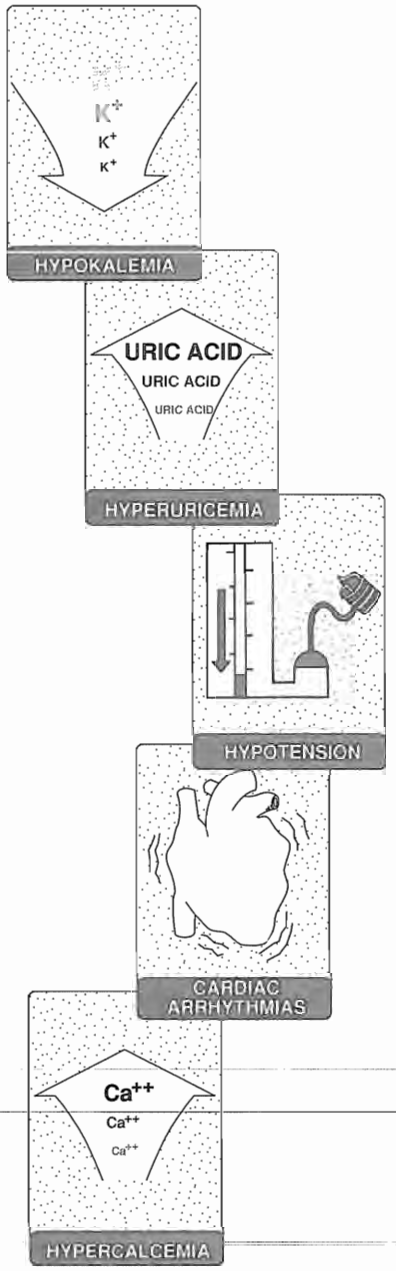


Figure 23.9
Summary of adverse effects commonly observed with thiazide diuretics.

3. Therapeutic uses:

a. Hypertension: Clinically, the thiazides have long been the mainstay of antihypertensive medication, since they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension (see p. 181 for details on treatment of hypertension). After 3–7 days of treatment, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily dosage level of the drug, which causes lower peripheral resistance without having a major diuretic effect. Many patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as β-adrenergic blockers (see p. 189).

b. Congestive heart failure: Thiazides can be the diuretic of choice in reducing extracellular volume in mild to moderate congestive heart failure (see p. 157). If the thiazide fails, loop diuretics may be useful.

c. Renal impairment: Patients with nephrotic syndrome accompanied by edema are initially treated with loop diuretics; only if this treatment fails are they given *metolazone* in conjunction with a loop diuretic.

d. Hypercalciuria: The thiazides can be useful in treating idiopathic hypercalciuria because they inhibit urinary Ca^{++} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

e. Diabetes insipidus: Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can substitute for the antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug.

4. Pharmacokinetics: The drugs are effective orally. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged biological half-life (40 hours). All thiazides are secreted by the organic acid secretory system of the kidney (see p. 224).

5. Adverse effects:

a. Potassium depletion: Hypokalemia is the most frequent problem encountered with the thiazide diuretics and can predispose patients on *digitalis* (see p. 160) to ventricular arrhythmias (Figure 23.9). Activation of the renin-angiotensin-aldosterone system by the decrease in intravascular volume contributes significantly to urinary K^+ losses. The K^+ deficiency can be overcome by *spironolactone*, which interferes with aldosterone action, or by administering *triamterene*, which acts to retain K^+ (see p. 223). Low sodium diets blunt the potassium depletion caused by thiazide diuretics.

b. Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, the uric acid deposits in the joints, and a full-blown attack of gout may result in individuals predisposed to gouty attacks. It is important, therefore, to perform periodic blood tests for uric acid levels.

c. Volume depletion: This can cause orthostatic hypotension or light-headedness.

d. Hypercalcemia: The thiazides inhibit the secretion of Ca^{++}, sometimes leading to elevated levels of Ca^{++} in the blood.

e. Hyperglycemia: Patients with diabetes mellitus, who are taking thiazides for hypertension, may become hyperglycemic and have difficulty in maintaining appropriate blood sugar levels.

f. Hypersensitivity: Bone marrow suppression, dermatitis, necrotizing vasculitis, and interstitial nephritis are very rare.

B. Hydrochlorothiazide

Hydrochlorothiazide is a thiazide derivative that has proven to be more popular than the parent drug. This is because it has far less ability to inhibit carbonic anhydrase as compared to *chlorothiazide*. It is also more potent, so that the required dose is considerably less than that of *chlorothiazide*. On the other hand, the efficacy is exactly the same as that of the parent drug.

C. Chlorthalidone

Chlorthalidone [klor THAL i done] is a thiazide derivative that behaves like *hydrochlorothiazide*. It has a very long duration of action and therefore is often used to treat hypertension. It is given once per day for this indication.

D. Thiazide analogs

1. **Metolazone:** *Metolazone* [me TOLE a zone] is more potent than the thiazides and, unlike the thiazides, causes Na^{+} excretion in advanced renal failure.

2. **Indapamide:** *Indapamide* [in DAP a mide] is a lipid soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. *Indapamide* is often used in advanced real failure to stimulate additional diuresis on top of that achieved by loop diuretics. *Indapamide* is metabolized and excreted by the gastrointestinal tract and the kidneys; it therefore is less likely to accumulate in patients with renal failure and may be useful in their treatment.

VII. POTASSIUM-SPARING DIURETICS

These agents act in the collecting tubule to inhibit Na^+ reabsorption, K^+ secretion, and H^+ secretion (Figure 23.10). Potassium-sparing diuretics are used primarily when aldosterone is present in excess. The major use of potassium-sparing agents is in the treatment of hypertension, most often in combination with a thiazide. It is extremely important that patients treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted.

A. Spironolactone

1. **Mechanism of action:** *Spironolactone* [spye row no LAK tone] is a synthetic aldosterone antagonist that competes with aldosterone for intracellular cytoplasmic receptor sites. The *spironolactone*-receptor complex is inactive, that is, it prevents translocation of the receptor complex into the nucleus of the target cell, and thus does not bind to DNA. This results in a failure to produce proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate the Na^+–K^+ exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na^+ reabsorption and therefore K^+ and H^+ secretion.

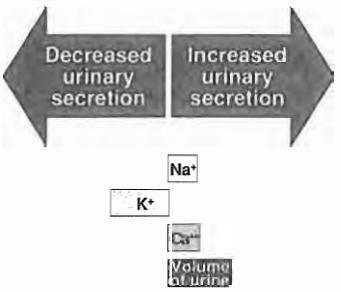


Figure 23.10
Relative changes in the composition of urine induced by potassium-sparing diuretics.

2. **Actions:** In most edematous states, blood levels of aldosterone are high, which is instrumental in retaining Na^+ (see p. 225). When *spironolactone* is given to a patient with elevated circulating levels of aldosterone, the drug antagonizes the activity of the hormone, resulting in retention of K^+ and excretion of Na^+ (Figure 23.10). Where there are no significant circulating levels of aldosterone, such as in Addison's disease (primary adrenal insufficiency), no diuretic effect of the drug occurs.

3. **Therapeutic uses:**

   a. **Diuretic:** Although *spironolactone* has a low efficacy in mobilizing Na^+ from the body in comparison with the other drugs, it has the useful property of causing the retention of K^+ (Figure 23.10). Because of this latter action, *spironolactone* is often given in conjunction with a thiazide or loop diuretic to prevent K^+ excretion that would otherwise occur with these drugs.

   b. **Secondary hyperaldosteronism:** *Spironolactone* is the only potassium-sparing diuretic that is routinely used alone to induce net negative salt balance. It is particularly effective in clinical situations associated with secondary hyperaldosteronism.

4. **Pharmacokinetics**: *Spironolactone* is completely absorbed orally and is strongly bound to proteins. It is rapidly converted to an active metabolite, *canrenone* [KAN ra none]. The action of *spironolactone* is largely due to the effect of *canrenone*, which has mineralocorticoid-blocking activity. *Spironolactone* induces hepatic cytochrome P-450.

5. **Adverse effects:** Because *spironolactone* chemically resembles some of the sex steroids, it does have minimal hormonal activity and may induce gynecomastia in males and menstrual irregularities in females. Because of this, the drug should not be given in high doses on a chronic basis. It is most effectively employed in mild edematous states where it is given for a few days at a time. At low doses, *spironolactone* can be used chronically with few side effects. Hyperkalemia, nausea, lethargy, and mental confusion can occur.

B. Triamterene and amiloride

Triamterene [trye AM ter een] and *amiloride* [a MIL oh ride] block Na^+ transport channels resulting in a decrease in Na^+–K^+ exchange; they have K^+–sparing diuretic actions similar to that of *spironolactone*. However, the ability of these drugs to block the K^+–Na^+ exchange site in the collecting tubule does not depend on the presence of aldosterone. Thus, they have diuretic activity even in individuals with Addison's disease. They, like *spironolactone*, are not very efficacious diuretics. Both *triamterene* and *amiloride* are frequently used in combination with other diuretics, usually for their potassium-sparing properties. For example, much like *spironolactone*, they prevent K^+ loss that occurs with thiazides and *furosemide*. The side effects of *triamterene* are leg cramps and the possibility of increased blood urea nitrogen (BUN) as well as uric acid and K^+ retention.

VIII. OSMOTIC DIURETICS

A number of simple, hydrophilic, chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN i tole] and *urea* [yu REE ah], result in some degree of diuresis. This is due to their ability to carry water with them into the tubular fluid. If the substance that is filtered subsequently undergoes little or no reabsorption, then the filtered substance will cause an increase in urinary output. Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to effect increased water excretion rather than Na^+ excretion, they are not useful in treating conditions in which Na^+ retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure, or acute renal failure due to shock, drug toxicities and trauma. Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis. [Note: *Mannitol* is not absorbed when given orally; the agent can only be given intravenously.]

Figure 23.11 summarizes the relative changes in urinary composition induced by diuretic drugs.

