Insulin and Oral Hypoglycemic Drugs

26

I. OVERVIEW

The pancreas is both an endocrine gland that produces the peptide hormones *insulin*, glucagon and somatostatin, and an exocrine gland that produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (β- or B-cells produce *insulin*, α_2- or A-cells produce glucagon, and α_1- or D-cells produce somatostatin). These hormones play an important role in regulating the metabolic activities of the body, and in doing so, help maintain the homeostasis of blood glucose.[1] Hyperinsulinemia (due, for example, to an insulinoma) can cause severe hypoglycemia. More commonly, a relative or absolute lack of *insulin* (such as in diabetes mellitus) can cause serious hyperglycemia. Administration of *insulin* preparations or hypoglycemic agents (Figure 26.1) can prevent morbidity and reduce mortality associated with diabetes.

II. DIABETES MELLITUS

Diabetes is not a single disease. Instead, it is a heterogeneous group of syndromes all characterized by an elevation of blood glucose caused by a relative or absolute deficiency of *insulin*. Frequently the inadequate release of *insulin* is aggravated by an excess of glucagon. Diabetes afflicts about 10 million individuals or about 5% of the population of the United States, and is the eighth leading cause of death in this country. Diabetics can be divided into two groups based on their requirements for *insulin: insulin*-dependent diabetes mellitus (IDDM or Type I) and non-*insulin*-dependent diabetes mellitus (NIDDM or Type II).[2] About one to two million patients have IDDM; the remaining 80 to 90% of diabetic patients have NIDDM. Figure 26.2 summarizes the characteristics of Types I and II diabetes.

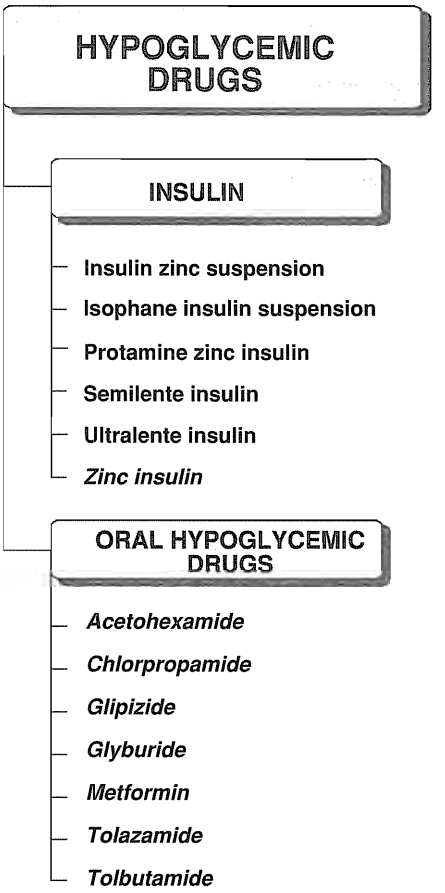

Figure 26.1
Summary of hypoglycemic agents.

[1,2]See p. 262 for Infolink references to other books in this series.

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

	Insulin-dependent diabetes	Non-insulin-dependent diabetes
Age of onset	Usually during childhood or puberty	Frequently over age 35
Nutritional status at time of onset of disease	Frequently undernourished	Obesity usually present
Prevalence	10-20% of diagnosed diabetics	80-90% of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells destroyed eliminating production of insulin	Inability of β-cells to produce appropriate quantities of insulin; insulin resistance; other unknown defects

Figure 26.2
Comparison of insulin-dependent diabetes and non-insulin-dependent diabetes.

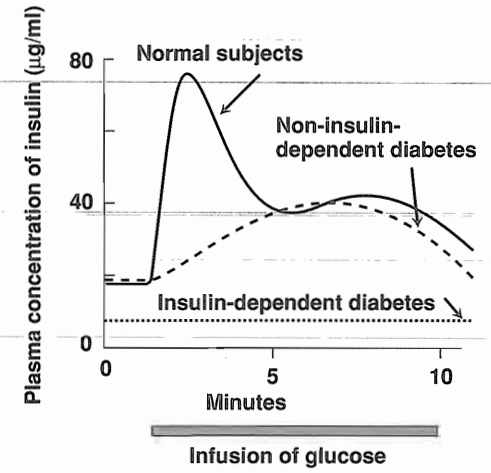

Figure 26.3
Release of insulin that occurs in response to constant infusion of glucose in normal subjects and in diabetic patients.

A. Type I diabetes (insulin-dependent diabetes mellitus, IDDM)

Insulin-dependent diabetes most commonly afflicts juveniles, but IDDM can also occur among adults (Figure 26.2). The disease is characterized by an absolute deficiency of *insulin* caused by massive β-cell lesions or necrosis. Loss of β-cell function may be due to invasion by viruses, the action of chemical toxins, or usually, through the actions of autoimmune antibodies directed against the β-cell. As a result of the destruction of β-cells, the pancreas fails to respond to ingestion of glucose, and the Type I diabetic shows classic symptoms of *insulin* deficiency (polydipsia, polyphagia and polyuria). Type I diabetics require exogenous *insulin* to avoid hyperglycemia and life-threatening ketoacidosis.

1. **Cause of Type I diabetes:** A burst of *insulin* secretion normally occurs after ingestion of a meal in response to transient increases in the levels of circulating glucose and amino acids. In the postabsorptive period, low, basal levels of circulating *insulin* are maintained through β-cell secretion. However, the Type I diabetic has virtually no functional β-cells, and can neither respond to variations in circulating fuels nor maintain even a basal secretion level of *insulin* (Figure 26.3). The development and progression of neuropathy, nephropathy and retinopathy are directly related to the extent of glycemic control (most often measured as blood levels of hemoglobin A_{1C}).[3]

2. **Treatment of Type I diabetes:** A Type I diabetic must rely on exogenous (injected) *insulin* in order to control hyperglycemia, maintain acceptable levels of glycosylated hemoglobin (HbA_{1c}), and avoid ketoacidosis. [Note: The rate of formation of HbA_{1C} is proportional to the average blood glucose concentration over the previous several months; thus, HbA_{1C} provides a measure of how well treatment has normalized blood glucose in diabetics.] The goal in administering *insulin* to Type I diabetics is to maintain blood glucose concentrations as close to normal as possible and to avoid wide swings in blood glucose levels that may contribute to long-term complications. The use of portable blood glucose analyzers facilitates close self-monitoring and treatment.

B. Type II diabetes (non-insulin-dependent diabetes mellitus, NIDDM)

Most diabetics are in this category. Genetic factors rather than viruses or autoimmune antibodies are apparently causal. The metabolic alterations observed are milder than those described for IDDM (for example, NIDDM patients typically are not ketotic), but the long-term clinical consequences can be just as devastating (for example, vascular complications and subsequent infection can lead to amputation of the lower limbs).

1. **Cause of Type II diabetes:** In NIDDM, the pancreas retains some β-cell function, resulting in variable *insulin* levels that are insufficient to maintain glucose homeostasis (see Figure 26.3).

[3]See p. 262 for Infolink references to other books in this series.

Patients with Type II diabetes are often obese. Type II diabetes is frequently accompanied by target organ *insulin* resistance that limits responsiveness to both endogenous and exogenous *insulin*. In some cases, *insulin* resistance is due to a decreased number or mutations of *insulin* receptors. However, an as yet undefined defect in the events that occur after *insulin* binds to its receptor is believed to account for resistance in most patients.

2. **Treatment of Type II diabetes:** The goal in treating Type II diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Weight reduction, exercise and dietary modification decrease *insulin* resistance and correct the hyperglycemia of Type II diabetes in some patients. However, most are dependent on pharmacologic intervention with oral hypoglycemic agents (Figure 26.4). *Insulin* therapy may be required to achieve satisfactory serum glucose levels. [Note: See Figure 26.2 for a summary comparison of Type I and Type II diabetes mellitus.]

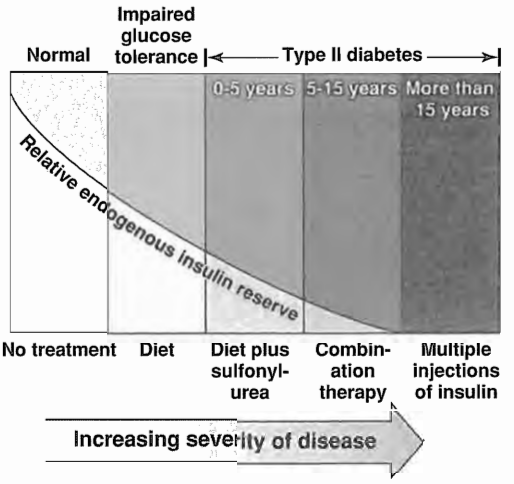

Figure 26.4
Duration of non-insulin-dependent (type II) diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.

III. INSULIN

Insulin [IN suh lin] is a small protein consisting of two polypeptide chains that are connected by disulfide bonds. It is synthesized as a precursor protein (pro-*insulin*) that undergoes proteolytic cleavage to form *insulin* and peptide C, both of which are secreted by the β-cells of the pancreas.[4] [Note: Normal individuals secrete less pro-*insulin* than *insulin*, whereas NIDDM patients secrete high levels of the prohormone. Since radioimmunoassays do not distinguish between the two *insulin* types, NIDDM patients may have lower levels of the active hormone than the assay indicates. Thus measurement of circulating C peptide provides a better index of *insulin* levels.]

A. Insulin secretion

Insulin secretion is regulated not only by blood glucose levels but also by other hormones and autonomic mediators. Secretion is most commonly triggered by high blood glucose which is taken up and phosphorylated in the β-cells of the pancreas. Adenosine triphosphate (ATP) levels rise and block K^+ channels, leading to membrane depolarization and an influx of Ca^{++}, which causes pulsatile *insulin* exocytosis. [Note: Glucose given by injection has a lower effect on *insulin* secretion than does glucose taken orally, because orally taken glucose stimulates production of digestive hormones by the gut, which in turn stimulate *insulin* secretion by the pancreas.]

B. Sources of insulin

Insulin is isolated from beef and pork pancreas. However, *human insulin* is replacing the animal hormone for therapy. *Human insulin* is produced by a special strain of Escherichia coli that has been genetically altered to contain the gene for *human insulin*. *Pork insulin* is closest in structure to *human insulin,* differing by only one amino acid.

[4]See p. 262 for Infolink references to other books in this series.

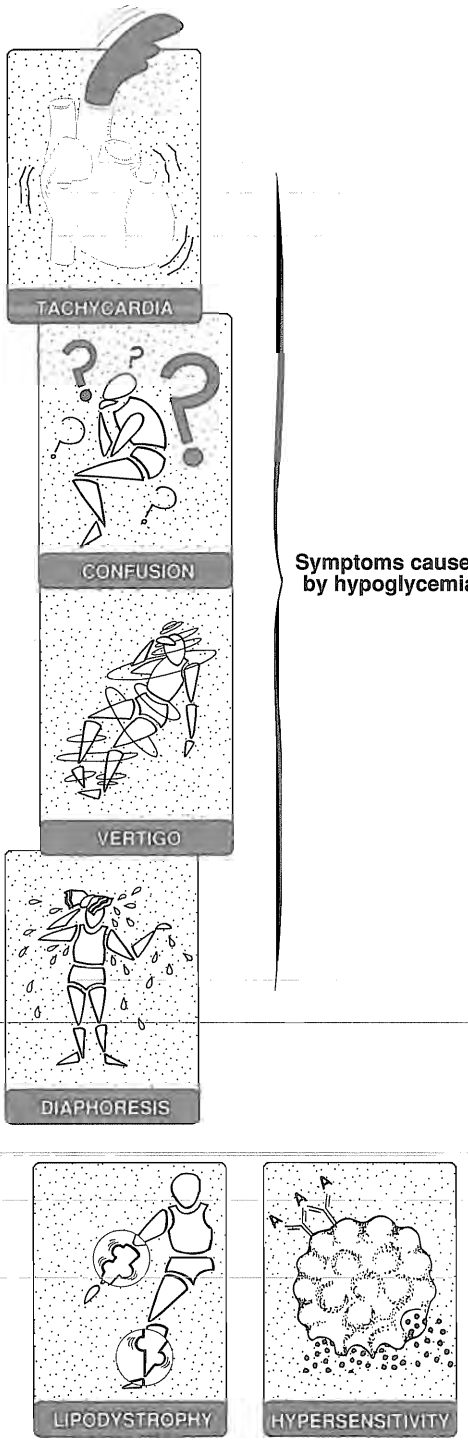

Figure 26.5
Adverse effects observed with *insulin*; Note: lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.

C. Insulin administration

Because *insulin* is a protein, it is degraded in the gastrointestinal tract if taken orally. It is therefore generally administered by subcutaneous injection. [Note: In a hyperglycemic emergency, regular *insulin* is injected intravenously.] *Insulin* is inactivated by the reducing enzyme, *insulin*ase, found mainly in the liver and kidney. *Insulin* preparations vary primarily in their times of onset of activity and duration of activity. This is due in large part to the size and composition of the *insulin* crystals in the preparations. [Note: The less soluble an *insulin* preparation is, the longer it acts.] Dose, site of injection, blood supply, temperature and physical activity can affect the duration of action of the various preparations. *Human insulin* is absorbed more quickly from its site of injection than are the beef or pork hormones. Thus, the duration of action of *human insulin* is shorter, and doses must be adjusted accordingly.

D. Adverse reactions to insulin

The symptoms of hypoglycemia are the most serious and common adverse reactions to an overdose of *insulin* (Figure 26.5). Long-term diabetics often do not produce adequate amounts of the counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hormone) that normally provide an effective defense against hypoglycemia. Other adverse reactions include lipodystrophy and allergic reactions. [Note: β-Blockers (p. 74) cause hypoglycemia. Because they inhibit the adrenergic physiologic symptoms of hypoglycemia, except for sweating, these drugs can mask the onset of *insulin* coma.]

IV. INSULIN PREPARATIONS

Most of the *insulin*s derived from beef and pork have been largely replaced by the human form synthesized utilizing recombinant DNA technology.

A. Rapid action insulin preparations

Regular *insulin* is a short-acting soluble crystalline zinc *insulin*. It is usually given subcutaneously (or intravenously in emergencies) and lowers blood sugar within minutes (Figure 26.6). It is the only *insulin* preparation suitable for intravenous administration. The buffered form is used in external *insulin* pumps. Both human recombinant and animal source *insulin* are availble in this form. A new type of insulin, which contains a modification in the amino acid sequence of naturally occuring insulin, has recently been approved. This insulin acts faster than regular insulin.

B. Intermediate action insulin preparations

1. **Semilente insulin suspension:** This *insulin* is an amorphous precipitate of *insulin* with zinc ion in acetate buffer that is not suitable for intravenous administration. Its onset of actions and peak effect are rapid, but somewhat slower than for regular *insulin*.

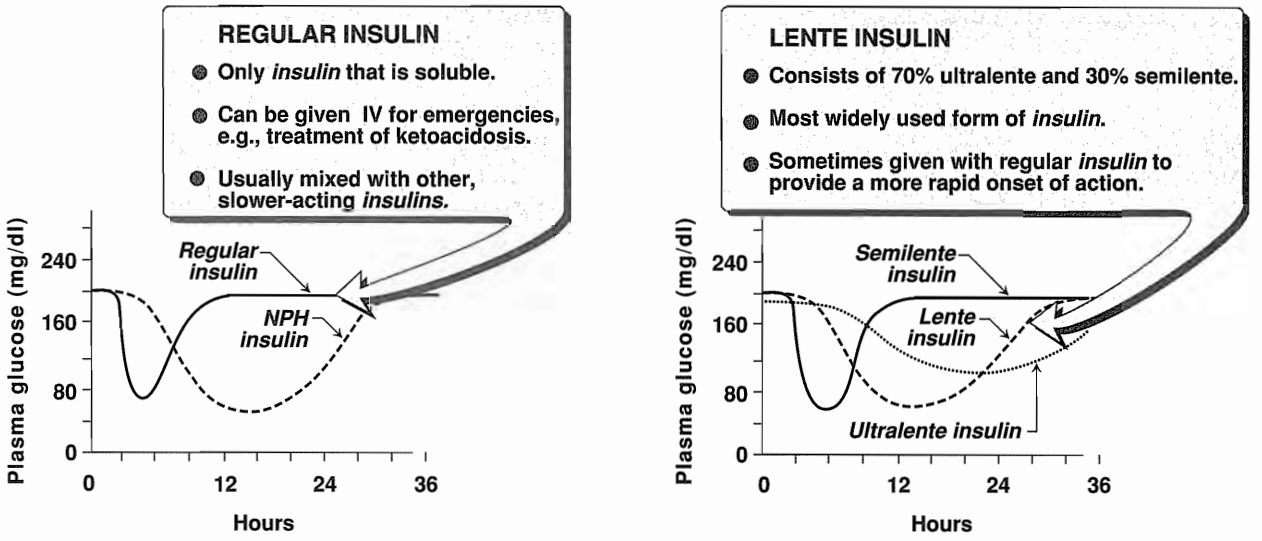

Figure 26.6
Extent and duration of action of various types of *insulin* (in a fasting diabetic). NPH= neutral protamine Hagedorn.

2. **Isophane insulin suspension:** This *insulin*, sometimes called neutral protamine Hagedorn, *NPH*, is a suspension of *crystalline zinc insulin* combined at neutral pH with the positively charged polypeptide, protamine. Its duration of action is intermediate. This is due to delayed absorption of the *insulin* because of conjugation of the *insulin* with protamine to form a less soluble complex. The *NPH* should only be given subcutaneously (never IV), and is useful in treating all forms of diabetes except diabetic ketoacidosis or emergency hyperglycemia.

3. **Lente insulin:** This *insulin* is a mixture of 30% semilente *insulin* (prompt acting) and 70% ultralente *insulin* (prolonged acting). This combination provides a relatively rapid absorption, with a sustained action making lente *insulin* the most widely used of the lente series of *insulins*. It is given only subcutaneously.

4. **Insulin combinations:** Combinations of human *insulins* such as 70% isophane + 30% regular, or 50% of each of these are also available.

C. Prolonged action insulin preparations

Ultralente *insulin* is a suspension zinc *insulin* (porcine or human) crystals in acetate buffer that is composed of large particles which are slow to dissolve, producing a slow onset of action and a long-lasting hypoglycemic effect.