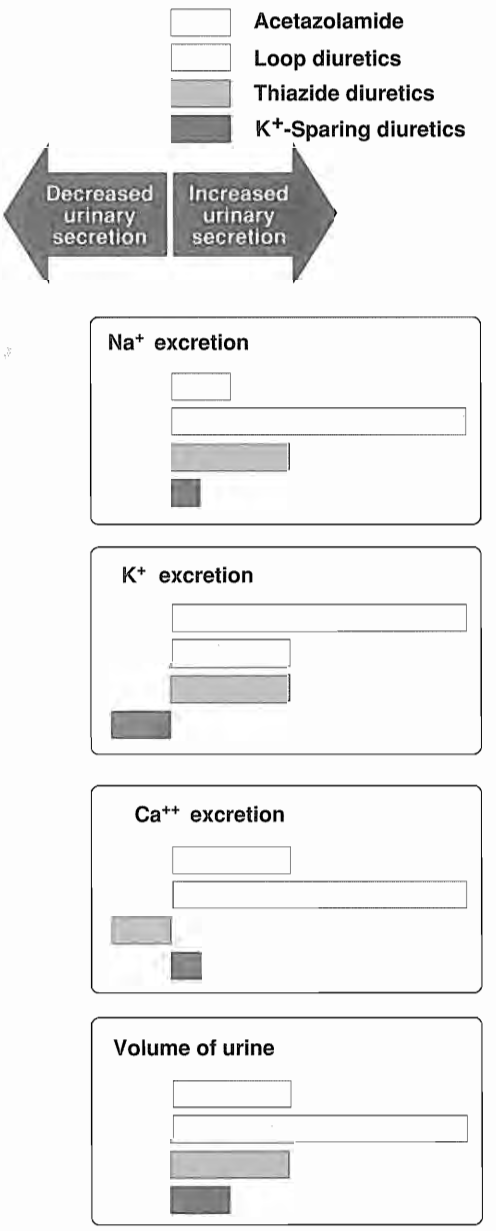


Figure 23.11
Summary of relative changes in urinary composition induced by diuretic drugs.

23.1–23.4 From the list of diuretic drugs below choose the agent that is most appropriate for the numbered conditions.

A. Acetazolamide
B. Amiloride
C. Chlorothiazide
D. Furosemide
E. Spironolactone
F. Triamterene

23.1 Acute pulmonary edema

Correct answer = D (Furosemide).

23.2 Acute hypercalcemia

Correct answer = D (Furosemide).

23.3 Essential hypertension

Correct answer = C (Chlorthiazide).

23.4 Glaucoma

Correct answer = A (Acetazolamide).

23.5-23.8 Match the drug from the list below to its appropriate target in the nephron.

A. Amiloride
B. Acetazolamide
C. Chlorthalidone
D. Ethacrynic acid
E. Spironolactone

23.5 $Na^+/K^+/2Cl^-$ cotransporter

Correct answer = D (Ethacrynic acid).

23.6 Carbonic anhydrase

Correct answer = B (Acetazolamide).

23.7 Aldosterone receptors

Correct answer = E (Spironolactone).

23.8 Na^+/Cl^- cotransporter

Correct answer = C (Chlorthalidone).

23.9-23.12 Match the drug from the list below to its most appropriate adverse effect.

A. Ethacrynic acid
B. Chlorthalidone
C. Acetazolamide
D. Furosemide
E. Spironolactone

23.9 Ototoxicity

Correct answer = D (Furosemide).

23.10 Hyperuricemia

Correct answer = B (Furosemide).

23.11 Gynecomastia (development of enlarged breats) in males

Correct answer = E (Spironolactone).

23.12 Metabolic acidosis

Correct answer = C (Acetazolamide).

23.13 Chlorothiazide can produce which one of the following actions?

A. Hyperkalemia
B. Hyperuricemia
C. Increase in blood pressure
D. Hypoglycemia in diabetic patients
E. Hypercalcemia

Correct answer = B. Thiazide decreases the excretion of uric aid by the acid secretory system. Hypokalemia is the most frequently encountered adverse effect of thiazide treatment. Chlorothiazide may induce hyperglycemia and hypotension.

23.14 In an Addisonian patient, all of the following agents would have diuretic actions EXCEPT which one?

A. Amiloride
B. Chlorothiazide
C. Triamterene
D. Spironolactone
E. Torsemide

Correct choice = D. Spironolactone competes with aldosterone, and thus the drug would have no effect in the absence of endogenous hormone.

Gastrointestinal and Antiemetic Drugs

24

I. OVERVIEW

This chapter describes drugs used to treat three common medical conditions involving the gastrointestinal tract: peptic ulcers, control of chemotherapy-induced emesis, and diarrhea and constipation. Many drugs described in other chapters also find application in the treatment of gastrointestinal disorders. For example, the morphine derivative *diphenoxylate* (see p. 244), which decreases peristaltic activity of the gut, is useful in the treatment of severe diarrhea, and the corticosteroid *dexamethasone* (see p. 275) has excellent antiemetic properties. Other drugs, (for example, H_2-receptor antagonists and proton pump inhibitors employed to heal peptic ulcers, and the selective inhibitors of the serotonin receptors, such as *ondansetron* or *granisetron*, which prevent vomiting) are used almost exclusively to treat gastrointestinal tract disorders.

II. DRUGS USED TO TREAT PEPTIC ULCER DISEASE

Although the pathogenesis of peptic ulcer disease is not fully understood, three major factors are recognized: infection with gram-negative Helicobacter pylori, increased hydrochloric acid secretion, and inadequate mucosal defense against gastric acid. Treatment approaches include (1) eradicating H. pylori infection, (2) reducing secretion of gastric acid or neutralizing the acid after it is released, and/or (3) providing agents that protect the gastric mucosa from damage. Figure 24.1 summarizes the agents effective in treating peptic ulcer disease.

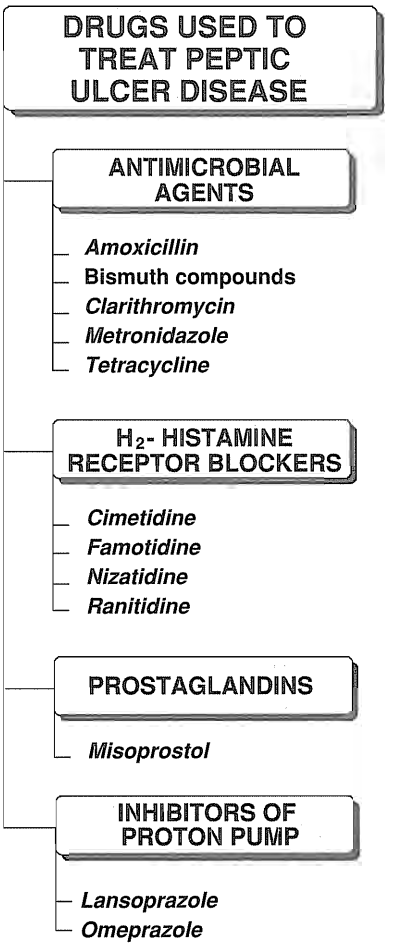


Figure 24.1
Summary of drugs used to treat peptic ulcer disease.
(Figure continues on next page.)

A. Antimicrobial agents

Optimal therapy of patients with peptic ulcer disease (both duodenal and gastric ulcers) who are infected with H. pylori requires antimicrobial treatment. To document infection with H. pylori, endoscopic biopsy of the gastric mucosa or various noninvasive methods are available, including serologic tests and breath tests for urea. Figure 24.2 shows a biopsy sample with H. pylori closely associated with the gastric mucosa. Eradication of H. pylori results in rapid healing

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

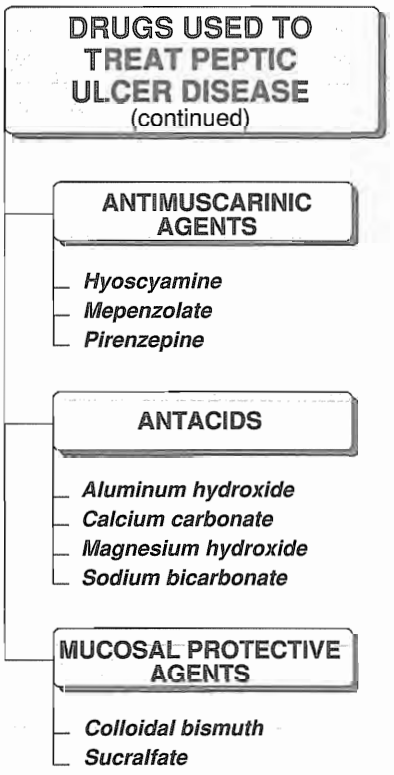


Figure 24.1 (continued)
Summary of drugs used to treat peptic ulcer disease.

Figure 24.2
Helicobacter pylori in association with gastric mucosa.

of active peptic ulcers and low recurrence rates (less than 15% compared to 60 to 100% per year for patients with initial ulcers healed by traditional antisecretory therapy). Successful eradication of H. pylori (80 to 90%) is possible with various combinations of antimicrobial drugs. For example, a current regimen of choice based on efficacy (about 90% eradication rate) and cost, is a two-week course of triple therapy with *bismuth*, *metronidazole* and *tetracycline*. Often an antisecretory drug is added (see p. 239). Second-line regimens include combinations of two antimicrobial agents (*metronidazole*, *amoxiciliin* or *clarithromycin*) with an antisecretory agent (preferably *omeprazole*). Treatment with a single antimicrobial drug is less effective (20 to 40% eradication rates).

B. Regulation of gastric acid secretion

Gastric acid secretion by parietal cells of the gastric mucosa is controlled by acetylcholine, histamine, prostaglandins E_2 and I_2, and gastrin (Figure 24.3). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of a H^+/K^+-ATPase proton pump that secretes hydrochloric acid (HCl) into the lumen of the stomach. In contrast, receptor binding of prostaglandins E_2 and I_2 diminishes gastric acid production. [Note: Histamine binding causes activation of adenylyl cyclase (see p. 421), whereas binding of prostaglandin E_2 and I_2 inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels).]

C. H_2-receptor antagonists

Although antagonists of the histamine H_2-receptor (H_2 antagonists) block the actions of histamine at all H_2 receptors (see p. 421), their chief clinical use is as inhibitors of gastric acid secretion. 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* [sye MET i deen], *ranitidine* [ra NYE ta deen], *famotidine* [fa MOE ti deen] and *nizatidine* [nye ZAT i deen], potently inhibit (>90%) basal, food-stimulated, and nocturnal secretion of gastric acid after a single dose. *Cimetidine* is the prototype histamine H_2-receptor antagonist.

1. **Actions:** The histamine H_2-receptor antagonists—*cimetidine, ranitidine, famotidine*, and *nizatidine*—act on H_2-receptors in the stomach, blood vessels, and other sites. They are competitive antagonists of histamine and are fully reversible. These agents completely inhibit gastric acid secretion induced by histamine, or gastrin. However, they only partially inhibit gastric acid secretion induced by *acetylcholine* or *bethanechol* .