D. Standard treatment vs. intensive treatment:

Standard treatment of patients with diabetes mellitus involves injection of *insulin* twice daily resulting in mean blood glucose levels in the range of 225 to 275 mg/dL, with HbA_{1C} of 8 to 9% of total hemoglobin. In contrast, intensive treatment seeks to normal-

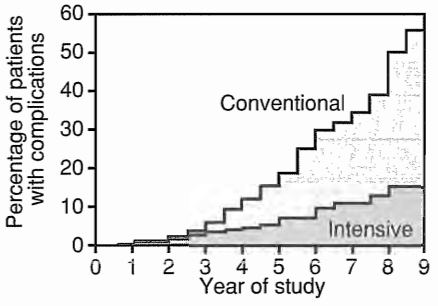

Figure 26.7
Effect of standard and intensive care on the long-term complications of diabetes.

ize blood glucose through more frequent injections of *insulin* (three or more times daily in response to monitoring blood glucose levels). Mean blood glucose levels of 150 mg/dL can be achieved, with an HbA_{1C} of approximately 7% of total hemoglobin. [Note: Normal mean blood glucose is approximately 110 mg/dL, and HbA_{1C} is 6% or less.] Thus, total normalization of blood glucose levels is not achieved even in intensively treated diabetic patients. Nonetheless, patients on intensive therapy show a 60% reduction in the long-term complications of diabetes—retinopathy, nephropathy, and neuropathy—compared to patients receiving standard care (Figure 26.7). However, the frequency of hypoglycemic episodes, coma, and seizures due to excessive *insulin* is particularly high with intensive treatment regimens .

V. ORAL HYPOGLYCEMIC AGENTS

These agents are useful in the treatment of patients who have non-*insulin*-dependent diabetes (NIDDM) but cannot be managed by diet alone. The patient most likely to respond well to oral hypoglycemic agents is one who develops diabetes after age 40 and has had diabetes less than 5 years. Patients with long-standing disease may require a combination of a hypoglycemic drug and *insulin* to control their hyperglycemia. Oral hypoglycemic agents should not be given to patients with Type I diabetes. Figure 26.8 summarizes some of the interactions of oral hypoglycemic agents with other drugs.

A. Sulfonylureas

The mechanisms of action of the sulfonylureas include: (1) stimulation of *insulin* release from the β-cells of the pancreas, (2) reduction of serum glucagon levels, and (3) increased binding of *insulin* to target tissues and receptors. The primary drugs used today are *tolbutamide* [tole BYOO ta mide], and the second generation derivatives, *glyburide* [GLYE byoor ide] and *glipizide* [GLIP i zide]. Given orally, they bind to serum proteins, are metabolized by the liver, and are excreted by the liver or kidney. These drugs are contraindicated in patients with hepatic or renal insufficiency, because delayed excretion of the drug, resulting in its accumulation, may cause hypoglycemia. Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds. The sulfonylureas traverse the placenta and can deplete *insulin* from the fetal pancreas; therefore the NIDDM pregnant women should be treated with *insulin*. [Note: *Acetohexamide* [a seat oh HEX a mide], and *tolazamide* [tole AZ a mide] are rarely used today. *Chlorpropamide* [klor PROE pa mide] should be avoided in the elderly. Its effects are very long lasting and it has the highest incidence of side effects in this drug group, causing hyponatremia, hypoglycemia, and if taken with alcohol, a disulfi-

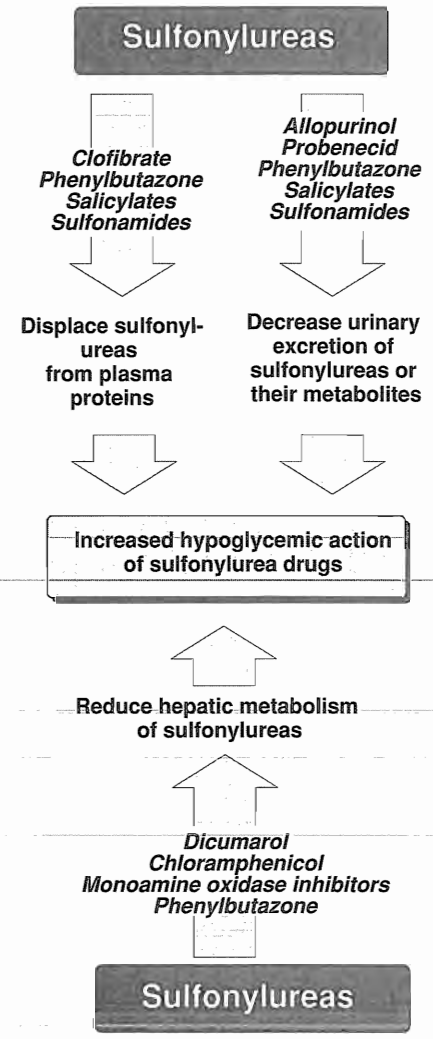

Figure 26.8
Drugs interacting with sulfonylurea drugs.

ram reaction (see p. 96) and hypotension.] Figure 26.9 summarizes some properties of the hypoglycemic drugs and Figure 26.10 illustrates some of the common adverse effects of these agents.

B. Biguanides

Metformin [MET for min] is now available in the United States. A biguanide, it differs from the sulfonylureas in not stimulating *insulin* secretion. The risk of hypoglycemia is less than with sulfonylurea agents. *Metformin* may be used alone or in combination with the sulfonylureas. *Metformin* acts primarily by decreasing hepatic glucose output, largely by inhibiting gluconeogenesis. A very important property is its ability to reduce hyperlipidemia (LDL and VLDL cholesterol concentrations fall and HDL cholesterol rises). The patient often loses weight. *Metformin* is considered by some experts as the drug of choice in newly diagnosed Type II diabetics. *Metformin* is well absorbed orally, is not bound to serum proteins and is not metabolized. Excretion is via the urine. Adverse effects are largely gastrointestinal. Rarely, potentially fatal lactic acidosis has occurred. [Note: *Phenformin*, a previous biguanide hypoglycemic agent, was withdrawn for this reason.] Long term use may interfere with B_{12} absorption. The drug is contraindicated in renal and hepatic insufficiency.

C. α-Glucosidase inhibitor

Recently, *acarbose* [ay KAR bose] has been approved as an orally active drug for the treatment of patients with NIDDM and as a possible adjunct to *insulin* for those with IDDM. *Acarbose* inhibits α-glucosidase in the intestinal brush border and thus decreases the absorption of starch and disaccharides. Consequently the postprandial rise of blood glucose is blunted. Unlike the other oral hypoglycemic agents, *acarbose* does not stimulate *insulin* release from the pancreas nor does it increase *insulin* action in peripheral tissues. Thus *acarbose* does not cause hypoglycemia. The drug can be used as monotherapy in those patients being controlled by diet or in combination with oral hypoglycemic agents, or with *insulin*. It is poorly absorbed and its major side effects are flatulence, diarrhea, and abdominal cramping.

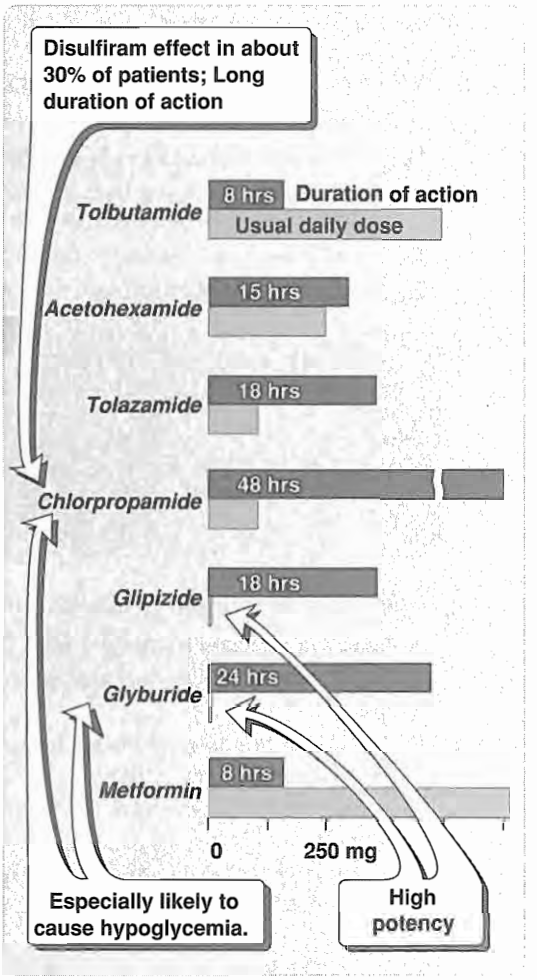

Figure 26.9
Summary of the properties of oral hypoglycemic agents.

Figure 26.10
Summary of the adverse effects observed with oral hypoglycemic agents.

Choose the ONE best answer.

26.1 Which one of the following statements is correct?

A. Sulfonylureas decrease the secretion of insulin.
B. Tolbutamide is effective in Type I diabetics.
C. Sulfonylureas increase both the release of insulin and the insulin-sensitivity of target tissue.
D. Glipizide increases glucagon secretion.
E. Chlorpropamide blocks insulin receptors.

Correct answer = C. Sulfonylureas increase both insulin release and target tissue sensitivity. Sulfonylureas cannot act to increase insulin secretion in Type I diabetics because these individuals have no β-cell function. Oral hypoglycemic agents often cause a decrease in glucagon release.

26.2 Which one of the following statements is correct?

A. Insulin can be administered orally.
B. Insulin is always required therapy in Type II diabetics.
C. Protamine is added to insulin to decrease the rate of absorption of the hormone.
D. Sulfonylureas are useful in the treatment of ketoacidosis.
E. Insulin acts by binding to receptors in the nucleus of target tissue.

Correct answer = C. Protamine complexes with insulin to form an insoluble complex that is slowly absorbed. Insulin is not administered orally because it is destroyed by proteases in the GI tract. Diet therapy and/or sulfonylureas are often effective without additional insulin in the therapy of Type II diabetics. Ketoacidosis is the most life-threatening consequence of Type I diabetics and requires adequate treatment with insulin, not sulfonylureas. Insulin acts by binding to specific receptors in the cell membrane, not in the nucleus.

26.3 All of the following are correct EXCEPT:

A. One of the most common side effects of oral hypoglycemic agents is gastrointestinal disturbance.
B. The most serious consequence of insulin overdose is hypoglycemia.
C. Weight reduction is often of therapeutic help in obese Type II diabetics.
D. Sulfonylureas are contraindicated in patients with hepatic insufficiency.
E. Insulin and glucagon have similar effects on metabolism.

Correct choice = E. Insulin and glucagon have opposite effects on metabolism. The other statements are correct.

26.4 A female patient with non-insulin-dependent diabetes has been maintained on an oral sulfonylurea hypoglycemic agent. She becomes pregnant. The doctor switches her to insulin. This is necessary for all of the following reasons EXCEPT:

A. Sulfonylureas can traverse the placenta and act on the islet cells of the pancreas of the fetus to deplete them of insulin.
B. Sulfonylureas may provoke pregnancy-induced hypertension.
C. Insulin does not pass through the placenta.
D. There is a greater demand for insulin in pregnancy than can be provided by sulfonylureas.

The correct answer= B In pregnancy, not only is the mother being treated with a drug but so is the fetus. In this case, it is important that the islet cells of the fetal pancreas not be affected by the sulfonylurea, otherwise the infant is born hypoglycemic. Sulfonylureas have no effect on blood pressure. The fact that insulin does not pass through the placenta allows the fetus to develop normally. With the growth of the fetus, there are greater demands on all body processes and thus an increased demand on insulin.

[1]See p. 269 in **Biochemistry** (2nd ed.) for a discussion of hormonal regulation of metabolism.

[2]See p. 295 in **Biochemistry** (2nd ed.) for a discussion of Type I and Type II diabetes.

[3]See p. 34 in **Biochemistry** (2nd ed.) for a discussion of hemoglobin A_{1c}.

[4]See p. 270 in **Biochemistry** (2nd ed.) for a discussion of biosynthesis of insulin.

Steroid Hormones

27

I. OVERVIEW

Steroid hormones include the sex hormones (androgens, progestins and estrogens), and the hormones of the adrenal cortex. Sex hormones produced by the gonads and adrenals are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. The gonadal hormones are used therapeutically in replacement therapy and, in the case of estrogen, for contraception and osteoporosis. The adrenal cortex produces two major classes of steroid hormones: the adrenocorticosteroids (glucocorticoids and mineralocorticoids) and the adrenal androgens. Their synthesis is stimulated by corticotropin (previously called adrenocorticotropic hormone, ACTH, see p. 247). Hormones of the adrenal cortex are used in replacement therapy, in the treatment and management of inflammatory diseases such as rheumatoid arthritis, in the treatment of severe allergic reactions, and in the treatment of some cancers (see p. 393). Inhibitors of adrenal cortical steroids are used to treat hormonal dysfunctions in which these compounds are produced in excess. Figure 27.1 lists the steroid hormones referred to in this chapter.

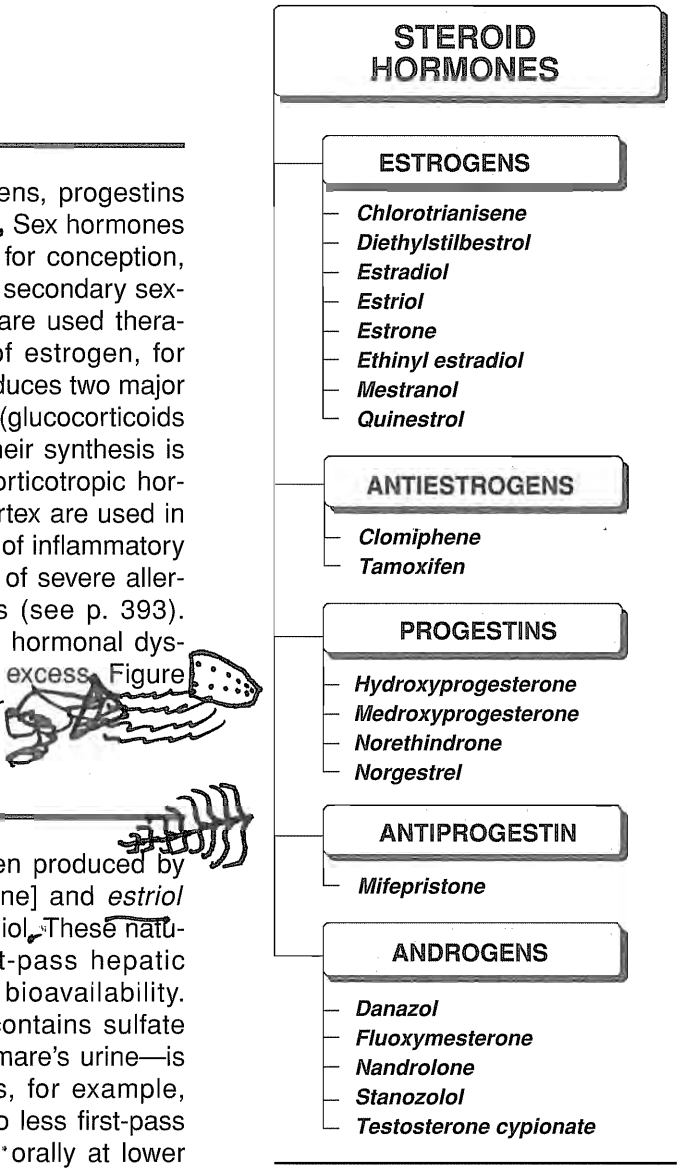

Figure 27.1
Summary of steroid hormones.
(figure continues on next page.)

II. ESTROGENS

Estradiol [ess tra DYE ole] is the most potent estrogen produced by women; the other major estrogens, *estrone* [ESS trone] and *estriol* [essTRI ole], have about one tenth the potency of estradiol. These naturally occurring steroids are subject to a large first-pass hepatic metabolism and when admistered orally show low bioavailability. PREMARIN—a preparation of conjugated estrogens (contains sulfate esters of *estrone* and *equilin*) obtained from pregnant mare's urine—is a widely used oral preparation. Synthetic estrogens, for example, *ethinyl estradiol* [ETH eye nil ess tra DYE ole], undergo less first-pass metabolism and thus are effective when administered orally at lower doses. Synthetic nonsteroidal compounds with estrogenic activity, for example, *diethylstilbestrol* [dye eth il stil BESS trol] [*DES*], *quinestrol* [kwin ESS trole], *chlorotrianisene* [klor oh trye AN i seen] and others, are used clinically.

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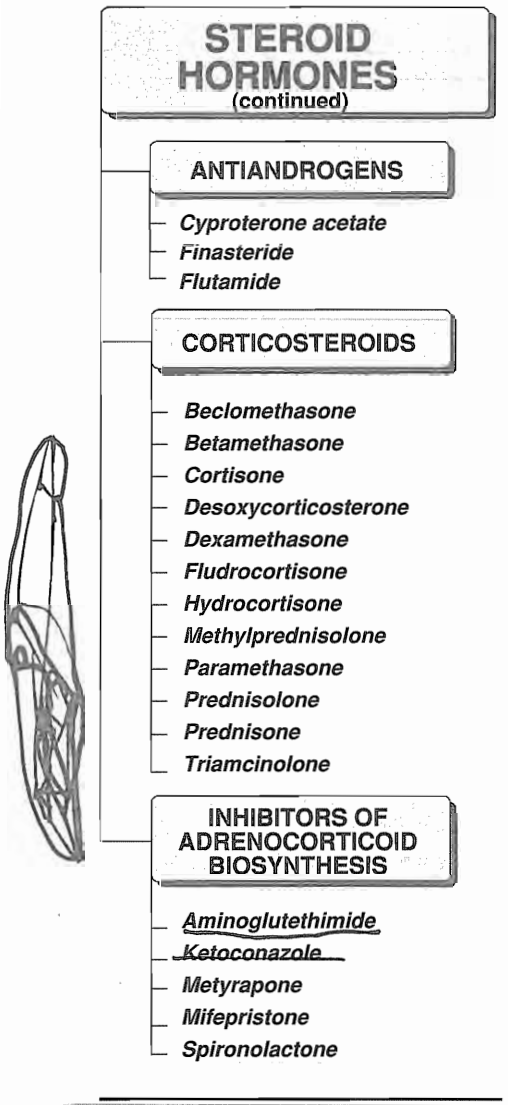
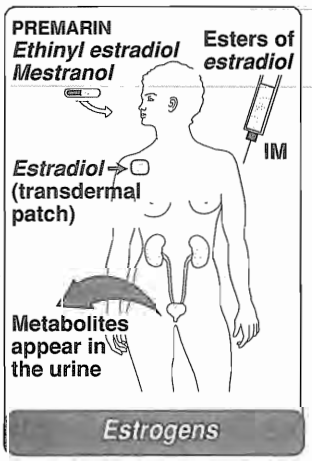


Figure 27.1 (continued)
Summary of steroid hormones.



A. Mechanism of action

Steroid hormones diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins (see p. 393). Affinity for the receptor varies with the particular estrogen. [Note: The estrogen receptor is a member of a superfamily of receptors that include those for thyroid hormones and vitamin D, as well as ligands not yet identified. The attachment of two estrogen-linked receptors to the genome is required for a response.] The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis, resulting in the synthesis of specific proteins that mediate a number of physiologic functions. [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and are therefore both receptor- and tissue-specific.]