2. **Therapeutic uses:**

   a. **Peptic ulcers:** All four agents are equally effective in promoting healing of duodenal and gastric ulcers. However, recurrence is common after treatment with H_2 antagonists is stopped (60 to

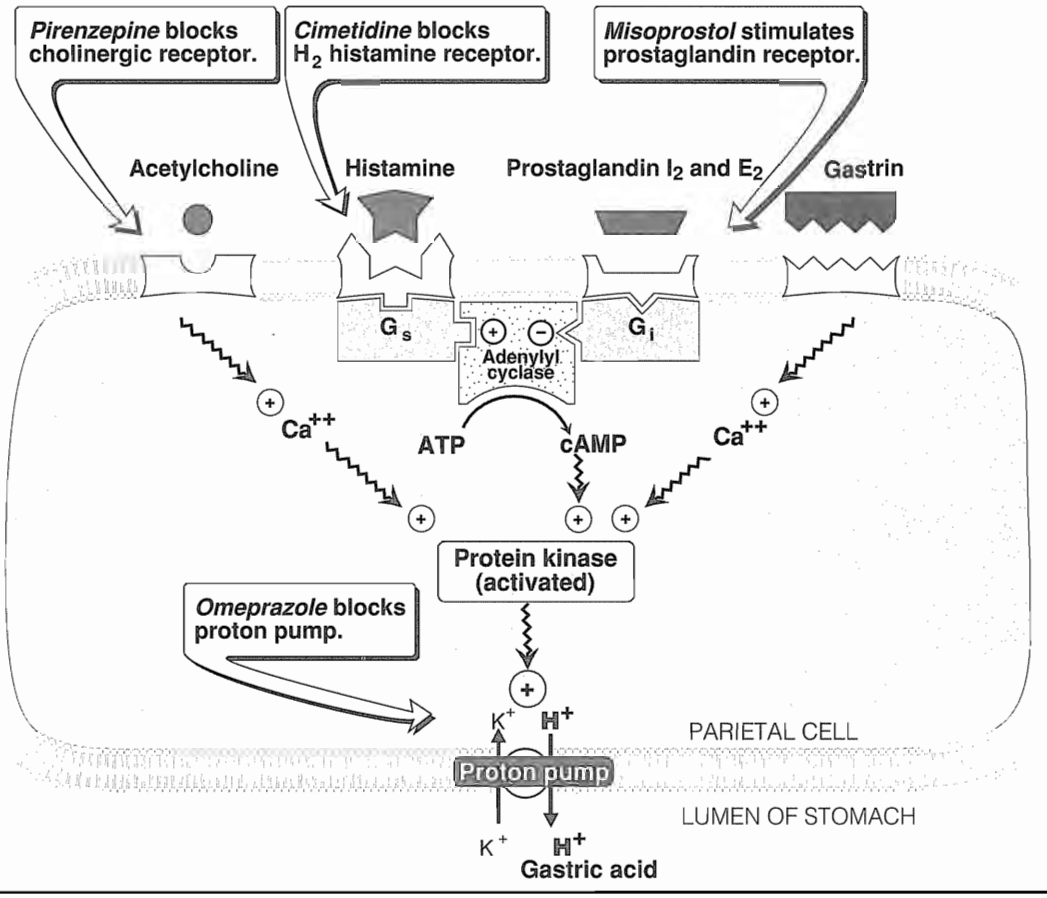


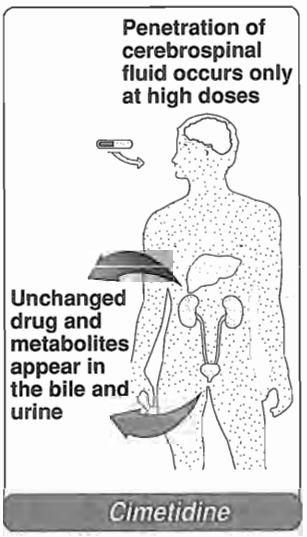
Figure 24.3
Effects of acetylcholine, histamine, prostaglandin I_2, and E_2, and gastrin on gastric acid secretion by the parietal cells of stomach; G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

100% per year). This can be effectively prevented by eradication of H. pylori, and H_2 antagonists continue to be widely used in peptic ulcer therapy in combination with antimicrobial drugs.

b. **Zollinger-Ellison syndrome:** Zollinger-Ellison syndrome is a rare condition in which a gastrin-producing tumor causes hypersecretion of HCl. With H_2 antagonists, the hypersecretion of gastric acid can be kept at safe levels in patients with Zollinger-Ellison syndrome.

c. **Acute stress ulcers:** These drugs are useful in managing acute stress ulcers associated with major physical trauma in high-risk patients in intensive care units.

d. **Gastroesophageal reflux disease (heartburn):** Low doses of H_2 antagonists, recently released for over-the-counter sale, appear to be effective for prevention and treatment of heartburn (gastroesophageal reflux). Because they act by stopping acid secretion, they may not relieve symptoms for at least 45 minutes. Antacids more efficiently neutralize secreted acid already in the stomach.



3. Pharmacokinetics:

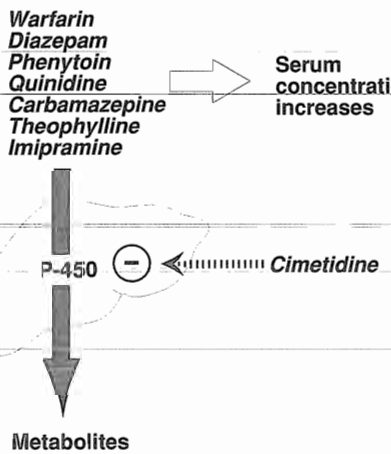
a. Cimetidine: *Cimetidine* and the other H_2-antagonists are given orally, distribute widely throughout the body (including in breast milk and across the placenta) and are excreted mainly in the urine. *Cimetidine* normally has a short serum half-life, which is increased in renal failure. Approximately 30% of a dose of *cimetidine* is slowly inactivated by the liver's microsomal mixed function oxygenase system (see p. 14); the other 70% is excreted unchanged in the urine.

b. Ranitidine: Compared to *cimetidine*, *ranitidine* is longer acting and is five to ten times more potent. *Ranitidine* has minimal side effects, and does not produce the antiandrogenic or prolactin-stimulating effects of *cimetidine*. Unlike cimetidine, it does not inhibit the mixed function oxygenase system in the liver, and thus does not affect the concentrations of other drugs.

c. Famotidine: *Famotidine* is similar to *ranitidine* in its pharmacologic action, but it is 20 to 160 times more potent than *cimetidine* and 3 to 20 times more potent than *ranitidine*.

d. Nizatidine: *Nizatidine* is similar to *ranitidine* in its pharmacologic action and potency. In contrast to *cimetidine*, *ranitidine*, and *famotidine* (which are metabolized by the liver), *nizatidine* is eliminated principally by the kidney. Since little first-pass metabolism occurs with *nizatidine*, its bioavailability is nearly 100%.

4. Adverse effects: The adverse effects of *cimetidine* are usually minor and are associated mainly with the major pharmacologic activity of the drug, namely reduced gastric acid production. Side effects occur only in a small number of patients and generally do not require discontinuation of the drug. The most common side effects are headache, dizziness, diarrhea, and muscular pain. Other central nervous system (CNS) effects (confusion, hallucinations) occur primarily in elderly patients or after prolonged administration. *Cimetidine* can also have endocrine effects, since it acts as a nonsteroidal antiandrogen. These effects include gynecomastia, galactorrhea (continuous release/discharge of milk), and reduced sperm count. *Cimetidine* inhibits cytochrome P-450 and can slow metabolism (and thus potentiate the action) of several drugs (for example, *warfarin*, *diazepam*, *phenytoin*, *quinidine*, *carbamazepine*, *theophylline*, *imipramine*), sometimes resulting in serious adverse clinical effects.



D. Prostaglandins

Prostaglandins E_2 and I_2, produced by the gastric mucosa, inhibit secretion of HCl and stimulate secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol* [miz o PROS tol], a stable analog of prostaglandin E_1, is currently the only agent approved for prevention of gastric ulcers induced by nonsteroidal anti-inflammatory agents (NSAIDs) (see p. 405). It is less effective than H_2 antagonists for acute treatment of peptic ulcers.

Although *misoprostol* has cytoprotective actions, it is clinically effective only at higher doses that diminish gastric acid secretion. Routine prophylactic use of *misoprostol* may not be justified except in patients taking NSAIDs who are at high risk of NSAID-induced ulcers, such as the elderly or patients with ulcer complications. Like other prostaglandins, *misoprostol* produces uterine contractions and is contraindicated during pregnancy. Dose-related diarrhea and nausea are the most common adverse effects.

E. Inhibitors of the H^+/K^+-ATPase proton pump

Omeprazole [om ME pary zol] is the first of a new class of drugs that binds to the H^+/K^+-ATPase enzyme system (proton pump) of the parietal cell, suppressing secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid (see Figure 24.3). A second proton pump inhibitor, *lansoprazole* [lan SOP ra zol], is also available.

1. **Actions:** At standard doses, both *omeprazole* and *lansoprazole* inhibit basal and stimulated gastric acid secretion more than 90%. Acid suppression begins within 1 to 2 hr after the first dose of *lansoprazole*, and slightly earlier with *omeprazole*.

2. **Therapeutic uses:** *Omeprazole* and *lansoprazole* are used for short-term treatment of erosive esophagitis and active duodenal ulcer, and for long-term treatment of pathologic hypersecretory conditions (for example, Zollinger-Ellison syndrome). Only *omeprazole* is approved for refractory gastroesophageal reflux disease and maintenance therapy of erosive esophagitis. Clinical studies to date have shown *lansoprazole*, like *omeprazole*, is more effective in the short term than the H_2 antagonist, *ranitidine*. *Omeprazole* is successfully used with antimicrobial regimens to eradicate H. pylori.

3. **Pharmacokinetics:** *Omeprazole* and *lansoprazole* are enteric-coated to protect them from premature activation by gastric acid. After absorption in the duodenum, they are transported to the acid parietal cell canaliculus, where they are converted to active species. Metabolites of these agents are excreted in urine and feces.

4. **Adverse effects:** *Omeprazole* and *lansoprazole* are generally well tolerated, but concerns about long-term safety have been raised. In animal studies, both drugs increase the incidence of gastric carcinoid tumors, possibly related to the effects of prolonged hypochlorhydria and secondary hypergastrinemia. Increased concentration of viable bacteria in the stomach have been reported with continued use of these drugs. *Omeprazole* interferes in the oxidation of *warfarin*, *phenytoin*, *diazepam* and *cyclosporine*; *lansoprazole* does not.

F. Antimuscarinic agents

Muscarinic receptor stimulation increases gastrointestinal motility and secretory activity (see p. 29). Cholinergic antagonists, such as *hyoscyamine*, are used as adjuncts in the management of peptic ulcer disease and Zollinger-Ellison syndrome, particularly in patients

refractory to standard therapies. In contrast to the classic anticholinergics, the relatively specific muscarinic M_1-receptor antagonist *pirenzepine* is under investigation for its clinical usefulness as an antisecretory agent (see p. 38). *Pirenzepine* suppresses basal and stimulated gastric acid secretion at doses having a minimal effect on salivary glands, the heart and eye.

G. Antacids

Antacids are weak bases that react with gastric acid to form water and a salt, thereby diminishing gastric acidity. Since pepsin is inactive at pH>4.0, antacids also reduce peptic activity. They may have other actions as well, such as reduction of H. pylori colonization and stimulation of prostaglandin synthesis.

1. **Chemistry of antacids:** Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, palatability and price. The acid-neutralizing ability of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying, allowing more time for the antacid to react). Commonly used antacids are salts of aluminum and magnesium, such as *aluminum hydroxide* (usually a mixture of $Al(OH)_3$ and aluminum oxide hydrates) or *magnesium hydroxide* [$Mg(OH)_2$] ("milk of magnesia"), either alone or in combination. Since calcium salts stimulate gastrin release, use of calcium-containing antacids, such as *calcium carbonate* [$CaCO_3$] (*Tums, Rolaids*) may be counterproductive. Systemic absorption of *sodium bicarbonate* [$NaHCO_3$] can produce transient metabolic alkalosis; this antacid is not recommended for long-term use.

2. **Therapeutic uses:** Aluminum- and magnesium-containing antacids can promote healing of duodenal ulcers; evidence for efficacy in treatment of acute gastric ulcer is less compelling.

3. **Adverse effects:** *Aluminum hydroxide* may be constipating; *magnesium hydroxide* may produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. In addition to the potential for systemic alkalosis, *NaHCO3* liberates CO_2, causing belching and flatulence. Absorption of cations from antacids (Mg^{++}, Al^{+++}, Ca^{++}) is usually not a problem in patients with normal renal function, but the sodium content of antacids can be an important consideration in patients with hypertension or congestive heart failure.

4. **Drug interactions:** It is usually advisable to avoid concurrent administration of antacids and other drugs. By altering gastric and urinary pH or delaying gastric emptying, antacids can affect rates of dissolution and absorption, bioavailability, and renal elimination of many drugs. By binding to drugs (for example, *tetracycline*), Al^{+++} compounds can form insoluble complexes that are not absorbed. On the other hand, antacids can increase the rate of absorption of some drugs, for example, *levodopa*.

H. Mucosal Protective Agents

These compounds, known as cytoprotective, have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

1. **Sucralfate:** This complex of aluminum hydroxide and sulfated sucrose, binds to positively charged groups in proteins, glycoproteins, etc, of both normal and necrotic mucosa. By forming complex gels with mucus, *sucralfate* [soo KRAL fate] creates a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin. It also stimulates prostaglandin release and mucus and bicarbonate output, and inhibits peptic digestion. By these and many other mechanisms, *sucralfate* effectively heals duodenal ulcers and is used in long-term maintenance therapy to prevent their recurrence. Because it requires an acidic pH for activation, *sucralfate* should not be administered with H_2 antagonists or antacids. Little of the drug is absorbed systemically. It is very well tolerated.

2. **Colloidal bismuth:** Preparations of this compound effectively heal peptic ulcers. In addition to their antimicrobial actions (see p. 236), they inhibit the activity of pepsin, increase mucus secretion and interact with proteins in necrotic mucosal tissue to coat and protect the ulcer crater.

III. DRUGS USED TO CONTROL CHEMOTHERAPY-INDUCED EMESIS

Although nausea and vomiting may occur in a variety of conditions (for example motion sickness, pregnancy, hepatitis) and are always unpleasant for the patient, it is the nausea and vomiting produced by many chemotherapeutic agents that demand effective management. Nearly 70 to 80% of all patients given chemotherapy experience nausea or vomiting. Several factors influence the incidence and severity of chemotherapy-induced emesis, including the specific chemotherapeutic drug (see Figure 24.4), dose, route and schedule of administration, and patient variables (for example, 10 to 40% of patients experience nausea or vomiting in anticipation of their chemotherapy [anticipatory vomiting]). Emesis not only affects quality of life, but can lead to rejection of potentially curative antineoplastic treatment. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances and nutrient depletion.

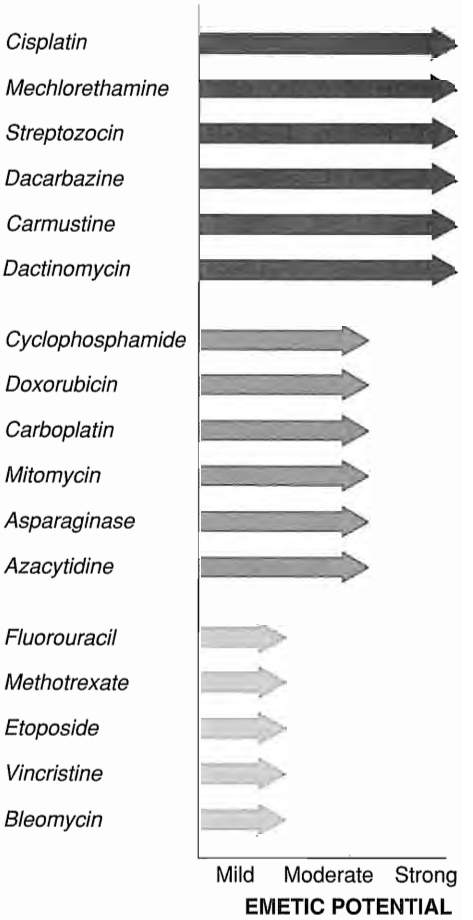


Figure 24.4
Comparison of emetic potential of anticancer drugs.

A. Mechanisms that trigger vomiting

Two brain stem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone, located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle) is outside the blood-brain barrier. Thus it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomit-

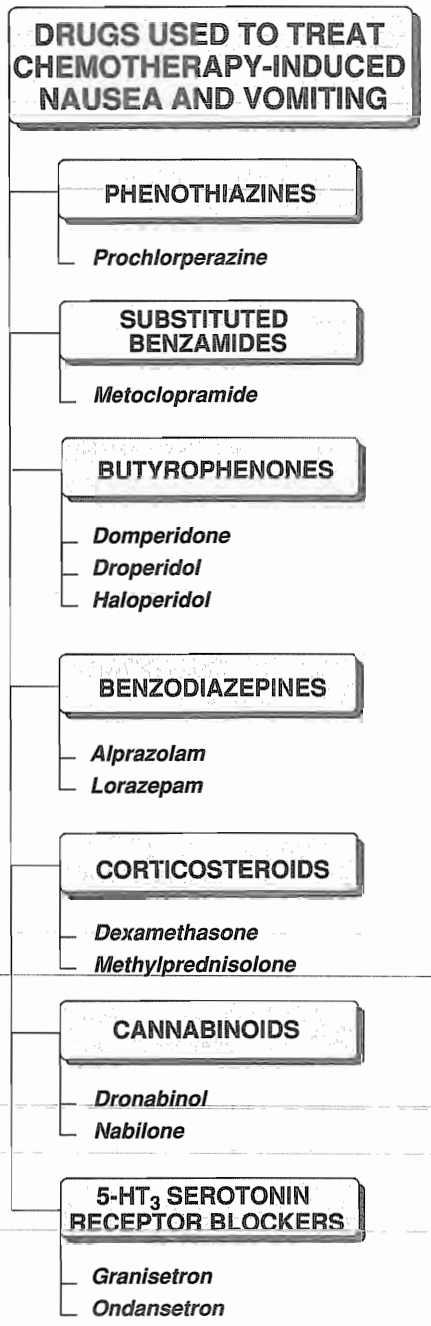


Figure 24.5
Summary of drugs used to treat chemotherapy-induced nausea and vomiting.

ing. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and gastrointestinal tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

B. Emetic actions of chemotherapeutic agents

Chemotherapeutic agents (or their metabolites) can directly activate the medullary chemoreceptor trigger zone or vomiting center; several neuroreceptors, including dopamine type 2 (DA_2, see p. 128) and serotonin type 3 ($5\text{-}HT_3$), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy, such as cues in the treatment room or the physician or nurse who administers the therapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the gastrointestinal tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa. The released serotonin activates $5\text{-}HT_3$ receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

C. Antiemetic drugs

Considering the complexity of the mechanisms involved in emesis, it is not surprising that antiemetics represent a variety of classes (Figure 24.5) and offer a range of efficacies (Figures 24.6 and 13.4). Anticholinergic drugs, especially the muscarinic receptor antagonist *scopolamine* (see p. 48), and H_1-receptor antagonists, such as *dimenhydrinate*), *meclizine* and *cyclizine* (see p. 422), are very useful in motion sickness, but are ineffective against substances that act directly on the chemoreceptor trigger zone. The major categories of drugs used to control chemotherapy-induced nausea and vomiting include:

1. **Phenothiazines:** The first group of drugs shown to be effective antiemetic agents, phenothiazines, such as *prochlorperazine* [proe klor PER a zeen], act by blocking dopamine receptors (see p. 129). They are effective against low or moderately emetogenic chemotherapeutic agents (for example, *fluorouracil* and *doxorubicin*, see Figure 24.5). Although increasing the dose improves antiemetic activity, side effects, including hypotension and restlessness, are dose-limiting. Other adverse reactions include extrapyramidal symptoms and sedation.

2. **Substituted benzamides:** One of several substituted benzamides with antiemetic activity, *metoclopramide* [met oh kloe PRA mide] is highly effective at high doses against the highly emetogenic *cisplatin*), preventing emesis in 30 to 40% of patients and reducing emesis in the majority. Antidopaminergic side effects, including sedation, diarrhea and extrapyramidal symptoms, limit its high-dose use. These adverse reactions are most common in younger patients.