B. Therapeutic uses of estrogens

The most frequent uses of estrogens are for contraception (see p. 268), for postmenopausal hormone therapy and for osteoporosis. Estrogens are also used extensively for replacement therapy in patients deficient in this hormone. Such a deficiency can be due to lack of development of the ovaries, menopause, or castration.

1. **Postmenopausal hormone therapy:** In the past, estrogen therapy was reserved for postmenopausal women experiencing "hot flashes", atrophic vaginitis and urethral changes, and women wishing to reduce the risk of osteoporosis. Today, evidence is accumulating that all (except for those with specific contraindications, such as a history of estrogen-dependent cancer) may experience multiple benefits from estrogen replacement therapy (Figure 27.2). For women who have not undergone a hysterectomy, a progestin is usually included with the estrogen therapy, since the combination reduces the risk of endometrial carcinoma associated with estrogen treatment alone. For women whose uterus has been surgically removed, unopposed estrogen therapy is recommended, since progestins may unfavorably alter the high density/low density lipoprotein (HDL/LDL) ratio[1]. [Note: The amounts of estrogen used in replacement therapy are substantially less than the doses used in oral contraception described on p. 268. Thus the adverse effects of estrogen replacement therapy tend to be less severe than side effects seen in women taking estrogen for contraceptive purposes.] Delivery of *estradiol* by transdermal patch is also effective in treating postmenopausal symptoms. Replacement therapy is not universally beneficial; the risk of breast and endometrial cancer is slightly increased and gallbladder disease is more common in women receiving estrogen. However, if these adverse affects are balanced against the favorable actions—particularly the cardioprotective effect—the cumulative effect of estrogen therapy is strongly beneficial. Figure 27.3 summarizes some of the agents useful in the treatment of osteoporosis.

2. **Primary hypogonadism:** Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with progestins is instituted to stimulate development of secondary sex characteristics in young women (11 to 13 years of age) with hypogonadism.

[1] See p. 278 for Infolink references to other books in this series.

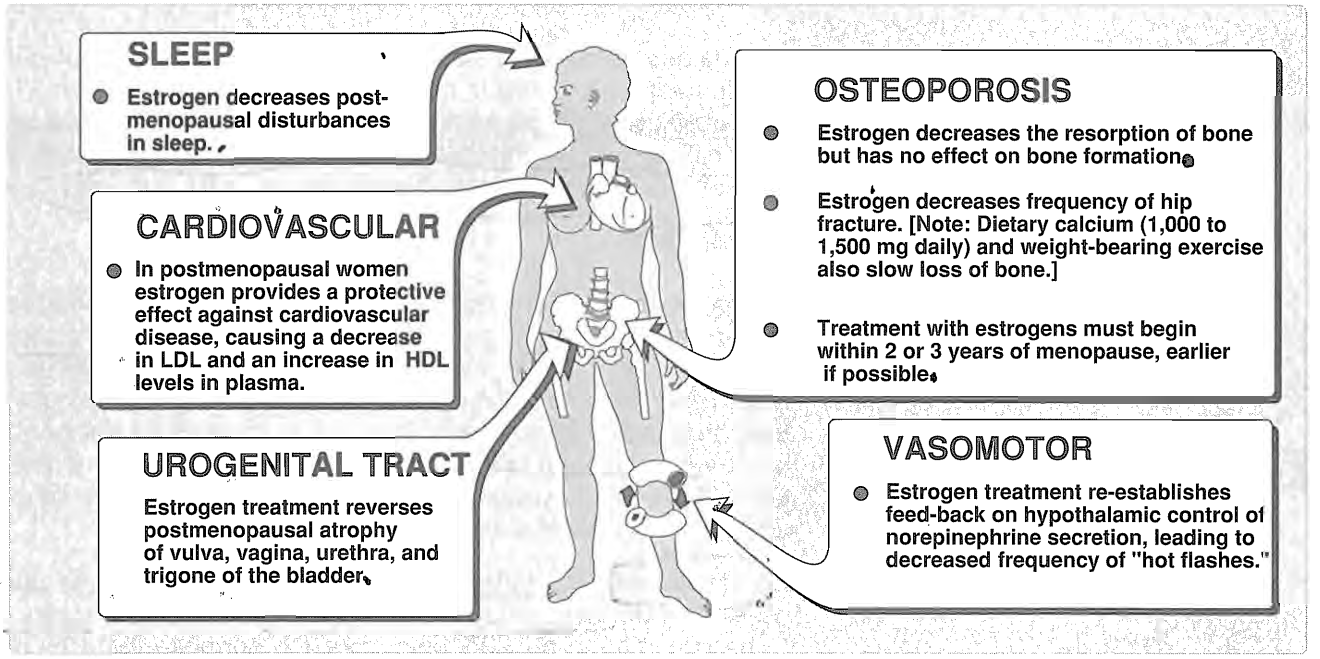


Figure 27.2
Benefits associated with postmenopausal estrogen replacement.

C. Pharmacokinetics

1. **Naturally occurring estrogens:** These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Estrogen is also quickly absorbed when administered intramuscularly. Administered orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver.

2. **The synthetic estrogen analogs:** These compounds, for example, *ethinyl estradiol* and *mestranol* [MES tra nole]), are well absorbed after oral administration, and through the skin or mucous membranes. *Mestranol* is quickly oxidized to *ethinyl estradiol,* which is metabolized more slowly than the naturally occurring estrogens by the liver and peripheral tissues. Being fat soluble, they are stored in adipose tissue from which they are slowly released. Therefore, the synthetic estrogen analogs have a prolonged action and higher potency as compared to natural estrogens.

3. **Metabolism:** Estrogens are transported in the blood bound to serum albumin and sex hormone-binding globulin. They are hydroxylated in the liver to derivatives that are subsequently glucuronidated or sulfated. These inactive products are excreted in the urine. [Note: In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism, causing feminization in males or signs of estrogen excess in females.]

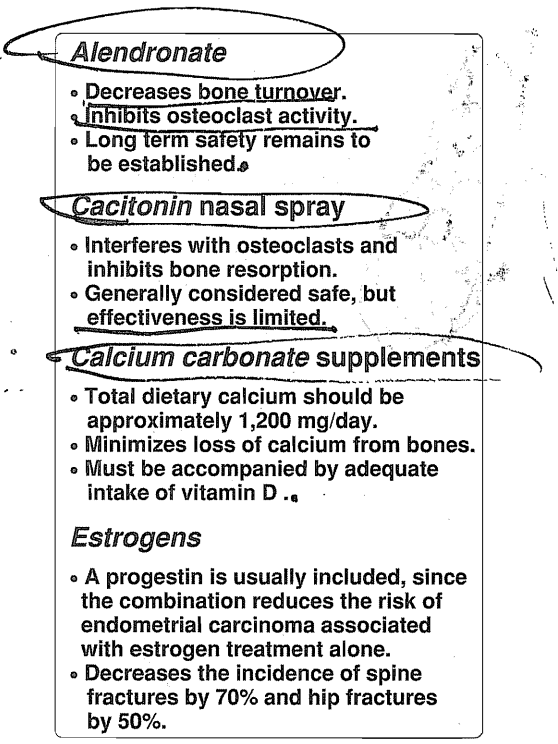


Figure 27.3
Drugs and dietary supplements used in the treatment of osteoporosis.

D. Adverse effects

Nausea and vomiting are the most common adverse effects of estrogen therapy. Other effects of estrogen are shown in Figure 27.4. *Diethylstilbestrol* has been implicated as the possible cause of a rare, clear cell cervical or vaginal adenocarcinoma observed among the daughters of women who took the drug during early pregnancy.

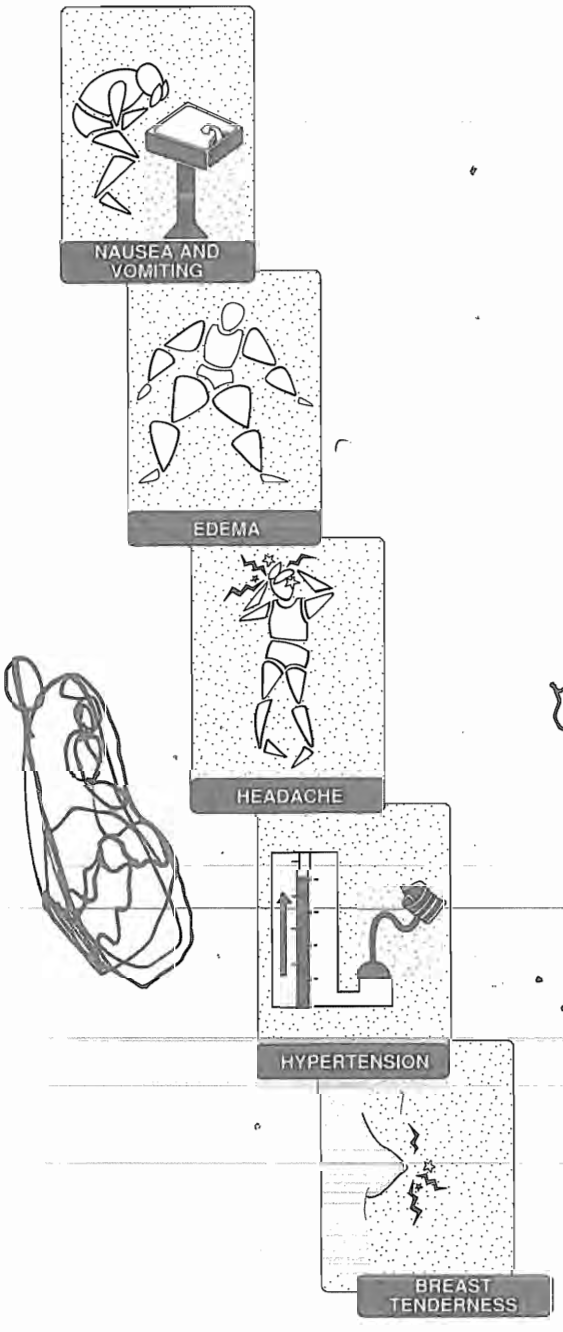


Figure 27.4
Some adverse effects associated with estrogen therapy.

E. Antiestrogens

Antiestrogens, which modify or oppose the action of estrogens, include the nonsteroidal antiestrogenic compounds *clomiphene* [KLOE mi feen] and its structurally related analog, *tamoxifen* [ta MOX i fen]. Both inhibit the action of estrogens by interfering with their access to receptor sites. They act as competitive antagonists or, in a low estrogen milieu, as weak agonists of the natural estrogens. These nonsteroidal antiestrogenic compounds are equally effective when given by mouth or by injection.

1. **Clomiphene:** By interfering with the negative feedback of estrogens on the hypothalamus and pituitary, *clomiphene* increases the secretion of gonadotropin-releasing hormone (Gn-RH) and gonadotropins, leading to a stimulation of ovulation. The drug has been used successfully to treat infertility associated with anovulatory cycles, but it is not effective in women whose ovulatory dysfunction is due to pituitary or ovarian failure. Adverse effects are dose-related and include ovarian enlargement, vasomotor flushes, and visual disturbances.

2. **Tamoxifen:** This drug competes for binding to the estrogen receptor and is currently used in the palliative treatment of advanced breast cancer in postmenopausal women (see p. 394). [Note: Normal breast growth is stimulated by estrogens. It is therefore not surprising that some breast tumors regress following treatment with antiestrogens.] *Tamoxifen's* most frequent adverse effects are hot flashes, nausea and vomiting. Menstrual irregularities and vaginal bleeding can also occur.

III. PROGESTINS

Progesterone, the natural progestin, is produced in response to luteinizing hormone (LH) by both females [secreted by the corpus luteum, primarily during the second half of the menstrual cycle (Figure 27.5), and by the placenta] and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of progesterone released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin, and therefore, further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation. (See Figure 27.5 for a summary of the hormones produced during the menstrual cycle.)

A. Therapeutic uses of progestins

The major clinical use of progestins is in contraception, in which they are generally used with estrogens, either in combination or in a sequential manner. *Progesterone* by itself is not used widely therapeutically because of its rapid metabolism, resulting in its low bioavailability. Synthetic progestins used in contraception are more stable to first-pass metabolism, allowing for lower doses when administered orally. These agents include *medroxyprogesterone acetate* [meh DROX ee proe JESS ter one], *hydroxyprogesterone acetate* [hye DROX ee proe JESS ter one], *norethindrone* [nor eth IN drone], and *norgestrel* [nor JESS trel]. [Note: *Norethindrone* and *norgestrel* are sometimes called the nortestosterone progestins because of their structural similarity to the androgen. They also possess some androgenic activity.] Other clinical uses of the progestins are in the control of dysfunctional uterine bleeding, the treatment of dysmenorrhea, suppression of postpartum lactation, and the management of endometriosis. They are also used to treat endometrial carcinomas.

B. Pharmacokinetics

Progesterone is rapidly absorbed after its administration by any route. It has a short half-life in the plasma, since it is almost completely metabolized in one passage through the liver. The glucuronidated metabolite (pregnanediol glucuronide) is excreted by the kidney. Synthetic progestins are less rapidly metabolized.

C. Adverse effects

The major adverse effects associated with the use of progestins are edema and depression. The androgen-like progestins can increase the ratio of LDL to HDL cholesterol, cause thrombophlebitis and pulmonary embolism, as well as acne, hirsutism and weight gain.

D. Antiprogestin

Mifepristone (also designated RU 486) is a progestin antagonist with partial agonist activity. [Note: *Mifepristone* is also a potent antiglucocorticoid (see p. 277).] Administration of this drug to females early in pregnancy results in most cases (85%) in abortion of the fetus due to the interference with progesterone and the decline in human chorionic gonadotropin (hCG). The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion. However, administration of *prostaglandin E_1* intravaginally, or *misoprostol* [miss oh PROH stol] orally, after a single oral dose of *mifepristone*, effectively terminates gestation. *Mifepristone* can also be used as a contraceptive, given once a month during the midluteal phase of the cycle when progesterone is normally high (Figure 27.5).

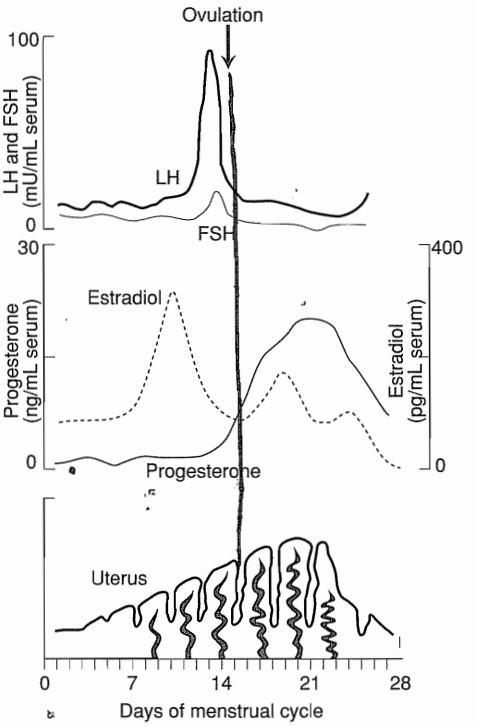


Figure 27.5
Menstrual cycle showing plasma levels of pituitary and ovarian hormones, and a schematic representation of changes in the morphology of the uterine lining. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

IV. ORAL AND IMPLANTABLE CONTRACEPTIVES

Drugs have been identified that decrease fertility by a number of different mechanisms, for example, preventing ovulation, impairing gametogenesis or gamete maturation, or interfering with gestation. Currently, interference with ovulation is the most common pharmacologic intervention for preventing pregnancy (Figure 27.6).

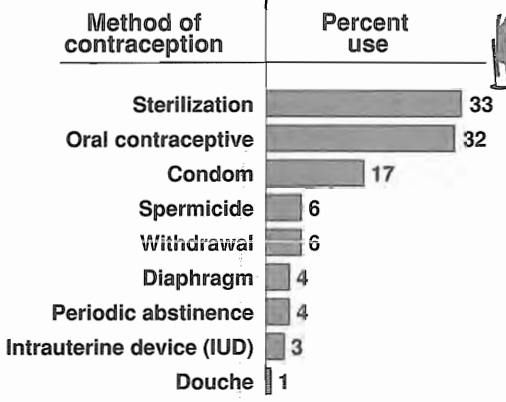


Figure 27.6
Comparison of contraceptive use among U.S. women ages 15 to 44 years.

A. Major classes of oral contraceptives

1. **Combination pills:** Products containing a combination of estrogen and a progestin are the most common type of oral contraceptives. The estrogen component suppresses ovulation while the progestin prevents implantation in the endometrium and makes the cervical mucus impenetrable to sperm. Combination pills contain a constant low dose of estrogen given over 21 days plus a concurrent low but increasing dose of progestin given over 3 successive 7-day periods (called the "triphasic regimen"). The pills are taken for 21 days followed by a 7-day withdrawal period to induce menses. [Note: Estrogens that are commonly present in the combination pills are *ethinyl estradiol* and *mestranol*.] These preparations are highly effective in achieving contraception (Figure 27.7).

2. **Progestin pills:** Products containing a progestin only, usually *norethindrone* or *norgestrel* (called a "mini-pill"), are taken daily on a continuous schedule. Progestin-only pills deliver a low, continuous dosage of drug. These preparations are less effective than the combination pill (Figure 27.7) and may produce irregular menstrual cycles more frequently than the combination product. The progestin-only pill has limited patient acceptance because of anxiety over the increased possibility of pregnancy and the frequent occurrence of menstrual irregularities.

3. **Progestin implants:** Subdermal capsules containing *levonorgestrel* offer long-term contraception. Six capsules, each the size of a match stick, are placed subcutaneously in the upper arm. The progestin is slowly released from the capsules providing contraceptive protection for approximately 5 years. The implant is cheaper than oral contraceptives, nearly as reliable as sterilization, and totally reversible if the implants are surgically removed. Once the progestin-containing capsules are implanted, this method of contraception does not rely on patient compliance. This may, in part, explain the low failure rate for the method of contraception. For example, Figure 27.8 shows that this use of *levonorgestrel* (NORPLANT) implants by adolescent mothers results in significantly lower rates of new pregnancies when compared to women using oral contraceptives. Principal side effects of the implants are irregular menstrual bleeding and headaches.

4. **Postcoital contraception:** A fourth type of contraceptive strategy uses high-dose estrogen (for example, *ethinyl estradiol* or *diethylstilbestrol*) administered within 72 hours of coitus and continued twice daily for 5 days (the "morning-after" pill). Alternatively, two doses of *ethinyl estradiol* plus *norgestrel* are given within 72 hours of coitus, followed by another two doses 12 hours later. A single dose of *mifepristone* has also been used.

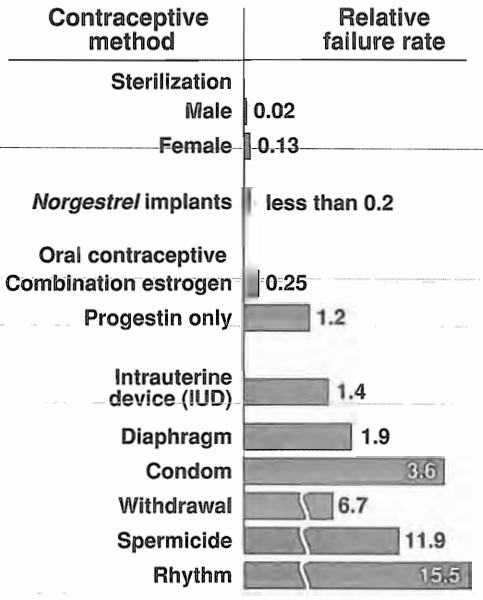


Figure 27.7
Comparison of failure rate for various methods of contraception. Longer bars indicate a higher failure rate, that is, more pregnancies.

B. Mechanism of action

The mechanism of action of these contraceptives is not completely understood. It is likely that the combination of estrogen and progestin administered over approximately a 3-week period inhibits ovulation,

[Note: The estrogen provides a negative feedback on the release of LH and FSH by the pituitary gland, thus preventing ovulation. The progestin stimulates normal bleeding at the end of the menstrual cycle.] Thickening of cervical mucus prevents access by the sperm.

C. Adverse effects

Most adverse effects are believed to be due to the estrogen component, but cardiovascular effects reflect the action of both estrogen and progestin. The incidence of side effects with oral contraceptives is relatively low and is determined by the specific compounds and combinations used.

1. **Major adverse effects:** The major side effects are breast fullness, depression, dizziness, edema, headache, nausea, and vomiting.

2. **Cardiovascular:** The most serious side effect of oral contraceptives is cardiovascular disease, including thromboembolism, thrombophlebitis, hypertension, and increased incidences of myocardial infarction and cerebral and coronary thrombosis. These adverse effects are most common among women who smoke and who are over 35 years of age, although they may affect women of any age.

3. **Carcinogenicity:** Oral contraceptives have been shown to decrease the incidence of endometrial and ovarian cancer. Their ability to induce other neoplasms is controversial. The production of benign tumors of the liver that may rupture and hemorrhage is rare.

4. **Metabolic:** Decreased dietary carbohydrate absorption by the intestine is sometimes associated with oral contraceptives, along with an increased incidence of abnormal glucose tolerance tests (similar to the changes seen in pregnancy).

5. **Serum lipids:** The combination pill causes a change in the serum lipoprotein profile: estrogen causes an increase in HDL and a decrease in LDL—a desirable occurrence—whereas progestins have the opposite effect. [Note: The potent progestin, *norgestrel*, causes the greatest increase in the LDL/HDL ratio. Therefore, estrogen-dominant preparations are best for individuals with elevated serum cholesterol.] Cholestatic jaundice, cholecystitis and cholangitis are also encountered.

6. **Contraindications:** Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and migraine headache.

Figure 27.8
Superiority of *levonorgestrel* in preventing pregnancy in adolescent mothers.

V. ANDROGENS

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosterone* [tess TOSS ter one], the most important androgen in humans, is synthesized by Leydig cells in the testes, and, in smaller amounts, by cells in the ovary of the female and in the adrenal gland. In adult males, *testosterone*

secretion by Leydig cells is controlled by hormonal signals from the hypothalamus (Gn-RH), by way of the pituitary gland secretion of FSH and LH (which was originally known as interstitial cell-stimulating hormone, (ICSH) in males). [Note: LH stimulates steroidogenesis in the Leydig cells, whereas FSH is necessary for the initiation of spermatogenesis.] *Testosterone* or its metabolite *5-α-dihydrotestosterone* (DHT, see later) inhibits production of these specific trophic hormones and thus regulates *testosterone* production (Figure 27.9). Synthetic modifications of the androgen structure are designed to (1) modify solubility and susceptibility to enzymatic breakdown (thus prolonging the half-life of the hormone), and (2) separate anabolic and androgenic effects.

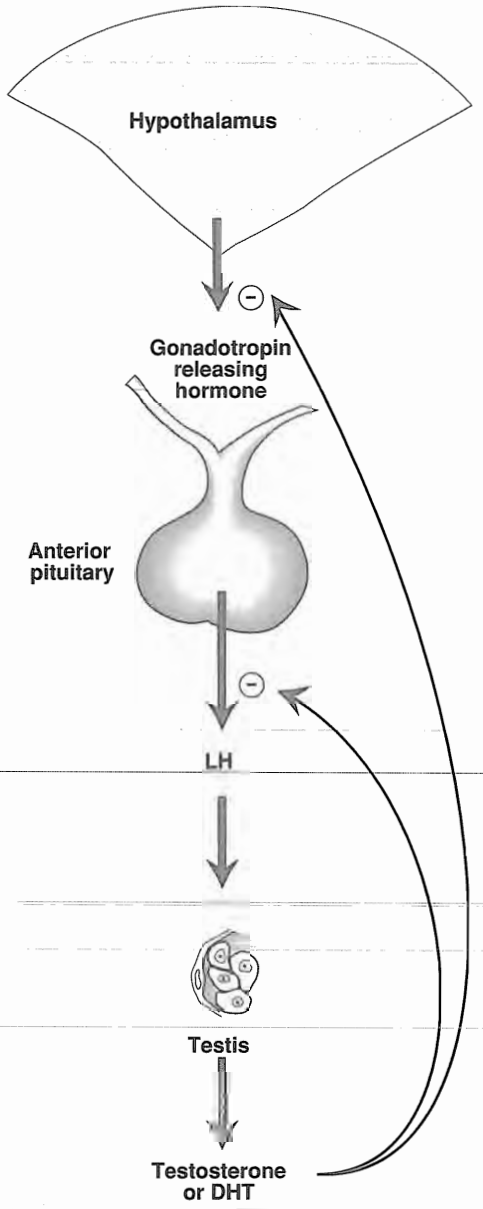


Figure 27.9
Regulation of secretion of testosterone.

A. Mechanism of action

Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although *testosterone* itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis and skin, *testosterone* is converted by 5-α-reductase to DHT, which binds to the receptor. In the brain *testosterone* is biotransformed to *estradiol*. The hormone/receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins.[2] [Note: *Testosterone* analogs that cannot be converted to DHT have less effect on the reproductive system than they do on the skeletal musculature.]

B. Therapeutic uses

1. **Androgenic effects:** Androgenic steroids are used in males with inadequate androgen secretion. [Note: Hypogonadism can be due to Leydig cell dysfunction or, secondarily, to failure of the hypothalamic-pituitary unit. In each instance, androgen is indicated.]

2. **Anabolic effects:** Anabolic steroids can be used to treat senile osteoporosis and severe burns, to speed recovery from surgery or from chronic debilitating diseases, and to counteract the catabolic effects of externally administered adrenal cortical hormones.

3. **Growth:** Androgens are used in conjunction with other hormones to promote skeletal growth in prepubertal boys with pituitary dwarfism.

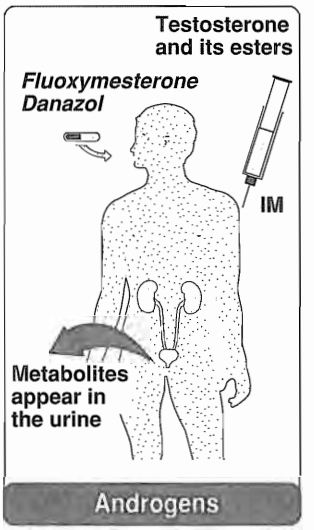
4. **Endometriosis:** *Danazol* [DA na zole], a mild androgen, is used in the treatment of endometriosis (ectopic growth of the endometrium).

5. **Unapproved use:** Androgenic steroids are used to increase lean body mass, muscle strength and aggressiveness in athletes and body builders (see "Adverse Effects").

[2]See p. 278 for Infolink references to other books in this series.

C. Pharmacokinetics

1. **Testosterone:** This agent is ineffective orally because of inactivation by first-pass metabolism. As with the other sex steroids, *testosterone* is rapidly absorbed by the liver and other tissues, and is metabolized to relatively or completely inactive compounds that are excreted primarily in the urine but also in the feces. *Testosterone* and its C-17-esters (for example, *testosterone cypionate* or *enanthate*) are administered intramuscularly. [Note: The addition of the esterified lipid makes the hormone more lipid-soluble, thereby increasing its duration of action.] *Testosterone* and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.



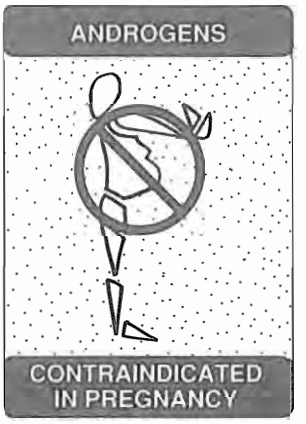
2. **Testosterone derivatives:** Agents such as *fluoxymesterone* [floo ox ee MESS te rone] and *danazol* also have a longer half-life in the body than does the naturally occurring androgen. *Fluoxymesterone* is effective when given orally, and it has a 1:2 androgenic to anabolic ratio. Because it is not readily converted to DHT, it is less active than *testosterone* in the reproductive system and does not induce puberty. It has a longer half-life than does *testosterone*.

D. Adverse effects

1. **In females:** Androgens can cause masculinization with acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women, because of the possible virilization of the female fetus.

2. **In males:** Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia.

3. **In children:** Androgens can cause growth disturbances resulting from premature closing of the epiphyseal plates and abnormal sexual maturation.



4. **General effects:** Androgens increase serum LDL and lower serum HDL levels; therefore they increase the LDL/HDL ratio and potentially increase the risk for premature coronary heart disease. Androgens can also cause fluid retention leading to edema.

5. **In athletes:** Use of anabolic steroids, (for example, *nandrolone* [nan DRO lone] or *stanozolol* [sta NO zo lol], by athletes can cause premature closing of the epiphysis of the long bones, which interrupts development. The high doses taken by these young athletes may result in hepatic abnormalities, increased aggression ("roid rage"), and psychotic episodes, as well as the other adverse effects described above.

E. Antiandrogens

Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. For example, at high doses, the antifungal *ketoconazole* (see p. 340) inhibits several of the cytochrome P-450 enzymes involved in steroid synthesis. *Finasteride* [fin AS ter eyed], the steroid-like drug recently approved for the treatment of benign prostatic hypertrophy (BPH), inhibits 5-α-reductase; the resulting decrease in formation of DHT by the prostate leads to a reduction in prostate size. Antiandrogens, such as *cyproterone acetate* [sih PROE ter one] and *flutamide* [FLOO ta mide] (see p. 395), act as competitive inhibitors of androgens. They inhibit the action of the androgens at the target cell. *cyproterone acetate* has been used to treat hirsutism in females; wherease *flutamide* is used in the treatment of prostatic carcinoma in males.

VI. ADRENAL CORTICOSTEROIDS

The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and secrete them (Figure 27.10). The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system (see p. 180). The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol [KOR ti sol]), which are concerned with normal metabolism and resistance to stress. The inner zona reticularis secretes adrenal androgens, such as dehydroepiandrosterone. Secretion by the two inner zones, and to some extent, the outer zone, is controlled by pituitary corticotropin, which is released in response to the hypothalamic corticotropin-releasing hormone (CRH, see p.247). Glucocorticoids serve as feedback inhibitors of corticotropin and corticotropin-releasing factor (CRF) secretion (Figure 27.10).

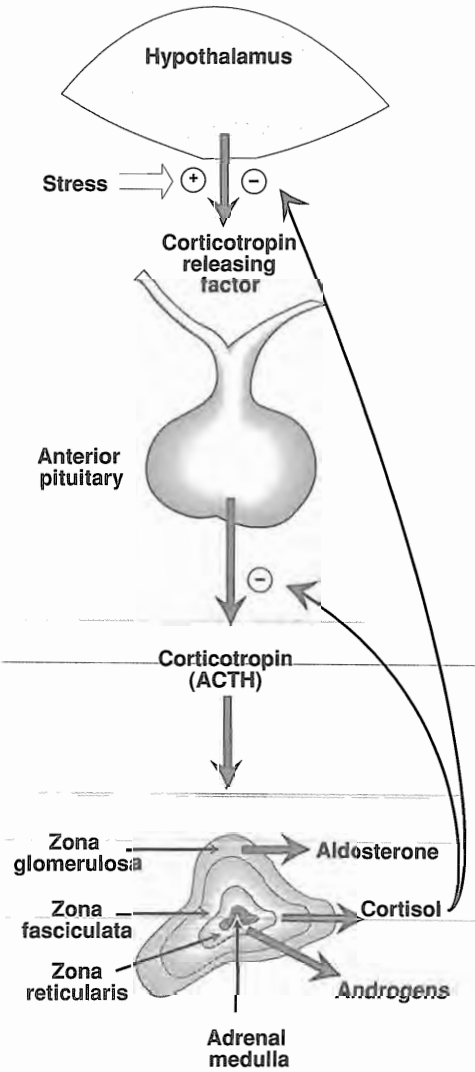


Figure 27.10
Regulation of corticosteroid secretion.

A. Mechanism of action

The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues. The receptor-hormone complex then translocates into the nucleus where it acts as a transcription factor to turn genes on or off, depending on the tissue. This mechanism requires time to produce an effect. There are other glucocorticoid effects, such as their requirement for catecholamine-mediated dilation of vascular and bronchial musculature or lipolysis, whose effects are immediate. The bases for these actions are unknown.

B. Actions

Some normal actions and some selected mechanisms of adrenocorticoids are described in this section. Understanding these actions aids the reader in better comprehending the results of adrenal insufficiency and the uses of adrenocorticoids as therapeutic agents in a variety of disorders.

1. Glucocorticoids

a. Promote normal intermediary metabolism: Glucocorticoids favor gluconeogenesis by both increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy needed for glucose synthesis. [Note: Glucocorticoid insufficiency may result in hypoglycemia, for example, during stressful periods or fasting.]

b. Increase resistance to stress: By raising plasma glucose levels, glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease. Glucocorticoids can cause a modest rise in blood pressure, apparently by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels. [Note: Individuals with adrenal insufficiency may respond to severe stress by becoming hypotensive.]

c. Alter blood cell levels in plasma: Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them to lymphoid tissue from the circulation. In contrast, they increase the blood levels of hemoglobin, erythrocytes, platelets and polymorphonuclear leukocytes. [Note: The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections. However, this property is important in the treatment of leukemia (see p. 393).]

d. Anti-inflammatory action: The most important therapeutic property of the glucocorticoids is their ability to dramatically reduce the inflammatory response and to suppress immunity. The exact mechanism is complex and incompletely understood. However, it is known that the lowering and inhibition of peripheral lymphocytes and macrophages play a role. Also involved is the indirect inhibition of phospholipase A_2 (due to the steroid mediated elevation of lipocortin), which blocks the release of arachidonic acid, the precursor of the prostaglandins and leukotrienes, from membrane-bound phospholipid (see p. 403).

e. Affect other components of the endocrine system: Feedback inhibition of corticotropin production by elevated glucocorticoids causes inhibition of further glucocorticoid synthesis as well as thyroid stimulating hormone production, whereas growth hormone production is increased.

f. Effects on other systems: These are mostly associated with the adverse effects of the hormones. High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers. Effects on the central nervous system that influence mental status have been identified. Chronic glucocorticoid therapy can cause severe bone loss. Myopathy leads patients to complain of weakness.

2. Mineralocorticoids

Mineralocorticoids help control the body's water volume and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on kidney tubule cells, causing a reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which is then lost in the urine. [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, whereas retention of sodium and water leads to an increase in blood volume and blood pressure (see p. 180). Hyperaldosteronism is treated with *spironolactone* (see p. 232).]

C. Therapeutic uses of the adrenal corticosteroids

Several semisynthetic derivatives of the glucocorticoids have been developed that vary in their anti-inflammatory potency, the degree to which they cause sodium retention, and their duration of action. These are summarized in Figure 27.11.

1. **Replacement therapy for primary adrenocortical insufficiency (Addison's disease):** This disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of patient response to corticotropin administration). *Hydrocortisone* [hye droe KOR ti sone], which is identical to the natural *cortisol*, is given to correct the deficiency. Failure to do so results in death. The dosage of *hydrocortisone* is divided so that two thirds of the normal daily dose is given in the morning and one third in the afternoon. [Note: The goal of this regimen is to approximate the daily hormone levels resulting from the circadian rhythm exhibited by cortisol, which causes plasma levels to be maximal around 8 A.M. and then to decrease throughout the day to their lowest level around 1 A.M.] Administration of *fludrocortisone* [floo droe KOR ti sone], a synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to raise the mineralocorticoid activity to normal levels.

2. **Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These deficiencies are caused by a defect either in CRF production by the hypothalamus or corticotropin production by the pituitary (see p. 247). [Note: Under these conditions, the adrenal cortex synthesis of mineralocorticoids is less impaired than that of glucocorticoids.] The adrenal cortex responds to corticotropin administration by synthesizing and releasing the adrenal corticosteroids. *Hydrocortisone* is also used for these deficiencies.

3. **Diagnosis of Cushing's syndrome:** Cushing's syndrome is caused by a hypersecretion of glucocorticoids that is due to either excessive release of corticotropin by the anterior pituitary or to an adrenal tumor. The *dexamethasone* suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome. This synthetic glucocorticoid suppresses cortisol release in individuals with pituitary-dependent Cushing's syndrome, but it does not suppress glucocorticoid release from adrenal tumors.