3. **Butyrophenones:** *Haloperidol*, *droperidol* and *domperidone* act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics, but high-dose *haloperidol* was found to

be nearly as effective as high-dose *metoclopramide* in preventing *cisplatin*-induced emesis.

4. **Benzodiazepines:** The antiemetic potency of *lorazepam* and *alprazolam* (see p. 89) is low. Their beneficial effects may be due to their sedative, anxiolytic and amnesic properties. These same properties make benzodiazepines useful in treating anticipatory vomiting.

5. **Corticosteroids:** *Dexamethasone* and *methylprednisolone* used alone are effective against mildly to moderately emetogenic chemotherapy. Their antiemetic mechanism is not known, but may involve blockade of prostaglandins. These drugs can cause insomnia and hyperglycemia in patients with diabetes mellitus.

6. **Cannabinoids:** Marijuana derivatives, including *dronabinol* [droe NAB i nol] and *nabilone*, are effective against moderately emetogenic chemotherapy. However, they are seldom first-line antiemetics because of their serious side effects, including dysphoria, hallucinations, sedation, vertigo, and disorientation. In spite of their psychotropic properties (see p. 105), the antiemetic action of cannabinoids may not involve the brain; synthetic cannabinoids having no psychotropic activity, nevertheless are antiemetic.

7. **5-HT3 serotonin receptor blockers:** The specific antagonists of the 5-HT_3 receptor, *ondansetron* [on DAN sah tron] and *granisetron* [gran IZ e tron], selectively block 5-HT_3 receptors in the periphery (visceral afferent fibers) and in the brain (chemoreceptor trigger zone). These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. One trial reported both drugs prevented emesis in 50 to 60% of *cisplatin*-treated patients. *Ondansetron* is approved also for prevention of postoperative nausea and/or vomiting. Headache is a common side effect. These drugs are costly.

8. **Combination regimens:** Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity (Figure 24.7). Corticosteroids, most commonly *dexamethasone*, increase antiemetic activity when given with high-dose *metoclopramide*, a 5-HT_3 antagonist, *phenothiazine*, *butyrophenone*, a cannabinoid or a benzodiazepine. Antihistamines, like *diphenylhydramine*, are often administered in combination with high-dose *metoclopramide* to reduce extrapyramidal reactions, or corticosteroids, to counter *metoclopramide*-induced diarrhea. Supplementing a cannabinoid regimen with *prochlorperazine* diminishes dysphoria.

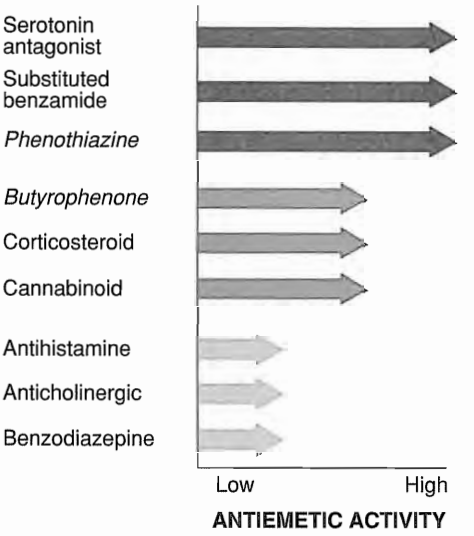


Figure 24.6
Comparison of potency of type of antiemetic drugs.

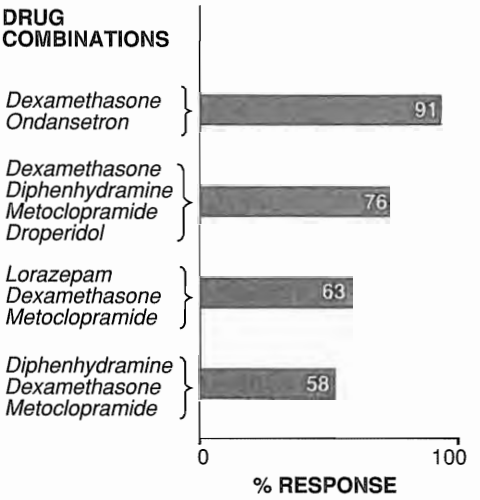


Figure 24.7
Effectiveness of antiemetic activity of some drug combinations against emetic episodes in first 24 hours after *cisplatin* chemotherapy.

IV. ANTIDIARRHEALS

Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport (Figure 24.8).

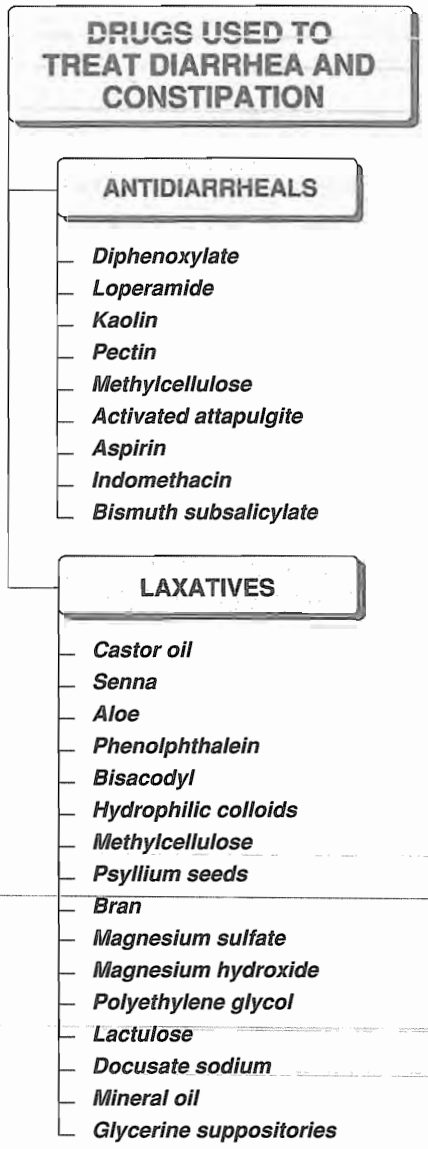


Figure 24.8
Summary of drugs used to treat diarrhea and constipation.

A. Antimotility agents

Two drugs widely used to control diarrhea are *diphenoxylate* [di PHEN ox a late and *loperamide* [loe PER a mide]. Both are analogues of *meperidine* (see p. 138) and have opioid-like actions on the gut, activating presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. Side effects include drowsiness, abdominal cramps and dizziness. Since these drugs can cause toxic megacolon, they should not be used in young children or patients with severe colitis.

B. Adsorbents

Adsorbent agents such as *kaolin*, *pectin*, *methylcellulose* and *activated attapulgite*, magnesium aluminum silicate, are widely used to control diarrhea, although their efficacy has not been documented by controlled clinical trials. Presumably these agents act by adsorbing intestinal toxins or microorganisms, or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents and can interfere with absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

Experimental and clinical observations indicate that non-steroidal anti-inflammatory agents (NSAIDs, see p. 403) such as *aspirin* and *indomethacin* are effective in controlling diarrhea. This antidiarrheal action is probably due to inhibition of prostaglandin synthesis. *Bismuth subsalicylate* (PEPTO-BISMOL), used for traveler's diarrhea, decreases fluid secretion in the bowel; its action may be due to its *salicylate* component.

V. LAXATIVES

Laxatives are commonly used to accelerate the movement of food through the gastrointestinal tract. These drugs can be classified on the basis of their mechanism of action as irritants or stimulants of the gut, bulking agents, and stool softeners.

A. Irritants and stimulants

Castor oil is broken down in the small intestine to ricinoleic acid, which is very irritating to the gut and promptly increases peristalsis. *Cascara*, *senna*, and *aloe* contain *emodin* which stimulates colonic activity. Onset of activity is delayed 6 to 8 hr because *emodin* is excreted into the colon after these agents are absorbed. *Emodin* may pass into breast milk. *Phenolphthalein* and *bisacodyl* are also potent stimulants of the colon. Adverse effects include abdominal cramps and the potential for atonic colon with prolonged use.

B. Bulking agents

The bulk laxatives include *hydrophilic colloids* (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing

peristaltic activity. Similar actions are produced by *agar*, *methylcellulose*, *psyllium seeds*, and *bran*. Saline cathartics such as *magnesium sulfate* and *magnesium hydroxide* are nonabsorbable salts that hold water in the intestine by osmosis, and distend the bowel, increasing intestinal activity and producing defecation in about one hour. Isosmotic electrolyte solutions containing *polyethylene glycol* are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. *Lactulose* is a semisynthetic disaccharide (fructose and galactose) that also acts as an osmotic laxative.

C. Stool Softeners

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include *docusate sodium*, *mineral oil* and *glycerin suppositories*.

Study Questions

Choose the ONE best answer

24.1 Which of the following is the most important approach in healing peptic ulcers?

A. Coating the ulcer crater
B. Eradicating infection with H. pylori
C. Inhibiting secretion of gastric acid at the proton pump
D. Blocking receptor activation of gastric acid secretion
E. Neutralizing secreted gastric acid

Correct answer = B. Eradication of H. pylori results in rapid healing of active peptic ulcers and low recurrence rates (less than 15% compared to 60 to 100% per year for patients with initial ulcers healed by traditional antisecretory thrapy).