4. **Replacement therapy for congenital adrenal hyperplasia (CAH):** This is a group of diseases resulting from an enzyme defect in the

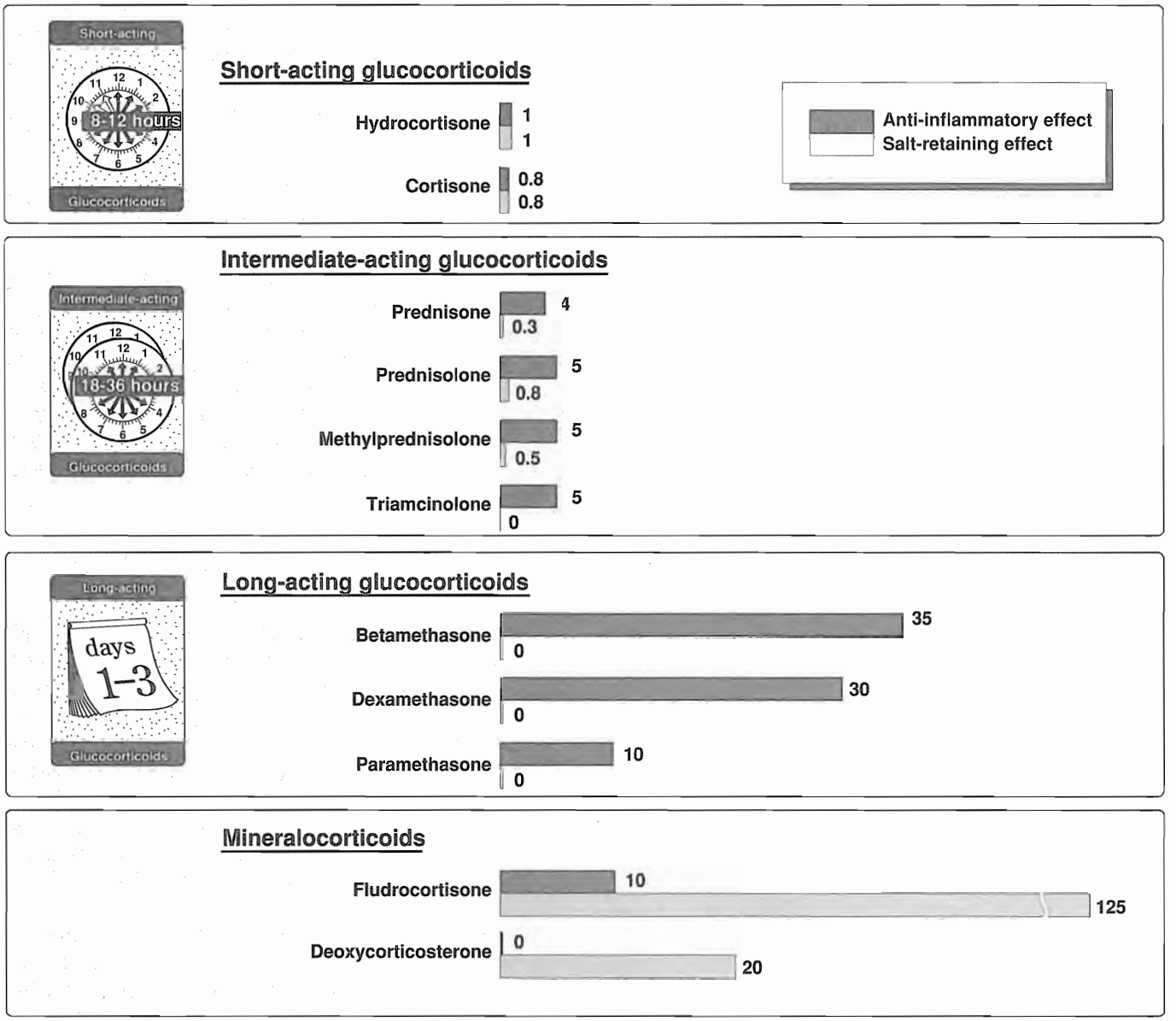


Figure 27.11
Pharmacologic properties of some commonly used natural and synthetic corticosteroids; activities are all relative to hydrocortisone =1. Time refers to duration of action.

synthesis of one or more adrenal steroid hormones. Treatment of this condition requires administration of sufficient corticosteroids to normalize the patient's hormone levels. Choice of replacement hormone depends on the site of the lesion.

5. **Relief of inflammatory symptoms:** Glucocorticoids dramatically reduce the manifestations of inflammations (for example, rheumatoid and osteoarthritic inflammations, inflammatory conditions of the skin), including the redness, swelling, heat, and tenderness that are commonly present at the inflammatory site. The effect of glucocorticoids on the inflammatory process is the result of their effects on the distribution, concentration, and function of leuko-

cytes. These effects include an increase in the concentration of neutrophils; a decrease in the concentration of lymphocytes (T and B cells), basophils, eosinophils and monocytes; and an inhibition of the ability of leukocytes and macrophages to respond to mitogens and antigens. Glucocorticoids also influence the inflammatory response by their ability to reduce the amount of histamine released from basophils and to inhibit the activity of kinins. [Note: The ability of glucocorticoids to inhibit the immune response is also a result of the other actions described above.]

6. **Treatment of allergies:** Glucocorticoids are useful in the treatment of the symptoms of drug, serum, and transfusion allergic reactions, bronchial asthma, and allergic rhinitis. These drugs are not, however, curative. [Note: *Beclomethasone dipropionate* [be kloe METH a sone], *triamcinolone* [tri am SIN o lone] and others are applied topically to the respiratory tract through inhalation from a metered dose dispenser (see p. 219). This minimizes systemic effects and allows the patient to significantly reduce or eliminate the use of oral steroids.]

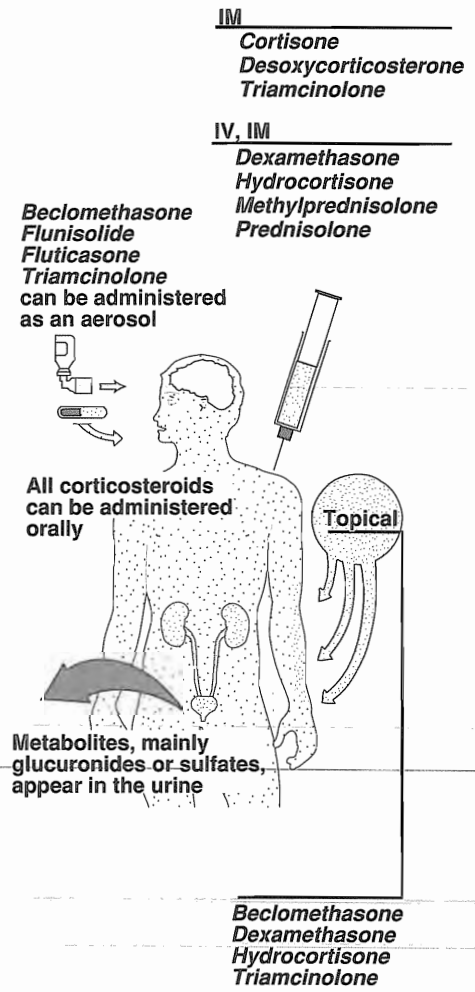


Figure 27.12
Routes of administration and elimination of corticosteriods.

D. Pharmacokinetics

1. **Absorption and metabolism:** Naturally occurring adrenal corticosteroids and their derivatives are readily absorbed from the gastrointestinal tract. Selected compounds can also be administered intravenously, intramuscularly, topically, or as an aerosol (Figure 27.12). Greater than 90% of the absorbed glucocorticoids are bound to plasma proteins: most to corticosteroid-binding globulin, and the remainder to albumin. Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate, and the products are excreted by the kidney. [Note: The half-life of adrenal steroids may increase dramatically in individuals with hepatic dysfunction.]

2. **Dosage:** In determining the dosage of adrenocortical steroids, many factors need to be taken into consideration, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and the time of day that a steroid is administered. For example, when large doses of the hormone are required over an extended period of time (more than 2 weeks), suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurs. To prevent this adverse effect, a regimen of alternate-day administration of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.

E. Adverse effects

The common side effects of long-term corticosteroid therapy are summarized in Figure 27.13. [Note: Increased appetite is not necessarily an adverse effect, since it is one of the reasons for the use of *prednisone* in cancer chemotherapy.] The classic Cushing-like syndrome—redistribution of body fat, puffy face, increased body hair growth, acne, insomnia and increased appetite—are observed when excess corticosteroids are present. Increased frequency of

cataracts also occurs with long-term corticosteroid therapy. Withdrawal from the drugs can be a serious problem, because if the patient has experienced hypothalamic-pituitary-adrenal suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal. This fact, coupled with the possibility of psychological dependence on the drug and the fact that withdrawal might cause an exacerbation of the disease, means that the individual schedule for withdrawal may be based on trial and error. The patient must be carefully monitored.

F. Inhibitors of adrenocorticoid biosynthesis

Several substances have proven to be useful as inhibitors of the synthesis of adrenal steroids: *metyrapone* [me TEER a pone], *aminoglutethimide* [a mee noe glu TETH i mide], *ketoconazole* [kee toe KON a zole], and *spironolactone*. *Mifepristone* competes with glucocorticoids for the receptor.

1. **Metyrapone** is used for the treatment of Cushing's syndrome and can be used for tests of adrenal function. [Note: *Dexamethasone* suppression is now used more commonly for diagnosis.] *Metyrapone* interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid, 11-deoxycorticosterone. The adverse effects encountered with *metyrapone* include salt and water retention, hirsutism, transient dizziness, and gastrointestinal disturbances.

2. **Aminoglutethimide** acts by inhibiting the conversion of cholesterol to pregnenolone. As a result, the synthesis of all hormonally active steroids is reduced. *Aminoglutethimide* has been used therapeutically in the treatment of breast cancer to reduce or eliminate androgen and estrogen production. In these cases it is used in conjunction with *dexamethasone*. *Aminoglutethimide* may also be useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids.

3. **Ketoconazole** (an antifungal agent, see p. 340) strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing's syndrome.

4. **Mifepristone** is a potent glucocorticoid antagonist as well as an antiprogestin (see p. 267). It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus. Its potential use in the treatment of Cushing's syndrome is being explored.

5. **Spironolactone** competes for the mineralocorticoid receptor and thus inhibits sodium reabsorption in the kidney (see p. 232). It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. The drug is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.

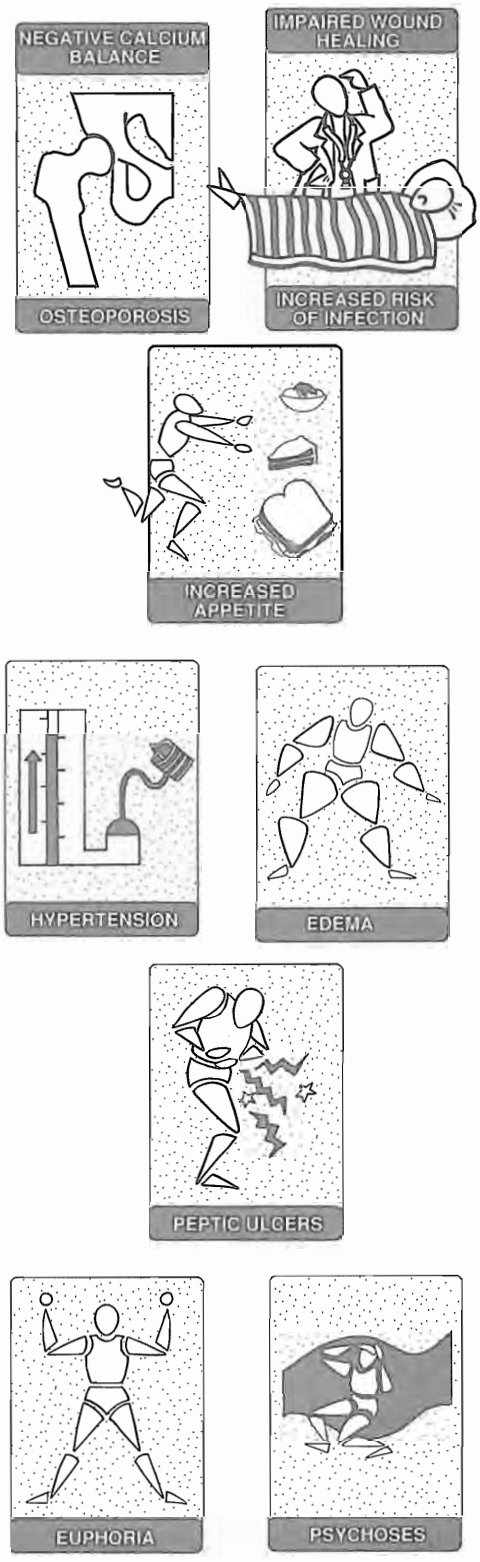


Figure 27.13
Some commonly observed effects of long-term corticosteroid therapy.

Choose the ONE best answer.

27.1 All of the following statements about glucocorticoids are correct EXCEPT:

A. They may produce peptic ulcers.
B. They are useful in the treatment of refractory asthma.
C. They are contraindicated in glaucoma.
D. They are used in the treatment of Addison's disease.
E. They exert their effect by binding to receptors in the cell membrane.

Correct answer = E. All steroid hormones bind to receptors in the nucleus or the cytosol.

27.2 Which one of the following statements is true?

A. Diethylstibestrol enhances fertility by blocking the inhibitory effect of estrogen on the pituitary.
B. Tamoxifen is an estrogen antagonist.
C. Dexamethasone has weak anti-inflammatory properties.
D. Estrogens are mainly excreted unchanged in the urine.
E. Tamoxifen is used to treat infertility.

Correct answer = B. Diethylstibestrol is a synthetic estrogen that acts directly on target tissues. Estrogens are secreted as sulfated or glucuronidated metabolites. Tamoxifen is used in the treatment of advanced breast cancer.

27.3 All of the following are adverse effects associated with the use of oral contraceptive agents EXCEPT:

A. Edema.
B. Breast tenderness.
C. Nausea.
D. Increased frequency of migraine headache.
E. Increased risk of ovarian cancer.

Correct choice = E. Oral contraceptive agents decrease the incidence of ovarian and endometrial cancers.

27.4 Estrogen replacement therapy in menopausal women

A. restores bone loss accompanying osteoporosis.
B. may induce "hot flashes".
C. may cause atrophic vaginitis.
D. is most effective if instituted at the first signs of menopause.
E. requires higher doses of estrogen than are required with oral contraceptive therapy.

Correct answer = D. Estrogens decrease but do not restore the age-related loss of bone. Vasomotor symptoms of menopause, such as hot flashes, are decreased with estrogen replacement therapy. Symptoms of menopause, such as atrophic vaginitis, are decreased with estrogen replacement therapy. Oral contraceptives contain higher doses of estrogen than those used with estrogen replacement therapy.

27.5 Progestins

A. are not produced in males.
B. increase HDL and decrease LDL.
C. attenuate the increased risk of endometrial cancer associated with estrogen-only oral contraceptive agents.
D. such as progesterone are widely used in oral contraceptives.
E. commonly induce weight loss.

The correct answer = C. Progesterone is synthesized by the testes in males. Progestins decrease HDL and increase LDL. When orally administered, progesterone is largely inactivated by hepatic first-pass metabolism. Weight gain is one of the side effects of progestins.

27.6 Which one of the following is a synthetic estrogen used in oral contraceptives?

A. Mestranol.
B. Norgestrel.
C. Clomiphene.
D. Estradiol.
E. Norethindrone.

Correct answer = A. Norgestrel and norethindrone are progestins, and clomiphene is an antiestrogen. Estradiol is largely inactivated by first-pass metabolism when administered orally.

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

[2]See p. 383 in **Biochemistry** (2nd ed.) for a discussion of the transcription of eukaryotic genes.

Principles of Antimicrobial Therapy

28

I. OVERVIEW

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity—the ability to kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative, rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism while still being tolerated by the host. Selective antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings.

II. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowledge of (A) the organism's identity and its sensitivity to a particular agent, (B) the site of the infection, (C) the safety of the agent, (D) patient factors and (E) the cost of therapy. However, some critically ill patients require empiric therapy, that is, immediate administration of drug(s) covering infections by both gram-positive and gram-negative microorganisms (Figure 28.1).

A. Empiric therapy prior to organism identification

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug sensitivity established. However, in the critically ill patient, such a delay could prove fatal and immediate empiric therapy is indicated.

1. **The acutely ill patient:** Acutely ill patients with infections of unknown origin for example, a neutropenic patient (one who has a reduction in neutrophil count, possibly indicating bacterial

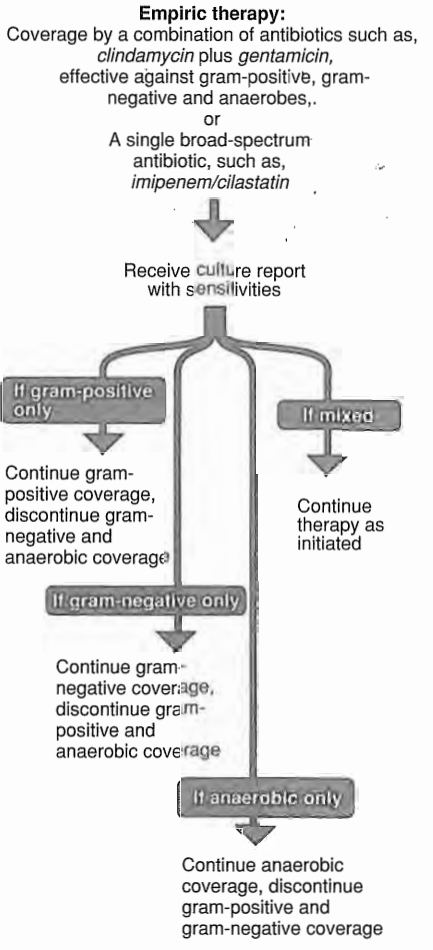


Figure 28.1
Therapeutic strategy in treating patients with an infection of unknown origin.

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

infection), or a patient with severe headache, a rigid neck, and sensitivity to bright lights (symptoms characteristic of meningitis) require immediate treatment. Therapy is initiated after specimens for laboratory analysis have been obtained but before the results of the culture are available.

2. **Selecting a drug:** The choice of drug in the absence of sensitivity data is influenced by site of infection and patient history, for example, whether the infection was hospital- or community-acquired, whether the patient is immunocompromised, as well as the patient's travel record and age. Empiric therapy with a combination of antibiotics or a single drug covering infections by both gram-positive and gram-negative microorganisms may be started initially. Figure 28.1 summarizes a typical therapeutic strategy for a patient with a suspected bacterial infection of unknown origin.

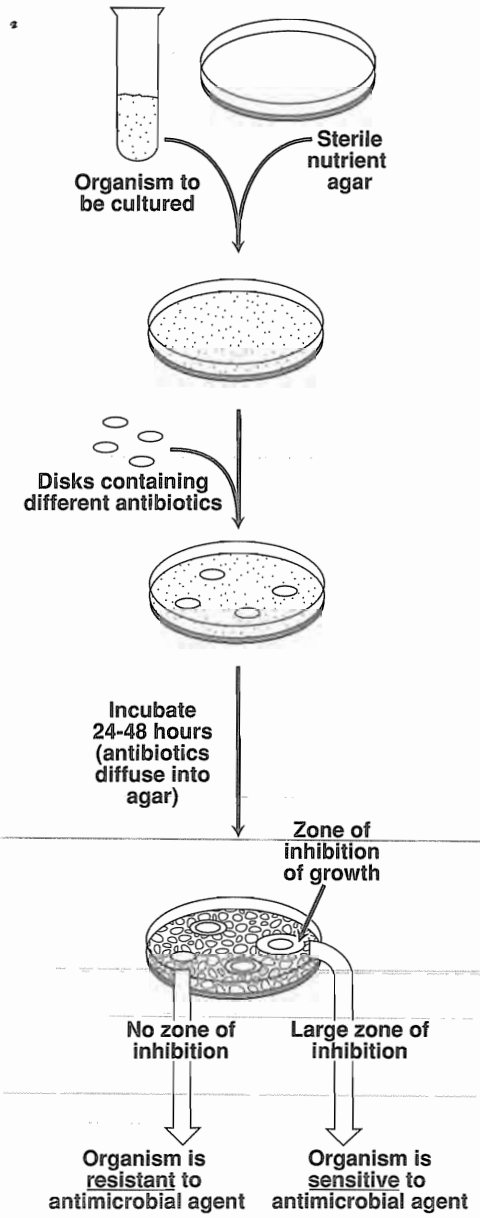


Figure 28.2
Disk diffusion method for determining the sensitivity of bacteria to antimicrobial agents.

B. Identification and sensitivity of the organism

Characterization of the organism is central to the selection of the proper drug. A rapid assessment of the nature of the organism can sometimes be made on the basis of differential stains, such as the Gram stain, but it is generally necessary to culture the infective organism in order to arrive at a conclusive diagnosis and to determine the sensitivity of the bacteria to antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating treatment if possible. Newer methods that use molecular biological techniques to identify microorganisms are making a public health impact in identification of the source of an outbreak of infectious diseases.

C. Laboratory methods of identification

The most commonly used method to test susceptibility to antibiotics has been disk diffusion, in which disks containing antibiotics are placed on culture dishes inoculated with the microorganism to be tested, and the organism's growth (resistance to the drug), or lack of growth (sensitivity to the drug) is then monitored (Figure 28.2). Although this method is still employed in some clinical laboratories, it is being replaced by miniaturized automated procedures that are much faster and more cost effective. In these procedures, plates, called panels, consist of wells containing reactants that permit assessment of unique characteristics of the organism (for example, fermentation of glucose). Other wells may hold various concentrations of clinically useful antibiotics. Results are obtained and printed automatically, identifying the organism and the minimal inhibitory concentration of the antibiotics to which it is susceptible.

D. The effect of the site of infection on therapy

Adequate levels of an antibiotic must reach the site of infection in order for the invading microorganism to be effectively eradicated. Natural barriers such as those described below may cause inadequate penetration of the drug into certain tissues such as the brain, prostate, and bone, although inflammation can influence the response to drug therapy in these tissues.

1. **Blood-brain barrier:** Treatment of central nervous system infections, such as meningitis, depends on the ability of a drug to penetrate into the cerebrospinal fluid (CSF). The blood-brain barrier (see p. 8) ordinarily excludes many antibiotics. However, inflammation facilitates penetration and allows sufficient levels of many (but not all) antibiotics to enter the CSF. [Note: For cure of meningitis, it is important that a bactericidal rather than a bacteriostatic effect is achieved in the CSF. Yet, this is not without its problems, since rapid bacteriolysis in the infected CSF will liberate high concentrations of bacterial cell walls and lipopolysaccharide that can exacerbate the inflammation. This has led to the use of adjunctive (simultaneous administration of) corticosteroids, which diminish the inflammatory process and neurologic sequelae.]

2. **Prostate:** Bacterial prostatitis is difficult to cure, probably because of the failure of many antibiotics to cross the prostatic epithelium, and, therefore, not entering the prostatic fluid and tissue. Furthermore, the pH of prostatic fluid is relatively acidic (pH 6.4) compared to the plasma (pH 7.4). *Trimethoprim*, a basic antimicrobic with a pK_a of 7.3 is effective in bacterial prostatitis. About 50% non-ionized in the plasma, and with good lipid solubility, the drug diffuses into the prostate and concentrates due to ion trapping in the relatively more acidic prostatic fluid (Figure 28.3). In contrast, acidic antibiotics tend to be predominantly ionized at plasma pH in the plasma and do not cross into the prostatic fluid. For example, consider *penicillin G,* which is poorly lipid soluble and has a pK_a of 2.7. The calculated ratio of charged to uncharged drug in the plasma is about 100,000, so it is not surprising that it is ineffective in the treatment of prostatitis even in susceptible organisms (see ion trapping, p. 24).

E. Status of the patient

In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, and liver must be considered. In women, pregnancy or breast-feeding an infant also affect the selection of the antimicrobial agent.

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system. Antibacterial drugs decrease the microbial population (bactericidal), or inhibit further bacterial growth (bacteriostatic, p. 283), but the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, infection with the human immunodeficiency virus (HIV), malnutrition, or advanced age can affect a patient's immunocompetency, as can therapy with immunosuppressive drugs. Higher than usual doses of bactericidal agents or longer treatment are required to eliminate the infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function (10% or less of normal) causes accumulation of antibiotics that are ordinarily eliminated by this route. This may lead to serious adverse effects unless controlled by adjusting the dose or the dosage schedule of the antibiotic. Although serum creatinine levels are sometimes used as an index of renal function for adjustment of drug regimens, direct monitoring of serum levels of some antibiotics is preferred to

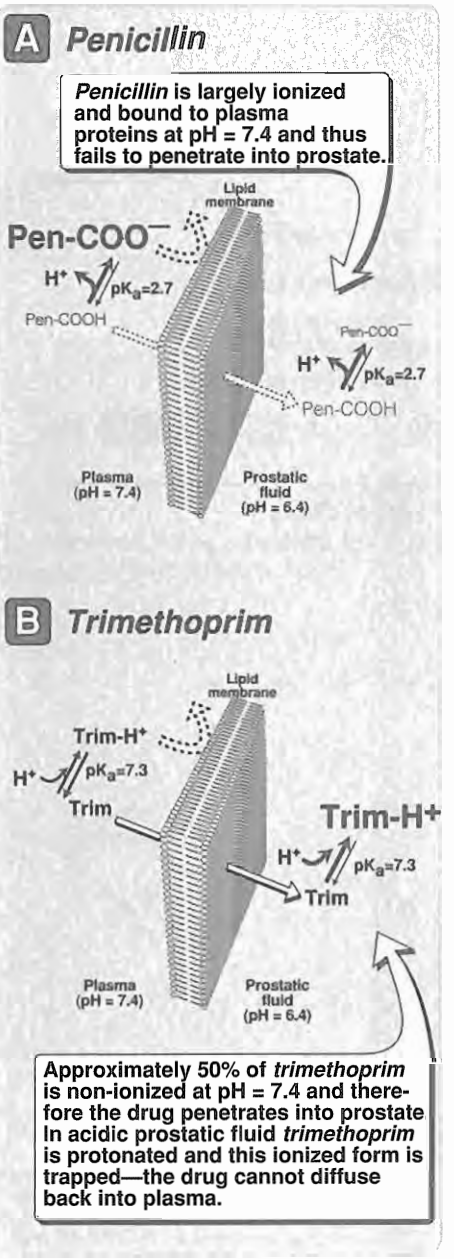


Figure 28.3
A. Diffusion of non-ionized form of a *penicillin* through prostatic membrane; B. Diffusion of non-ionized form of *trimethoprim* through prostatic membrane.

identify maximum and minimum values. Rising minimum values alert the physician to potential toxicity. [Note: The number of functioning nephrons decreases with age. Thus elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys. Antibiotics that undergo extensive metabolism or are excreted via the biliary route are favored in such patients.]

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, *erythromycin*, *tetracycline*) are contraindicated in treating patients with liver disease.

4. **Poor Perfusion:** Decreased circulation to an anatomic area, as in the lower limbs of the diabetic, reduces the amount of antibiotic that reaches the extremities and makes infections notoriously difficult to treat.

5. **Pregnancy:** All antibiotics cross the placenta. Adverse effects to the fetus are rare, except for tooth dysplasia and inhibition of bone growth encountered with the tetracyclines. However, some anthelmintics are embryotoxic and teratogenic (p. 359). Aminoglycosides should be avoided in pregnancy because of their ototoxic effect in the fetus.

6. **Lactation:** Drugs administered to a lactating mother may enter the nursing infant via the breast milk. Even though the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be enough to cause problems.

7. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *chloramphenicol* (see p. 320) and sulfonamides (see p. 289). Young children should not be treated with tetracyclines (see p. 311) which affect bone growth, or fluoroquinolones (see p. 323), which interfere with cartilage growth.

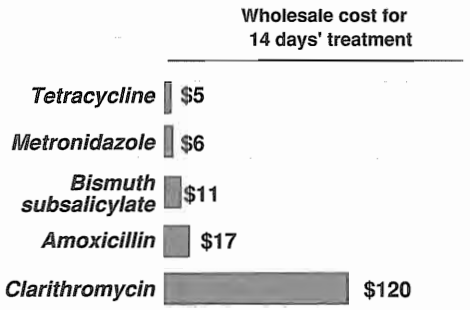


Figure 28.4
Cost of some drugs for treatment of peptic ulcers caused by Helicobacter pylori.

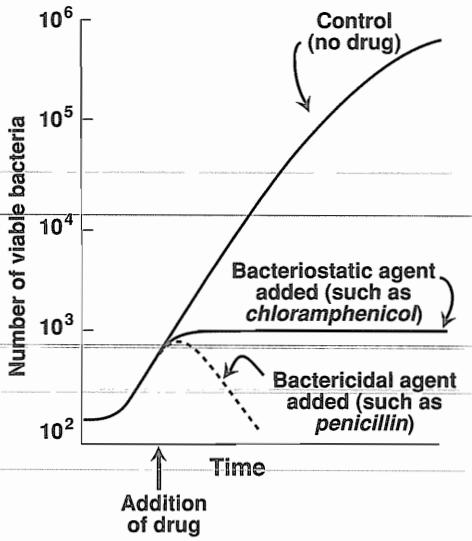


Figure 28.5
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

F. Safety of the agent

Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs because they interfere with a site unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) are less specific and are reserved for life-threatening infections because of the drug's potential for serious toxicity. [Note: Safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity (see Section E).]

G. Cost of therapy

Often, several drugs may show similar efficacy in treating an infection, but vary widely in cost. Figure 28.4 illustrates the cost of some antibacterial agents showing similar efficacy in eradicating the gram-negative bacillus Helicobacter pylori from the gastric mucosa. None of these agents shows a clear therapeutic superiority and thus a combination of *metronidazole* with *bismuth subsalicylate* plus one other antibiotic is usually employed. Selecting *clarithromycin* would have a considerable cost impact.

III. BACTERIOSTATIC VERSUS BACTERICIDAL DRUGS

Antimicrobial drugs are classified as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection. For example, Figure 28.5 shows a laboratory experiment in which the growth of bacteria is arrested by the addition of a bacteriostatic agent. Note that viable organisms remain, even in the presence of the bacteriostatic drug. By contrast, addition of a bactericidal agent kills bacteria and the total number of viable organisms decreases. Though practical, this classification may be too simplistic because it is possible for an antibiotic to be bacteriostatic for one organism and cidal for another, (for example, *chloramphenicol* is static against gram negative rods and cidal against Pneumococci).

IV. CHEMOTHERAPEUTIC SPECTRA

The chemotherapeutic spectrum of a particular drug refers to the species of organisms affected by that drug. In this book, bacteria that are commonly encountered as infectious agents are presented in pie charts in which each segment represents a general class of microorganisms, for example, gram-positive cocci (Figure 28.6A). In each section of the text covering a particular antibiotic, the microbial classes that are generally treated with that agent are highlighted (Figure 28.6B). [Note: One section of the pie chart is labeled "Other" and represents any of several microorganisms specifically covered in different chapters.]

A. Narrow spectrum

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacteria (Figure 28.6B).

B. Extended spectrum

Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria.

C. Broad spectrum

Drugs such as *tetracycline* and *chloramphenicol* affect a wide variety of microbial species and are referred to as broad spectrum antibiotics (Figure 28.6C). Administration of broad spectrum antibiotics can drastically alter the nature of the normal bacterial flora and can precipitate a superinfection of an organism, such as candida whose growth is normally kept in check by the presence of other microorganisms.

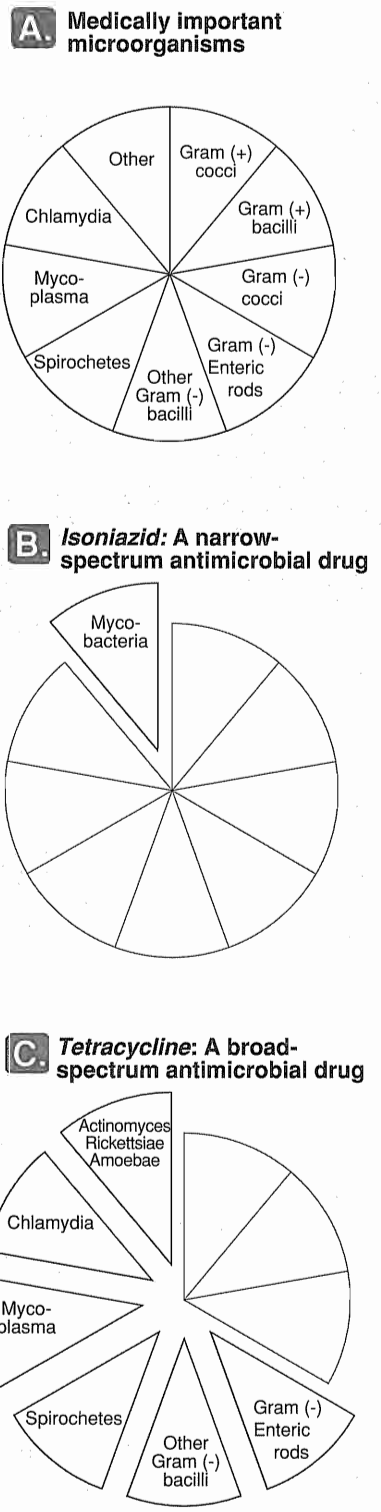


Figure 28.6
A. Medically important bacterial species. B. *Isoniazid*, a narrow-spectrum antimicrobial agent. C. *Tetracycline*, a broad-spectrum antimicrobial agent.

V. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat with the single agent that is most specific for the infecting organism. This strategy reduces the possibility of superinfection, decreases the emergence of resistant organisms (see section VI), and minimizes toxicity.. However, situations in which combinations of drugs are employed do exist, for example, the treatment of tuberculosis benefits from drug combinations (p. 331).

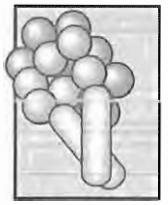
A. Advantages of drug combinations

Certain combinations of antibiotics,such as β-lactams and aminoglycosides, show synergism, that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, they should only be used in special situations summarized in Figure 28.7)

B. Disadvantages of drug combinations

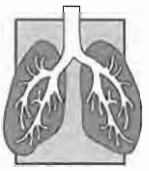
A number of antibiotics act only when organisms are growing. Thus, concomitant administration of a second agent that results in bacteriostasis may interfere with the action of the first drug that is bactericidal.

1 **When mixed infections are present.**



2 **In the treatment of enterococcal endocarditis with *penicillin* and *streptomycin* or cryptococcal meningitis infections with *amphotericin B* in combination with *flucytosine*.**

3 **When there is a risk of developing resistant organisms, for example, *isoniazid* plus *pyrazinamide* and *rifampin* in the treatment of tuberculosis.**



4 **When the greatest antimicrobial coverage is desirable (for example, sepsis, meningitis) or in infections of unknown origin.**

Figure 28.7
Some clinical situations in which combinations of antimicrobial drugs are indicated.

VI. DRUG RESISTANCE

Bacteria are said to be resistant if their growth is not halted by the maximal level of an antibiotic that is tolerated by the host. Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are resistant to *vancomycin*. However, microbial species normally responsive to a particular drug may develop resistant strains. Many organisms have adapted, through spontaneous mutation or acquired resistance and selection, and developed more virulent strains many of which are resistant to multiple antibiotics. The emergence of these resistant strains has been ascribed to the imprudent and inappropriate use of antibiotics in conditions that might resolve without treatment or which are not amenable to antibiotic therapy, for example, the common cold. Health professionals are obligated to use antibiotic agents with thoughtful restraint.

A. Genetic alterations leading to drug resistance

Resistance develops due to the ability of DNA to: 1) undergo spontaneous mutation, or 2) move from one organism to another. In the first instance, chromosomal alteration may occur by insertion, deletion or substitution of one or more nucleotides within the genome[1].

1. **Spontaneous mutations of DNA:** The resulting mutation may persist, be corrected, or be lethal to the cell. However, if the cell survives, it may replicate and transmit properties to daughter cells, thus producing resistant strains that may proliferate under certain

[1] See p. 288 for Infolink references to other books in this series.

selective pressures. An example is the emergence of *rifampin*-resistant Mycobacterium tuberculosis when *rifampin* is used as a single drug (see p. 334) .

2. **DNA transfer of drug resistance:** Of particular clinical concern is resistance acquired due to DNA transfer from one organism to another. Resistance properties are usually encoded in extrachromosomal R factors (plasmids). These may enter cells by processes such as transduction (phage-mediated), transformation or, most importantly, bacterial conjugation.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance may be mediated by a variety of mechanisms, such as lack of or an alteration in a target site, lowered penetrability of the drug due to decreased permeability, or increased efflux or presence of antibiotic-inactivating enzymes (Table 28.1).

1. **Modification of target sites:** Alteration of the target site through mutation can confer resistance as occurs with the penicillin binding proteins in *methicillin*-resistant S. aureus, or the enzyme dihydrofolate reductase, which is less sensitive to inhibition in organisms resistant to *trimethoprim*.

Table 28.1 MECHANISMS OF RESISTANCE TO ANTIBIOTICS

Drugs showing resistance due to altered targets	Drugs showing resistance due to decreased accumulation		Drugs showing resistance due to enzymatic inactivation of drug
	↓ Permeability	↑ Efflux	
Aminoglycosides			
Chloramphenicol			*Chloramphenicol*
Clindamycin			
Fluoroquinolones	Fluoroquinolones	Fluoroquinolones	
β-Lactams	β-Lactams		β-Lactams
Macrolides			Macrolides
Rifampin			
Sulfonamides			
Tetracycline	*Tetracycline*	*Tetracycline*	*Tetracycline*
Trimethoprim			
Vancomycin			

Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoroquinolones.

β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalosporins by producing β-lactamases. However resistant organisms may also have altered porin channels through which cephalosporins do not pass.

Tetracycline was effective against gynecologic infection due to bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.

β-Lactamases destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to *penicillin* because of penicillinase activity.

2. **Decreased accumulation:** Decreased penetrability of an agent can protect organisms against that antibiotic because it is unable to gain access to the site of action due to the presence of either a lipopolysaccharide layer (gram-negative bacteria) or of an efflux system that pumps out the drug (*tetracyclines*, *primaquine*).

3. **Enzymic inactivation:** The ability to destroy or inactivate the antimicrobial agent also can confer resistance on microorganisms. For example, β-lactamases destroy many penicillins and cephalosporins and an acetyltransferase can convert *chloramphenicol* to an inactive compound.