Questions 24.2–24.7

For each numbered description below, select the most appropriate drug from the following list:

A. Granisetron
B. Ondansetron
C. Dexamethasone
D. Meclizine
E. Lorazepam
F. Metoclopramide

24.2 Given in combination regimens to enhance antiemetic potency

Correct answer = C (Dexamethasone)

24.3 Highly effective against cisplatin-induced emesis

Correct answer = A (Granisetron)

24.4 Can cause extrapyramidal side effects

Correct answer = F (Metoclopramide)

24.5 Approved for managing postoperative nausea and/or vomiting

Correct answer = B (Ondansetron)

24.6 Useful in managing nausea and vomiting due to motion sickness

Correct answer = D (Meclizine)

24.7 Low antiemetic potency

Correct answer = E (Lorazepam)

Questions 24.8–24.13

For each numbered description below, select the most appropriate drug from the following list:

A. Bismuth subsalicylate
B. Phenolphthalein
C. Docusate sodium
D. Loperamide
E. Magnesium sulfate
F. Activated attapulgite

24.8 Softens the stool

Correct answer = C (Docusate sodium)

24.9 May adsorb intestinal toxins

Correct answer = F (Activated attapulgite)

24.10 Diminishes fluid secretion in the bowel

Correct answer = A (Bismuth subsalicylate)

24.11 Irritates the gut and causes increased peristalsis

Correct answer = B (Phenolphthalein)

24.12 Retains water and produces intestinal distension

Correct answer = E (Magnesium sulfate)

24.13 Inhibits peristalsis

Correct answer = D (Loperamide)

Questions 24.14–24.17

For each numbered description below, select the most appropriate drug from the following list:

A. Lansoprazole
B. Misoprostol
C. Prostaglandin E_2
D. Sucralfate
E. Al^{+++}-containing antacids
F. Metronidazole

24.14 Approved for prevention of NSAID-induced gastric ulcers

Correct answer = B (Misoprostol)

24.15 Diminishes gastric acid production by inhibiting adenylyl cyclase

Correct answer = C (Prostaglandin E_2)

24.16 Can alter absorption of other drugs

Correct answer = E (Al^{+++}-containing antacids)

24.17 Binds to mucosa forming physical barrier to HCl and pepsin

Correct answer = D (Sucralfate)

Questions 24.18–24.22

For each numbered description below, select the most appropriate drug from the following list:

A. Sodium bicarbonate
B. Cimetidine
C. Bismuth compounds
D. Diphenoxylate
E. Dronabinol
F. Prochlorperazine

24.18 Gynecomastia

Correct answer = B (Cimetidine)

24.19 Metabolic alkalosis

Correct answer = A (Sodium bicarbonate)

24.20 Extrapyramidal symptoms

Correct answer = F (Prochlorperazine)

24.21 Dysphoria

Correct answer = E (Dronabinol)

24.22 Toxic megacolon

Correct answer = D (Diphenoxylate)

Hormones of the Pituitary and Thyroid

25

I. OVERVIEW

The neuroendocrine system, which is controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues. The nervous system communicates locally by electrical impulses and neurotransmitters directed through neurons to other neurons or to specific target organs, such as muscle or glands. Nerve impulses generally act within milliseconds. In contrast, the endocrine system releases hormones into the blood stream, which carries these chemical messengers to target cells throughout the body. Hormones have a much broader range of response times than do nerve impulses, requiring from seconds to days or longer to cause a response that may last for weeks or months. The two regulatory systems are closely interrelated. For example, in several instances, the release of hormones is stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses. Chapters 25–27 in this text focus on drugs that affect the synthesis and/or secretion of specific hormones. In this chapter, the central role of the hypothalamic and pituitary hormones in regulating body functions is briefly presented. In addition, drugs affecting thyroid hormone synthesis and/or secretion are discussed (Figure 25.1).

II. HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The hormones secreted by the hypothalamus and the pituitary are all peptides or low molecular weight proteins that act by binding to specific receptor sites on their target tissues. The hormones of the anterior pituitary are regulated by neuropeptides, called either releasing or inhibiting factors or hormones, which are produced in cell bodies in the hypothalamus and reach the cells of the pituitary by the hypophysial portal system (Figure 25.2). The interaction of the releasing hormones with their receptors results in synthesis and release of the hormones by the pituitary into the circulation. Each hypothalamic regulatory hormone controls the release of a specific hormone from

HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

- *Corticotropin (ACTH)*
- *Gonadotropin-releasing hormone (GnRH)*
- *Growth hormone releasing hormone (GHRH), sermorelin*
- *Luteinizing hormone-releasing hormone (LHRH), leuprolide, goserelin, nafarelin, histrelin*
- *Somatostatin, octreotide*
- *Somatotropin (GHIH), somatrem*

HORMONES OF THE POSTERIOR PITUITARY

- *Desmopressin*
- *Oxytocin*
- *Vasopressin (ADH)*

DRUGS AFFECTING THE THYROID

- *Iodide*
- *Levothyronine*
- *Methimazole*
- *Propylthiouracil*
- *Thyroxine*
- *Triiodothyronine*

Figure 25.1
Some of the hormones and drugs affecting the hypothalamus, pituitary and thyroid.

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

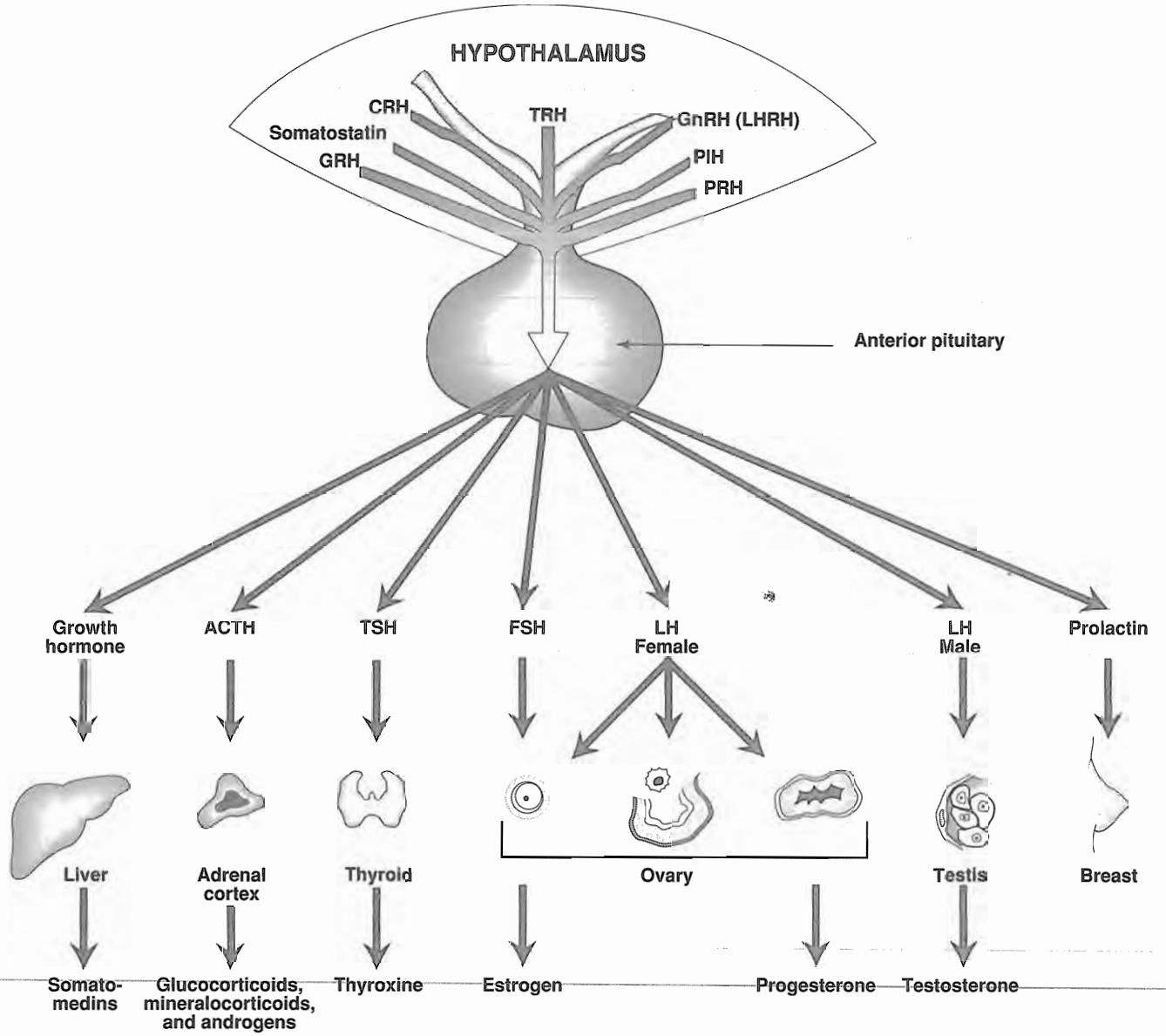


Figure 25.2
Hypothalamic-releasing hormones and actions of anterior pituitary hormones. GRH= growth hormone-releasing hormone; TRH= thyrotropin-releasing hormone; CRH= corticotropin-releasing hormone; GnRH (LHRH)=gonadotropin-releasing hormone (luteinizing hormone-releasing hormone); PIH= prolactin-inhibiting hormone (dopamine); and PRH= prolactin-releasing hormone; ACTH= adrenocorticotropic hormone; TSH= thyrotropin-stimulating hormone; FSH= follicle-stimulating hormone; LH= luteinizing hormone

the anterior pituitary. The hypothalamic releasing hormones are primarily used for diagnostic purposes (that is, to determine pituitary insufficiency). [Note: The hypothalamus also synthesizes the hormones vasopressin and oxytocin, which are transported to the posterior pituitary where they are stored until released.] Although a number of pituitary hormone preparations are currently used therapeutically for specific hormonal deficiencies (examples of which follow), most of these agents have limited therapeutic applications. Hormones of the anterior and posterior pituitary are administered either intramuscularly (IM), subcutaneously (SC) or intranasally but not orally, because their

peptidic nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

A. Adrenocorticotropic hormone (ACTH or corticotropin)

ACTH is a product of the posttranslational processing of the larger precursor polypeptide, pro-opiomelanocortin. Its target organ is the adrenal cortex where corticotropin [kor ti koe TROE pin] binds to specific receptors on the cell surfaces. The occupied receptors activate G protein-coupled processes to increase cAMP, which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol → pregnenolone), concluding with the synthesis and release of the adrenocorticosteroids, and the adrenal androgens (Figure 25.3). The availability of synthetic adrenocorticosteroids with specific properties (see p. 275) has limited the use of corticotropin to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison's disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary). Therapeutic corticotropin preparations are extracts from the anterior pituitaries of domestic animals, or synthetic human ACTH. The latter, *cosyntropin* [ko sin TROE pin], is preferred for diagnosis of adrenal insufficiency. Toxicities are similar to those of glucocorticoids. Antibodies can form to ACTH derived from animal sources. [Note: The anterior pituitary is stimulated to synthesize corticotropin by corticotropin-releasing hormone (CRH), produced by the hypothalamus (see Figure 25.3). CRH is used diagnostically to differentiate between Cushing's syndrome and ectopic ACTH-producing cells.]