VII. PROPHYLACTIC ANTIBIOTICS

Certain clinical situations (Figure 28.8) require the use of antibiotics for the prevention rather than the treatment of infections. Since the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which benefits outweigh the potential risks. The duration of prophylaxis is dictated by the duration of the risk of infection.

VIII. COMPLICATIONS OF ANTIBIOTIC THERAPY

Selective toxicity to the invading organism does not insure the host against adverse effects, since the drug may produce an allergic response or be toxic in ways unrelated to the drug's antimicrobial activity.

A. Hypersensitivity

Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity

High serum levels of certain antibiotics may cause toxicity by affecting cellular processes in the host directly. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the hair cells of the organ of Corti.

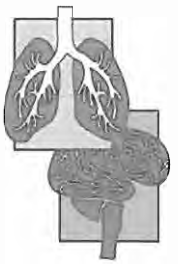
C. Superinfections

Drug therapy, particularly with broad spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections are often difficult to treat.

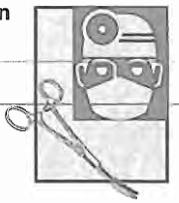
1 **Prevention of streptococcal infections in patients with a history of rheumatic heart disease. Patients may require 20 years of treatment.**

2 **Pretreatment of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, to prevent seeding of prosthesis.**

3 **Prevention of tuberculosis or meningitis among individuals who are in close contact with infected patients.**



4 **Treatment prior to certain surgical produres (such as bowel surgery, joint replacement and some gynecologic interventions) to prevent infection.**



5 **Treatment of the mother with *zidovudine* to protect the fetus in the case of an HIV-infected pregnant woman.**

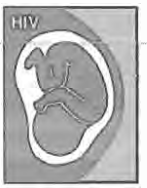


Figure 28.8
Some clinical situations where prophylactic antibiotics are indicated.

IX. CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobial drugs can be classified in a number of ways, for example, according to their chemical structure (β-lactams, aminoglycosides), mechanism of action (cell wall synthesis inhibitors), or activity against particular types of organisms (bacteria, fungi, viruses). The following chapters will be organized by the mechanisms of action of the drug (Figure 28.9) or according to the type of organisms affected by the drug.

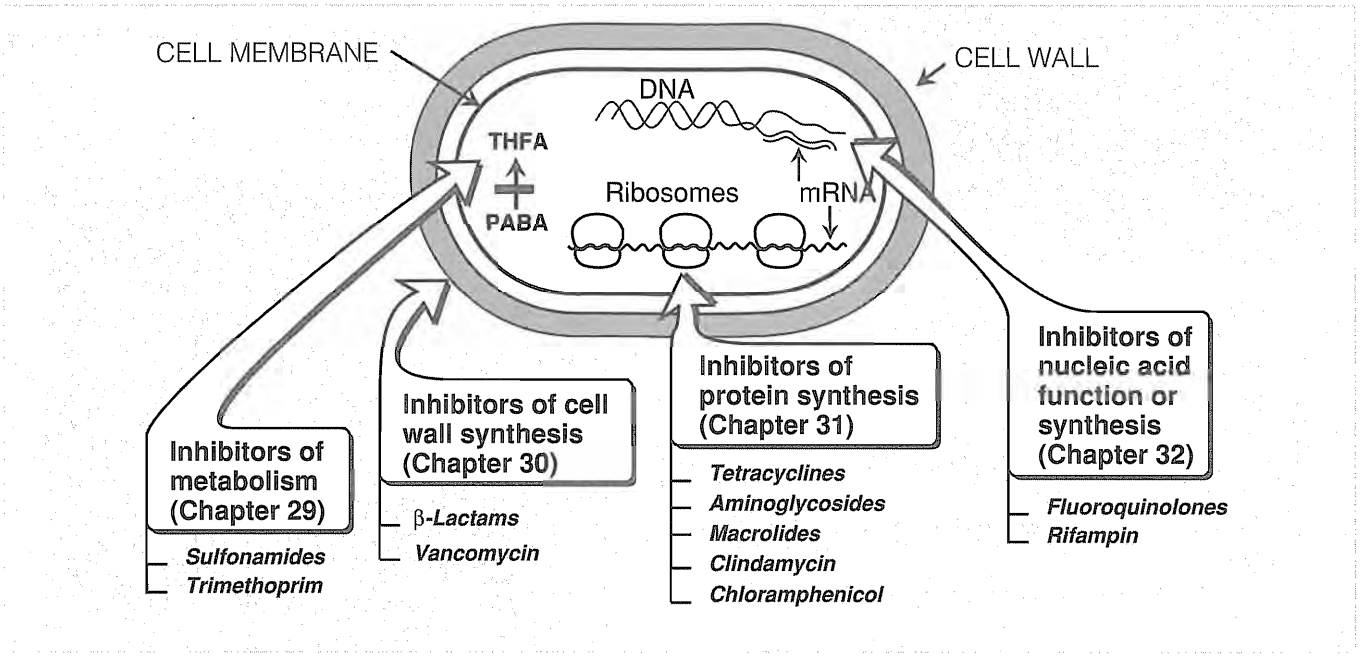


Figure 28.9
Classification of some antimicrobial agents by their sites of action.

Study Questions

Choose the ONE best answer.

28.1 All of the following clinical indications may require a combination of antibiotics (rather than a single agent) EXCEPT:

A. treatment of mixed infections.
B. treatment of enterococcal endocarditis.
C. treatment of tuberculosis.
D. treatment of cryptococcal meningitis.
E. treatment of gonorrhea.

Correct answer = E. Combinations of antibiotics are not indicated in the treatment of gonorrhea. Most Neisseria gonorrhoeae, the causative organism, respond to a single agent—for example, ceftriaxone, a third generation cephalosporin. Combinations of antibiotics are indicated in the treatment of mixed infections, enterococcal endocarditis (with penicillin and streptomycin) and cryptococcal meningitis infection (amphotericin B in combination with flucytosine. Drug combinations are also indicated when there is a risk of developing resistant organisms (for example, isoniazid plus pyrazinamide and rifampin in the treatment of tuberculosis, and when the greatest antimicrobial coverage is desirable (for example, sepsis, meningitis) or in infections of unknown origin.

28.2 Which one of the following patients is least likely to require antimicrobial treatment tailored to the individual's condition?

A. Patient undergoing cancer chemotherapy.
B. Patient with kidney disease.
C. Elderly patient.
D. Patient with hypertension.
E. Patient with liver disease.

Correct answer = D. Elevated blood pressure would not be expected to markedly influence the type of antimicrobial treatment employed. Anticancer drugs often suppress the immune function, and these patients require additional antibiotics to eradicate infections. Impaired renal function may lead to accumulation of toxic levels of antimicrobial drugs. Renal and hepatic function are often decreased among the elderly. Impaired liver function may lead to the accumulation of toxic levels of antimicrobial drugs.

28.3 In which one of the following clinical situations is the prophylactic use of antibiotics NOT warranted?

A. Prevention of meningitis among individuals in close contact with infected patients.
B. Patient with a heart prosthesis having a tooth removed.
C. Presurgical treatment for implantation of a hip prosthesis.
D. Patient who complains of frequent respiratory illness.
E. Presurgical treatment in gastrointestinal procedures.

Correct answer = D. Respiratory illness may be of viral origin; further, consequence of chronic disorder may not warrant prophylactic use of antibiotics. Meningitis is a sufficiently contagious and serious disease to warrant prophylactic use of antibiotics. Following a tooth extraction bacteria of the oral cavity can readily enter the circulation and colonize on a prosthesis, causing a serious and often fatal infection. Infection following implantation of a hip prosthesis is such a serious complication that prophylactic antibiotics are warranted. Infection is such a serious complication of gastrointestinal surgery that prophylactic antibiotics are warranted.

28.4 A 60-year old woman who had undergone chemotherapy for lymphoma the week previously is brought to the emergency room. She has a fever of 101°F and is confused. Respiration is rapid and blood pressure is 78/40. She is neutropenic. Gram stains of the urine and sputum are negative. Which one of the following actions is most likely to be beneficial to this patient?

A. Send a clinical sample to the laboratory for identification and then administer an appropriate antibiotic.
B. Administer a broad spectrum antibiotic like tetracycline.
C. Administer a combination such as clindamycin and an aminoglycoside
D. Administer clindamycin
E. Administer aztreonam.

Correct answer = C. This patient is seriously ill and to wait for identification and sensitivity of the organism would no doubt lead to a worsened condition. Tetracycline is not indicated because it is bacteriostatic and the patient is neutropenic. Its spectrum of activity also does not cover infections due to Pseudomonas aeruginosa, a frequent cause of infection in these patients. Therefore, empiric therapy is required that would employ an antibiotic or a combination of antibiotics to: (1) cover both gram positive and gram negative organisms as well as anaerobes; (2) be bactericidal; (3) cover Pseudomonas aeruginosa; and (4) have good penetrability into tissues. Neither clindamycin or aztreonam by themselves meet these criteria, whereas clindamycin plus an aminoglycoside is appropriate.

[1]See p. 390 in **Biochemistry** (2nd ed.) for a discussion of mutations in DNA.

Folate Antagonists

29

I. OVERVIEW

Folic acid coenzymes are required for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds required for cellular growth and replication. In the absence of folic acid, cells cannot grow or divide. The sulfa drugs are inhibitors of folic acid synthesis. They originated from the dye prontosil, which was shown in the early 1930's to be effective against hemolytic streptococcal infections because the body converted it to *sulfanilamide* [sul fa NIL a mide]. Many congeners of the latter compound were synthesized and found to be effective in the treatment of infectious diseases. Today, particularly in developing countries, the sulfas are still employed because of their low cost and efficacy in certain bacterial infections such as those of the urinary tract, and trachoma. However, due to the emergence of resistant bacterial strains, development of patient allergies, and the advent of the penicillins, the sulfas were less frequently prescribed for a time, until their synergistic effect with *trimethoprim* was recognized. With the introduction in the mid-1970s of the synergistic combination of *sulfamethoxazole* [sul fa meth OX a zole] with *trimethoprim* [try METH oh prim] (generic name, *co-trimoxazole* [co try MOX a zole]), there has been a renewed interest in the sulfonamides. *Co-trimoxazole* is effective in treating conditions such as *Pneumocystis carinii* pneumonia, or *ampicillin-* or *chloramphenicol*-resistant systemic salmonella infections. [Note: Inhibitors of the reduction of folate to its active cofactor form, such as *methotrexate*, are also used in the treatment of certain rapidly growing cancers (see p. 378).]

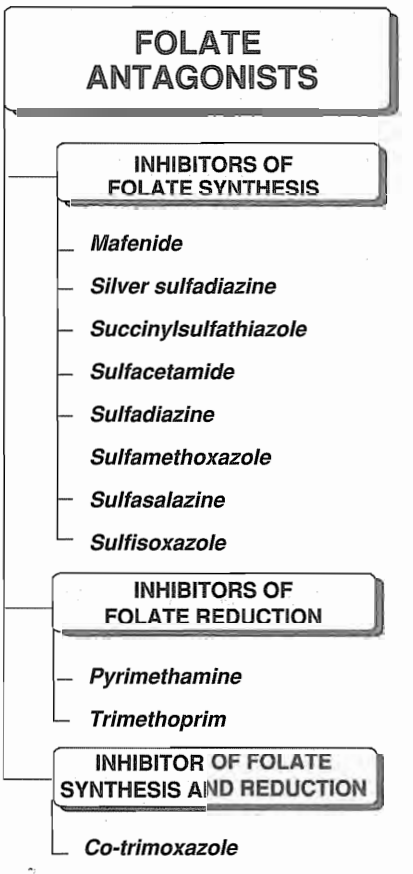


Figure 29.1
Summary of folate antagonists.

II. SULFONAMIDES

All sulfonamides in clinical use are synthetic structural analogs of p-aminobenzoic acid (PABA). They differ from each other not only in their chemical and physical properties but also in their pharmacokinetics.

A. Mechanism of action

Being impermeable to folic acid, many bacteria must rely on their ability to synthesize folate from PABA, pteridine, and glutamate. In contrast, human beings cannot synthesize folic acid and must obtain preformed folate as a vitamin in their diet. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the enzyme dihydropteroate synthetase, thus preventing the synthesis

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

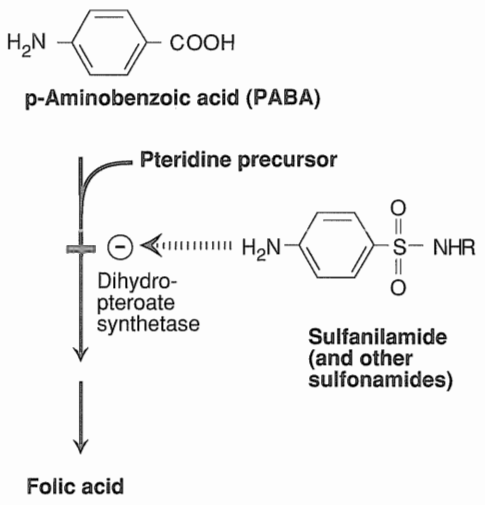


Figure 29.2
Competitive inhibition of folic acid synthesis by sulfonamides.

of bacterial folic acid and formation of its one-carbon carrying cofactors.[1] This deprives the cell of essential cofactors for purine, pyrimidine, and amino acid synthesis (Figure 29.2, see also Figure 29.5).

B. Antibacterial spectrum

The sulfas, including *co-trimoxazole* (*sulfamethoxazole* plus *trimethoprim*, see p. 293), are bacteriostatic. These drugs are active against selected enterobacteria, chlamydia, Pneumocystis, and nocardia. Typical clinical applications are shown in Figure 29.3. In addition, *sulfadiazine* [sul fa DYE a zeen] in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py ri METH a meen] is the only effective form of chemotherapy for toxoplasmosis (p. 353).

C. Resistance

Only organisms that synthesize their own folate are sensitive to the sulfonamides. Bacterial resistance to the sulfas can arise from plasmid transfers or random mutations. The resistance is generally irreversible and may be due to any of the following three possibilities. [Note: Organisms resistant to one member of this drug family are resistant to all, but they may be susceptible to *co-trimoxazole*.]

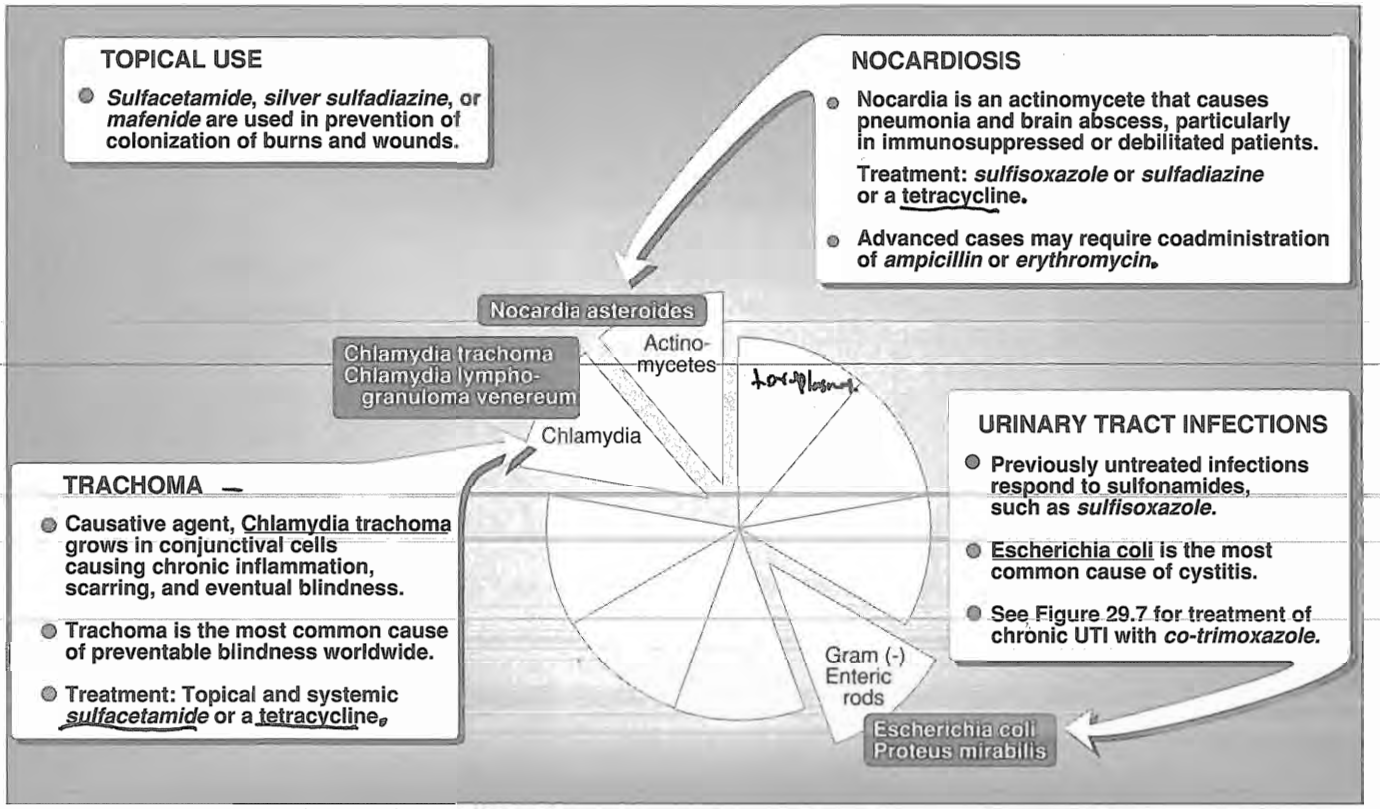


Figure 29.3
Typical therapeutic applications of sulfonamides. UTI= urinary tract infection.

[1]See p. 296 for Infolink references to other books in this series.

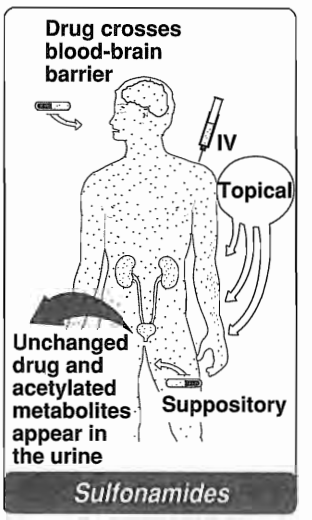
1. **Altered enzyme:** Bacterial dihydropteroate synthetase can undergo mutation or be transferred via a plasmid to result in a decreased affinity for the sulfas. The drugs therefore become less effective competitors of PABA.

2. **Decreased uptake:** Permeability to sulfas may be reduced in some resistant strains.

3. **Increased PABA synthesis:** Enhanced production of the natural substrate, PABA, by the microorganism through selection or mutation can overcome the inhibition of the dihydropteroate synthetase by the sulfas.

D. Pharmacokinetics

1. **Administration:** Most sulfa drugs are well absorbed after oral administration. *Sulfasalazine* [sul fa SAL a zeen], when administered orally or as a suppository, is reserved for treatment of chronic inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis), because it is not absorbed. Similarly, *succinylsulfathiazole* [suks in ill sul fa THI a zole] is used for the treatment of salmonella and shigella carriers. Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. Because of the risk of sensitization, sulfas are not usually applied topically. In burn units, creams of *mafenide acetate* (*p-aminomethylbenzensulfonamide*) or *silver sulfadiazine* have been effective in reducing burn sepsis. However, superinfections with resistant bacteria or fungi may occur.



2. **Distribution:** Sulfa drugs are distributed throughout body water and penetrate well into cerebrospinal fluid, even in the absence of inflammation. They can also pass the placental barrier and into breast milk. Sulfa drugs are bound to serum albumin in the circulation; the extent of binding depends on the particular agent.

3. **Metabolism:** The sulfas are acetylated at N4, primarily in the liver. The product is devoid of antimicrobial activity, but it retains the toxic potential to precipitate at neutral or acidic pH, causing crystalluria ("stone formation") and therefore potential damage to the kidney (Figure 29.4). *Sulfasalazine* is effective in the treatment of inflammatory bowel disease because local intestinal flora split the drug into *sulfapyridine* and *5-aminosalicylate*. The latter exerts the antiinflammatory effect. Absorption of *sulfapyridine* can lead to toxicity in patients who are slow acetylators.

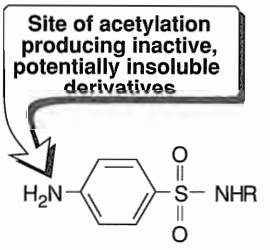


Figure 29.4
Inactivation of sulfonamides.

4. **Excretion:** Elimination of sulfas is by glomerular filtration. Therefore, depressed kidney function causes accumulation of both the parent compounds and their metabolites.

E. Adverse effects

1. **Crystalluria:** Nephrotoxicity develops as a result of crystalluria. Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug and promoting its ion-

ization. Newer agents, such as *sulfisoxazole* [sul fi SOX a zole] and *sulfamethoxazole* are more soluble at urinary pH than are the older sulfonamides (for example, *sulfadiazine*) and are less liable to cause crystalluria.

2. **Hypersensitivity:** Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, are fairly common. The latter occurs more frequently with the longer acting agents. [Note: Many drugs are derived from the sulfas and cross allergenicity has been reported for the diuretics, *acetazolamide*, *thiazides*, *furosemide*, *bumetanide*, *diazoxide* (see p. 226) and the sulfonylurea hypoglycemic drugs (see p. 260).]

3. **Hemopoietic disturbances:** Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency[2] (p. 351). Granulocytopenia and thrombocytopenia can also occur.

4. **Kernicterus:** This disorder may occur in newborns because sulfas displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the central nervous system.

5. **Drug potentiation:** Transient potentiation of the hypoglycemic effect of *tolbutamide* (see p. 260) or the anticoagulant effect of *warfarin* or of *bishydroxycoumarin* (see p. 199) results from their displacement from binding sites on serum albumin. Free *methotrexate* (see p. 378) levels may also rise through displacement.

6. **Contraindications:** Sulfas should be avoided in newborns and infants less than 2 months old as well as pregnant women at term, due to the danger of kernicterus. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving *methenamine* (see p. 327) for urinary tract infections.

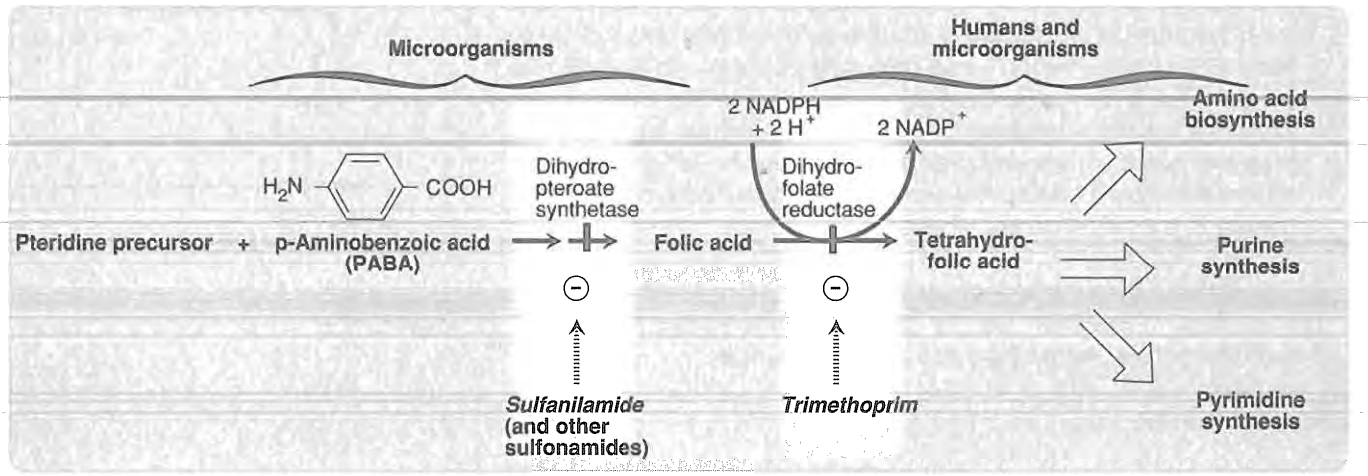


Figure 29.5
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

[2]See p. 296 for Infolink references to other books in this series.

III. TRIMETHOPRIM

Trimethoprim [trye METH oh prim], a potent inhibitor of bacterial dihydrofolate reductase[3], exhibits an antibacterial spectrum similar to the sulfonamides. However, *trimethoprim* is most often compounded with *sulfamethoxazole*.

A. Mechanism of action

The active form of folate is the tetrahydro-derivative that is formed through reduction by dihydrofolate reductase. This enzymatic reaction (Figure 29.5) is inhibited by *trimethoprim*, leading to a decrease in the folate coenzymes for purine, pyrimidine, and amino acid synthesis. Bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the drug's selective toxicity. [Note: Examples of other folate reductase inhibitors include *pyrimethamine*, which is used with sulfonamides in parasitic infections (see p. 353), and *methotrexate*, which is used in cancer chemotherapy (see p. 378).]

B. Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole* (see p. 290); however, *trimethoprim* is 20 to 50 times more potent than the sulfonamide. *Trimethoprim* may be used alone in acute urinary tract infections and in the treatment of bacterial prostatitis (though fluoroquinolones are preferred).

C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for the drug.

D. Pharmacokinetics

The pharmacokinetic characteristics of *trimethoprim* are similar to *sulfamethoxazole*, but higher concentrations are achieved in the relatively acidic prostatic and vaginal fluids since it is a weak base. *Trimethoprim* undergoes O-demethylation.

E. Adverse effects

Trimethoprim can produce the effects of folate deficiency, that is, megaloblastic anemia, leukopenia, and granulocytopenia. These reactions can be reversed by the simultaneous administration of *folinic acid*, which does not enter bacteria (see p. 379).

IV. CO-TRIMOXAZOLE

Trimethoprim is most often compounded with the sulfa drug, *sulfamethoxazole*. The resulting combination, called *co-trimoxazole*, shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 29.6). The combination was selected because of the similarity in the pharmacokinetics of the two drugs.

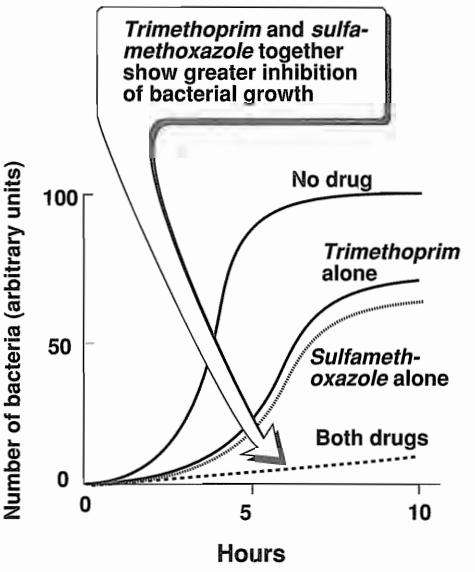


Figure 29.6
Synergism between *trimethoprim* and *sulfamethoxazole* on the inhibition of growth of Escherichia coli

[3]See p. 296 for Infolink references to other books in this series.

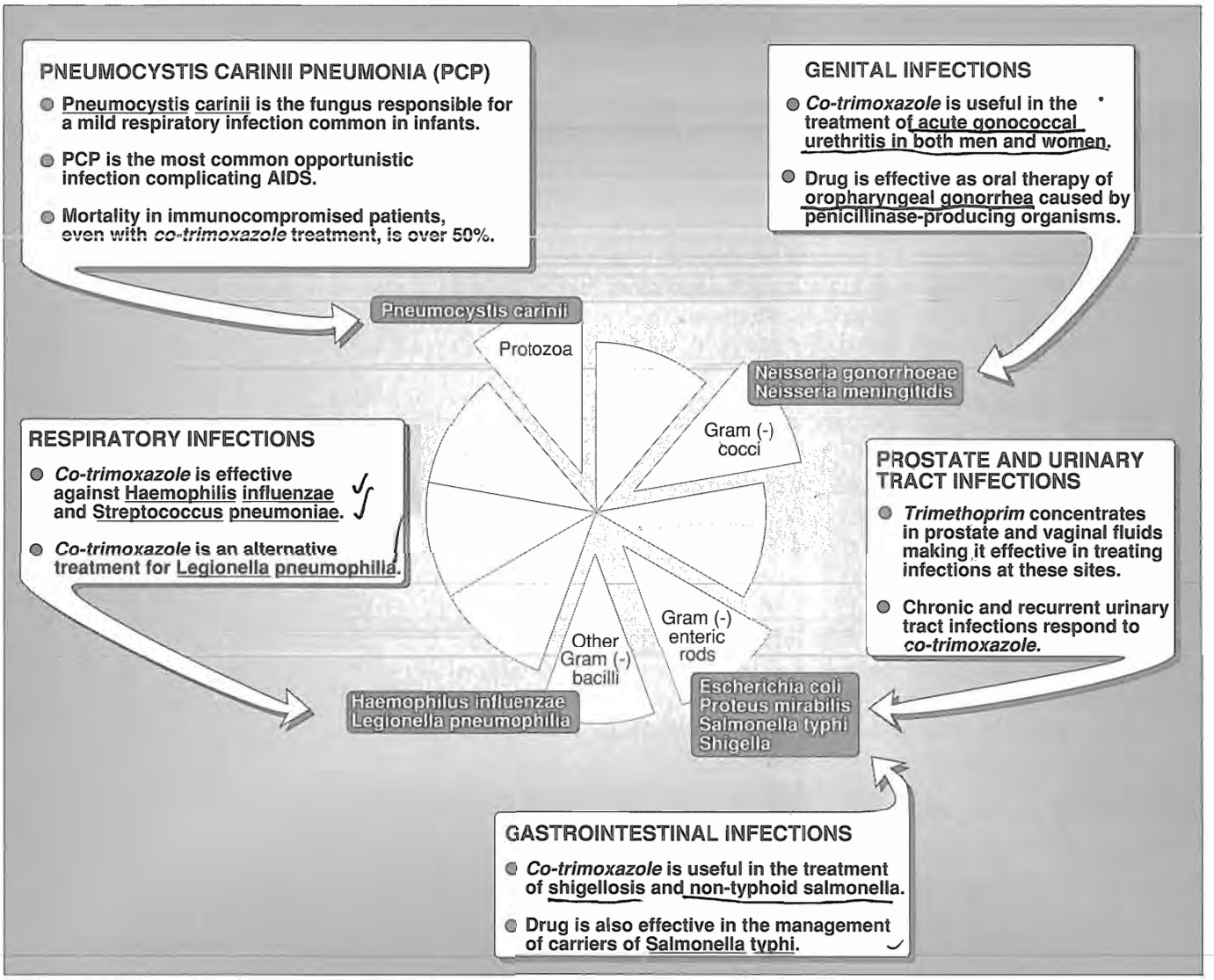


Figure 29.7
Typical therapeutic applications of *co-trimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

A. Mechanism of action

The synergistic antimicrobial activity of *co-trimoxazole* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: *sulfamethoxazole* inhibits the incorporation of PABA into folic acid, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate (see Figure 29.5). *Co-trimoxazole* exhibits more potent antimicrobial activity than *sulfamethoxazole* or *trimethoprim* alone (seed Figure 29.6).

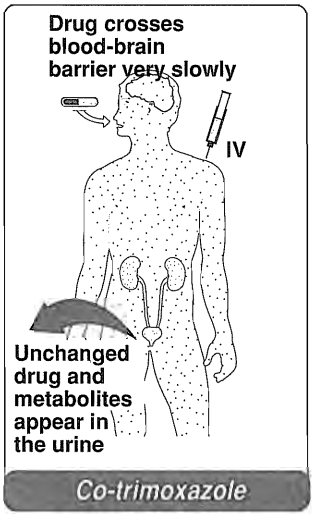
B. Antibacterial spectrum

The combination of *trimethoprim-sulfamethoxazole* has a broader spectrum of action than the sulfas (Figure 29.7).

C. Resistance

Resistance to the *trimethoprim-sulfamethoxazole* combination is less frequently encountered than resistance to either of the drugs alone because it requires simultaneous resistance to both drugs.

D. Pharmacokinetics



1. **Administration and metabolism:** *Trimethoprim* is more lipid-soluble than *sulfamethoxazole* and has a greater volume of distribution. Administration of 1 part of *trimethoprim* to 5 parts of the sulfa drug produces a ratio of the drugs in the plasma of 20 parts of *sulfamethoxazole* to 1 part *trimethoprim*. This ratio is optimal for the antibiotic effect. *Co-trimoxazole* is generally administered orally. An exception involves intravenous administration to patients with severe pneumonia caused by Pneumocystis carinii, or to patients who cannot take the drug by mouth.

2. **Fate:** Both agents distribute throughout the body. *Trimethoprim* concentrates in the relatively acidic milieu of prostatic and vaginal fluids and accounts for the use of the *trimethoprim-sulfamethoxazole* combination in infections at these sites. Both parent drugs and their metabolites are excreted in the urine.

E. Adverse effects

1. **Dermatologic:** Reactions involving the skin are very common and may be severe in the elderly.

2. **Gastrointestinal:** Nausea, vomiting as well as glossitis, and stomatitis are not unusual.

3. **Hematologic:** Megaloblastic anemia, leukopenia, and thrombocytopenia may occur; all of these effects may be reversed by the concurrent administration of *folinic acid* (see p. 379), which protects the patient and does not enter the microorganism. Hemolytic anemia may occur in patients with glucose-6-phosphate deficiency due to the *sulfamethoxazole* (see p. 351).

4. **HIV patients:** These immunocompromised patients with Pneumocystis pneumonia frequently show drug-induced fever, rashes, diarrhea and/or pancytopenia.

5. **Drug Interactions:** Prolonged prothrombin times in patients receiving *warfarin* have been reported. Plasma half-life of *phenytoin* (see p. 147) may be increased due to an inhibition of its metabolism. *Methotrexate* (see p. 378) levels may rise due to displacement from albumin binding sites by the *sulfamethoxazole.*

Choose the ONE best answer.

29.1 Sulfonamides are useful in the treatment of which one of the following?

A. Influenza.
B. Gonorrhea.
C. Most streptococcal infections.
D. Urinary tract infections.
E. Meningococcal infections.

Correct answer = D. Sulfonamides at one time were the mainstay of the treatment of uncomplicated infections of the urinary tract.

29.2 Trimethoprim:

A. is less potent than sulfamethoxazole.
B. inhibits the enzyme dihydropteroate synthetase.
C. lowers the ratio of tetrahydrofolate to folate in the organism
D. resistance has not been observed in microorganisms.
E. stimulates purine synthesis.

Correct answer = C. Trimethoprim is 20 to 50 times more potent than sulfamethoxazole. It inhibits the enzyme dihydrofolate reductase, thus preventing both purine and pyrimidine synthesis. Trimethoprim resistance has been observed *in gram-negative bacteria* caused by the presence of a plasmid that codes for an altered dihydrofolate reductase with a lower affinity for the drug.

29.3 All of the following statements concerning sulfonamides are correct EXCEPT:

A. They require actively growing cultures for maximum antimicrobial activity.
B. Allergic reactions are frequent adverse effects.
C. Treatment of patients with severe renal insufficiency may lead to crystalluria.
D. They diminish activity of warfarin.
E. They compete with p-aminobenzoic acid for the enzyme dihydropteroate synthetase.

Correct choice = D. Transient potentiation of the anticoagulant effect of vitamin K antagonists, such as warfarin or bis-hydroxycoumarin, results *from their displacement from binding sites on* serum albumin. Sulfonamides are bacteriostatic and are most effective against growing microorganisms, where they are competitive inhibitors of dihydropteroate synthetase. Allergic reactions and crystalluria are the two most common adverse effects associated with sulfonamide treatment. The sulfonamides tend to have low solubilities and to form crystals in the kidney or bladder, particularly if urinary output is low.

29.4 Sulfonamides increase the risk of neonatal kernicterus because they

A. diminish the production of plasma albumin.
B. increase the turnover of red blood cells.
C. inhibit the metabolism of bilirubin.
D. compete for bilirubin binding sites on plasma albumin.
E. depress the bone marrow.

Correct answer = D. Increased release of albumin-bound bilirubin increases the plasma concentration of free bilirubin, which can penetrate the CNS.

Questions 29.5 - 29.7: For each phrase, select the ONE drug (A-E) that is most closely associated with it. Each drug (A-E) may be selected once, more than once, or not at all.

A. Sulfasalazine
B. Sulfacetamide
C. Trimethoprim-sulfamethoxazole
D. Mafenide acetate
E. Sulfisoxazole

29.5 It is used to prevent infections among burn patients.

Correct answer = D. Creams containing mafenide acetate are used in burn units where they are used prophylactically to protect against infection with a variety of gram-negative and gram-positive microorganisms.

29.6 It is used in the treatment of ulcerative colitis.

Correct answer = A. Sulfasalazine is reserved for treatment of ulcerative colitis because the drug is not absorbed from the gut and acts locally.

29.7 It is effective in the treatment of pneumonia caused by Pneumocystis carinii.

Correct answer = C. Co-trimoxazole is currently the drug of choice, although high doses are required.

[1]See p. 250 in **Biochemistry** (2nd ed.) for a discussion of synthesis of folic acid and formation of its one-carbon carrying cofactors.

[2]See p. 115 in **Biochemistry** (2nd ed.) for a discussion of the causes of hemolytic anemia encountered in patients with glucose 6-phosphate dehydrogenase deficiency.

[3]See p. 325 in **Biochemistry** (2nd ed.) for a discussion of a role of dihydrofolate reductase in metabolism.