B. Growth hormone (somatotropin)

Somatotropin [soe ma tee TROE pin] is a large polypeptide, released by the anterior pituitary in response to growth hormone-releasing hormone (GHRH) produced by the hypothalamus. It is produced synthetically by recombinant DNA technology. Growth-hormone (GH) from animal sources is ineffective in humans. *Somatotropin* influences a wide variety of biochemical processes, for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline also boosts cartilage synthesis Therefore, *somatotropin* is used in the treatment of growth-hormone (GH) deficiency in children. [Note: It is important to establish whether the deficit in GH is actually due to hypopituitarism, since normal thyroid status is essential to successful somatotropin therapy.] A therapeutically equivalent drug, *somatrem* [soe ma TREM], contains an extra terminal methionyl group not found in *somatotropin*. Though the half-lives of these drugs are short, about 25 minutes, they induce the release from the liver of somatomedin, the insulin-like growth factor-I (IGF-I) that is responsible for subsequent growth hormone-like actions. *Somatotropin* and *somatrem* should not be used in individuals with closed epiphyses or with an enlarging intracranial mass. [Note: Infusion of GHRH, known as *sermorelin* [ser moe REH lyn], can be used to assess the status of GH deficiency.]

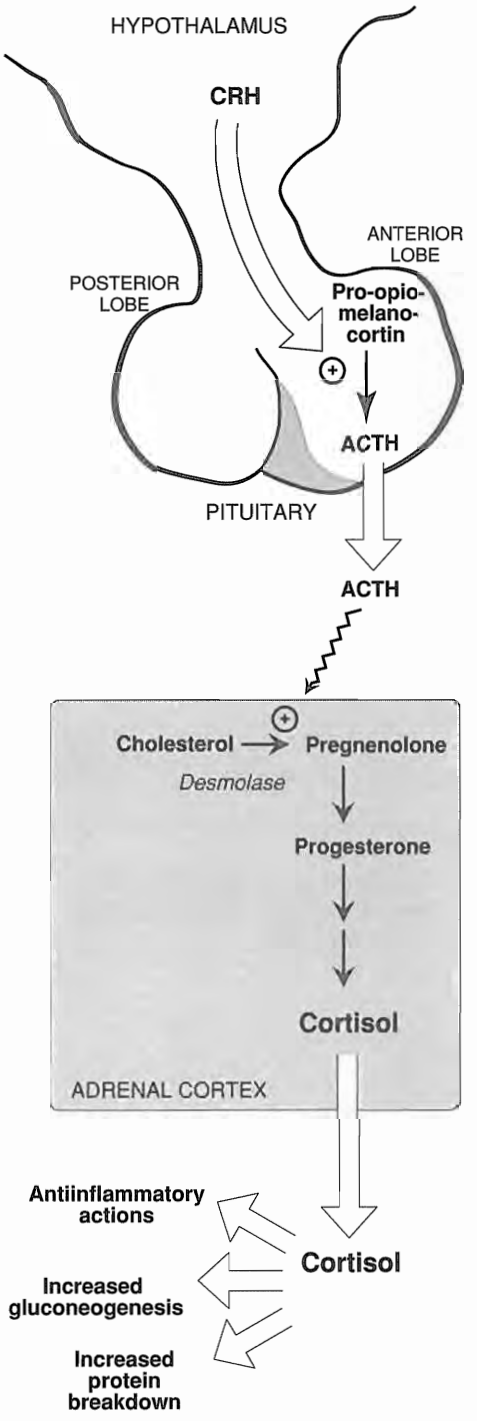


Figure 25.3
Secretion and actions of adrenocorticotropic hormone (ACTH). CRH, corticotropin-releasing hormone.

C. Growth hormone-inhibiting hormone (somatostatin)

Originally isolated from the hypothalamus, *somatostatin* is a small polypeptide that is also found in neurons throughout the body, as well as in the intestine and pancreas. *Somatostatin* therefore predictably has a number of actions. *Octreotide* [awk TREE oh tide] is a synthetic octapeptide analog of *somatostatin*. It has a much longer half-life than the natural compound and has found use in the treatment of acromegaly caused by hormone-secreting tumors, and secretory diarrhea associated with tumors producing the vasoactive intestinal peptide (VIP). Adverse effects of *octreotide* treatment are flatulence, nausea, and steatorrhea.

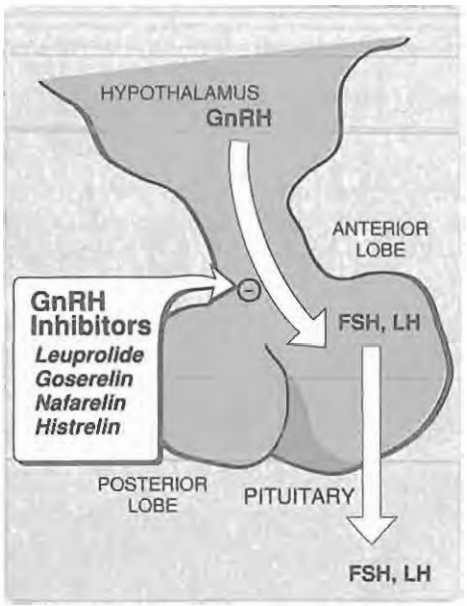


Figure 25.4
Secretion of follicle-stimulating hormone (FSH) and lutenizing hormone (LH).

D. Gonadotropin-releasing hormone (GnRH)/luteinizing hormone-releasing hormone (LHRH)

GnRH, a decapeptide obtained from the hypothalamus, controls the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. GnRH is employed to stimulate gonadal hormone production in hypogonadism. A number of synthetic analogs, such as *leuprolide* [loo PROE lide], *goserelin* [gah SER e lin], *nafarelin* [Neh FAR e lin] *and histrelin* [HIS TRE lin], act as inhibitors of *GnRH* (Figure 25.4). These are effective in suppressing production of the gonadal hormones, and thus are effective in the treatment of prostatic cancer (see p. 395), endometriosis, and precocious puberty.

E. Gonadotropins: human menopausal gonadotropin (hMG), FSH (urofolitropin), human chorionic gonadoptropin (hCG)

The gonadotropins find use in the treatment of infertility in men and women. *Meotropin* (hMG) is partially broken down *FSH* and LH and is obtained from the urine of menopausal women. The *chorionic gonadotropin* (h*CG*) is a placental hormone and an LH agonist. It is also excreted in the urine. Both these hormones are injected intramuscularly. Injection of *hMG* or *FSH* over a period of 5-12 days causes ovarian follicular growth and maturation, and with subsequent injection of *hCG*, ovulation occurs. In men who are lacking gonadoptropins, treatment with *hCG* causes external sexual maturation, and with the subsequent injection hMG spermatogenesis occurs. Adverse effects include ovarian enlargement, and possible hypovolemia. Multiple births are not uncommon. Men may develop gynecomastia.

III. HORMONES OF THE POSTERIOR PITUITARY

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, *vasopressin* and *oxytocin*, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary and released in response to specific physiologic signals, such as high plasma osmolarity or parturition, respectively. Both are nonapeptides with a circular structure due to a disulfide bridge (Figure 25.5). Reduction of the disulfide inactivates the hormones. They are susceptible to proteolytic cleavage and thus are given parenterally. Both have very short half-lives.

A. Oxytocin

Oxytocin [ox ee TOE sin], originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to stimulate uterine contraction to induce or reinforce labor or to promote breast milk ejection. [Note: The sensitivity of the uterus to *oxytocin* increases with the duration of pregnancy when it is under estrogenic dominance.] To induce labor, the drug is administered intravenously. However, when used to induce "milk let-down", it is given as a nasal spray. *Oxytocin* causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Although toxicities are uncommon when the drug is used properly, hypertensive crises, uterine rupture, water retention and fetal death have been reported. Its antidiuretic and pressor activities are very much lower than those of *vasopressin*. [Note: *Oxytocin* is contraindicated in abnormal fetal presentation, fetal distress and premature births.]

B. Vasopressin

Vasopressin [vay soe PRESS in] (*antidiuretic hormone*, *ADH*), is structurally related to *oxytocin* (Figure 25.5). The chemically-synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. *Vasopressin* has both antidiuretic and vasopressor effects. In the kidney it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus the major use of *vasopressin* is to treat diabetes insipidus. It also finds use in controlling bleeding due to esophageal varices or colonic diverticula. Other effects of *vasopressin* are mediated by the V_1 receptor, found in vascular smooth muscle, liver and other tissues. As might be expected the major toxicity is water intoxication and hyponatremia. Headache, bronchoconstriction and tremor also can occur. Caution must be used in treating patients with coronary artery disease, epilepsy and asthma.

C. Desmopressin

Because of the pressor properties of *vasopressin*, this compound has been modified to *desmopressin* [dez moe PRESS in] (1-desamino-8-D-arginine vasopressin). This analog is now preferred for diabetes insipidus and nocturnal enuresis because it is largely free of pressor effects and is longer-acting than *vasopressin*. *Desmopressin* is conveniently administered intranasally. However, local irritation may occur.

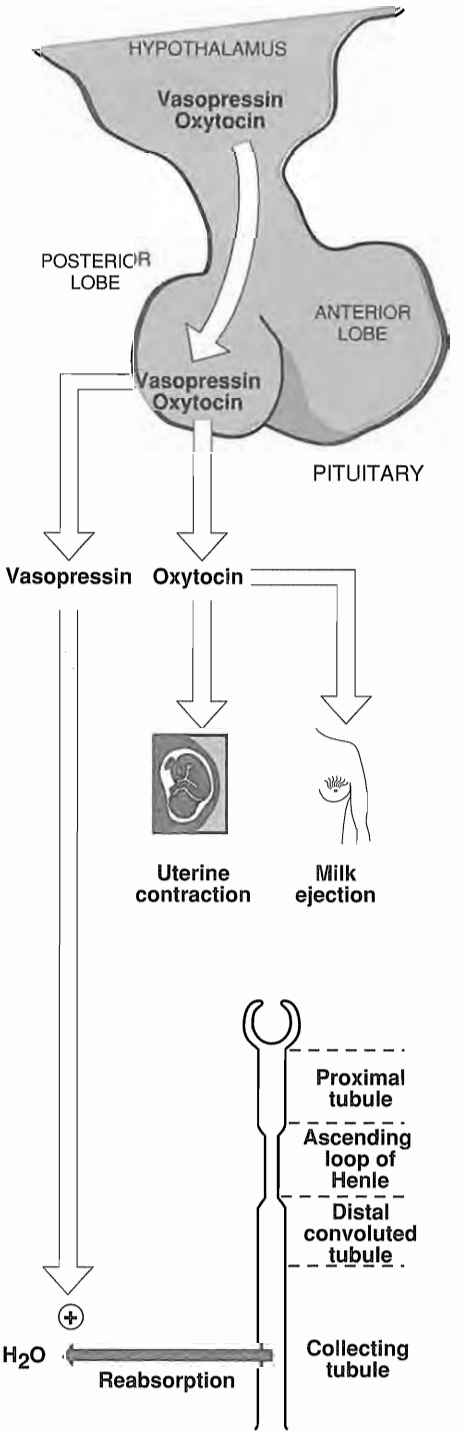


Figure 25.5
Actions of oxytocin and vasopressin.

IV. THYROID HORMONES

The thyroid gland facilitates normal growth and maturation by maintaining the level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are T_3 (triiodothyronine, the most active form), and T_4 (thyroxine). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing (in children this can cause mental retardation and dwarfism). If, however, an excess of thyroid hormones is

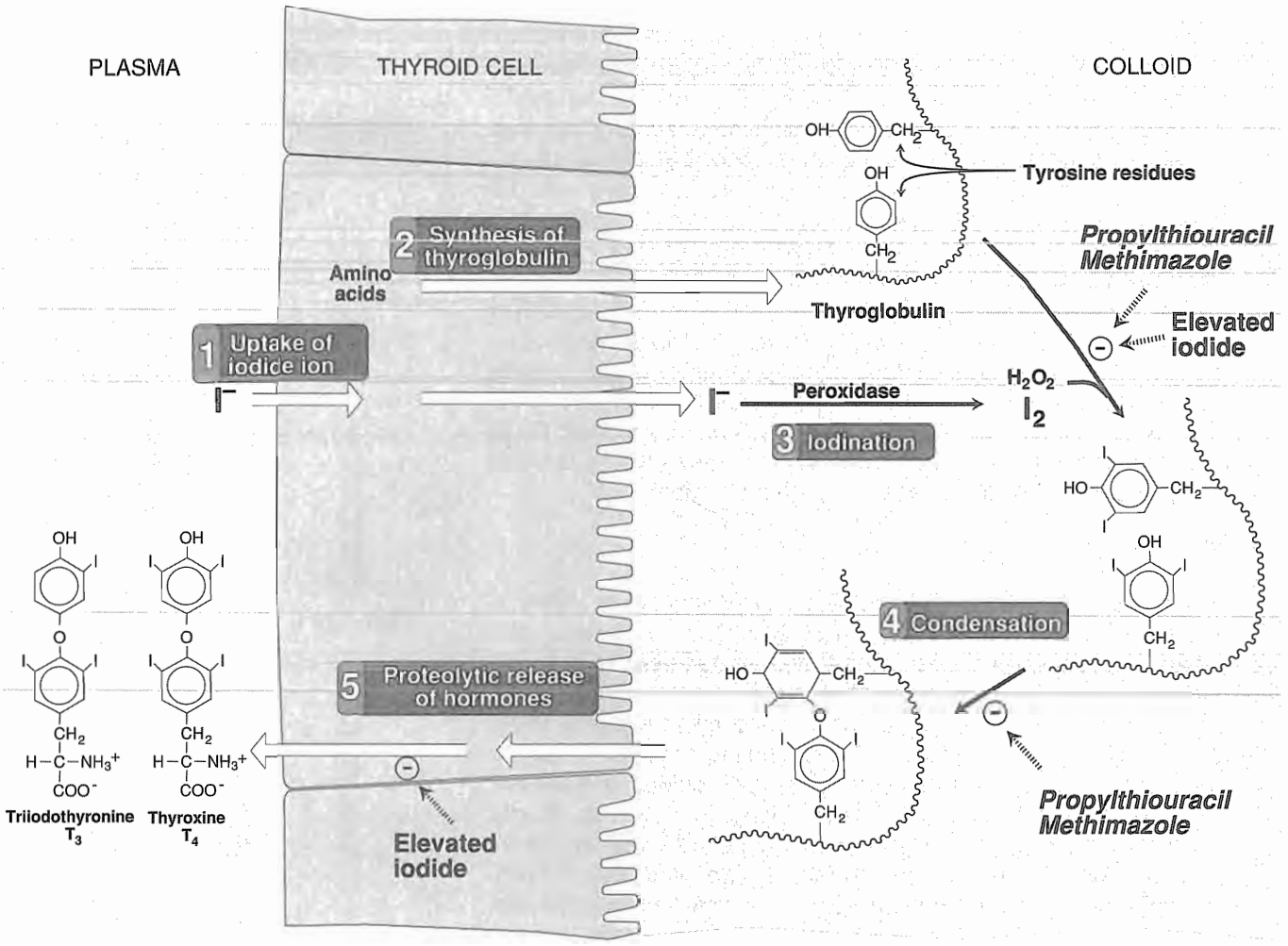


Figure 25.6
Biosynthesis of thyroid hormones.

secreted (hyperthyroidism), tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess heat production can occur. In mammals, the thyroid gland also secretes the hormone calcitonin, a serum calcium-lowering hormone.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with colloid (thyroglobulin), the storage form of thyroid hormone. A diagram of the steps in thyroid hormone synthesis and secretion is shown in Figure 25.6.

1. **Regulation of synthesis:** Thyroid function is controlled by a tropic hormone, thyrotropin-stimulating hormone (TSH, thyrotropin), a glycoprotein synthesized by the anterior pituitary (see Figure 25.2). TSH generation is governed by the hypothalamic thy-

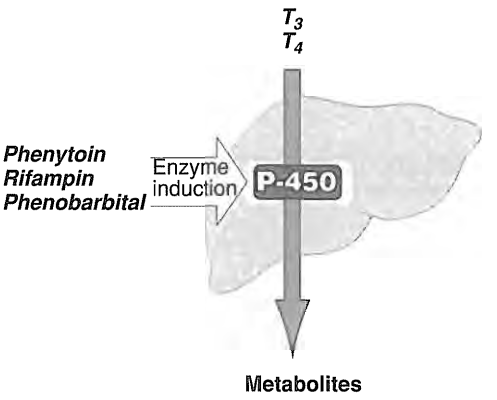
rotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. Condensation of two diiodotyrosine residues gives rise to T_4 or T_3 still bound to the protein. The hormones are released following proteolytic cleavage of the thyroglobulin.

2. **Regulation of secretion:** Secretion of TSH by the anterior pituitary is stimulated by the hypothalamic TRH. Feedback inhibition of both TRH and TSH secretion occurs with high levels of circulating thyroid hormone or iodide. Most of the hormone (T_3 and T_4) is bound to thyroxine-binding globulin in the plasma.

3. **Pharmacokinetics:** Both T_4 and T_3 are absorbed after oral administration. T_4 is converted to T_3 by one of two distinct deiodinases, depending on the tissue. T_3 combines with a receptor to stimulate subsequent protein synthesis necessary for normal metabolism. The hormones are metabolized through the microsomal P-450 system. Drugs such as *phenytoin*, *rifampin*, *phenobarbital*, etc. that induce the P-450 enzymes accelerate metabolism of the thyroid hormones.

B. Treatment of hypothyroidism

Hypothyroidism is treated with *levothyroxine* (T_4). The drug is given once daily because of its long half-life. Steady state is achieved at 6-8 weeks. Toxicity is directly related to thyroxine levels and manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat and unexplained weight loss.



C. Treatment of hyperthyroidism (thyrotoxicosis)

Excessive amounts of thyroid hormones in the circulation are associated with a number of disease states, including Graves' disease, toxic adenoma, goiter, and thyroiditis, among others. The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of the hormones from the follicle.

1. **Removal of part or all of the thyroid:** This can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells.

2. **Inhibition of thyroid hormone synthesis:** The thioamides, *propylthiouracil* [proe pill thye oh YOOR a sil] (*PTU*) and *methimazole* [meth IM a zole], are concentrated in the thyroid where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T_3 and T_4 (see Figure 25.6). *PTU* can also block the conversion of T_4 to T_3. [Note: These drugs have no effect on the thyroglobulin already stored in the gland; therefore observation of any clinical effect of these drugs may be delayed until thyroglobulin stores are depleted.] The thioamides are well absorbed from the gas-

trointestinal tract, but they have short half-lives. Several doses of *PTU* are required per day, whereas a single dose of *methimazole* suffices due to the duration of its antithyroid effect. The effects of these drugs are slow in onset and thus they are not effective in the treatment of thyroid storm. Relatively rare adverse effects include agranulocytosis, rash, and edema.

3. **Propranolol:** β-Blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism (see p. 75).

4. **Blockade of hormone release:** A pharmacologic dose of *iodide* inhibits the iodination of tyrosines, thus decreasing the supply of stored thyroglobulin. *Iodide* also inhibits thyroid hormone release by mechanisms not yet understood. Today, *iodide* is rarely used as sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm), or prior to surgery, since it decreases the vascularity of the thyroid gland. *Iodide* is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks. *Iodide* is administered orally. Adverse effects are relatively minor and include sore mouth and throat, rashes, ulcerations of mucous membranes, and a metallic taste in the mouth.

Study Questions

Choose the ONE best answer.

25.1 Symptoms of hyperthyroidism include all of following EXCEPT:

A. tachycardia.
B. nervousness.
C. poor resistance to cold.
D. body wasting.
E. tremor.

Correct choice = C. An individual with hyperthyroidism often experiences excess heat production.

25.2 Which of the following best describes the effect of propylthiouracil on thyroid hormone production?

A. It blocks the release of thyrotropin-releasing hormone.
B. It inhibits uptake of iodide by thyroid cells.
C. It prevents the release of thyroid hormone from thyroglobulin.
D. It blocks iodination and coupling of tyrosines in thyroglobulin to form thyroid hormones.
E. It blocks the release of hormones from the thyroid gland.

Correct answer = D. Propylthiouracil blocks the synthesis of the thyroid hormones, but does not affect the uptake of iodide, proteolytic cleavage of thyroglobulin, or the release of hormones from the thyroid gland. The thyroid hormones inhibit the secretion of thyroid-stimulating hormone from the anterior pituitary.

25.3 Hyperthyroidism can be treated by all but which one of the following?

A. Triiodothyronine
B. Surgical removal of the thyroid gland
C. Iodide
D. Propylthiouracil
E. Methimazole

Correct answer = A. Triiodothyronine is a thyroid hormone that is overproduced in hyperthyroidism.