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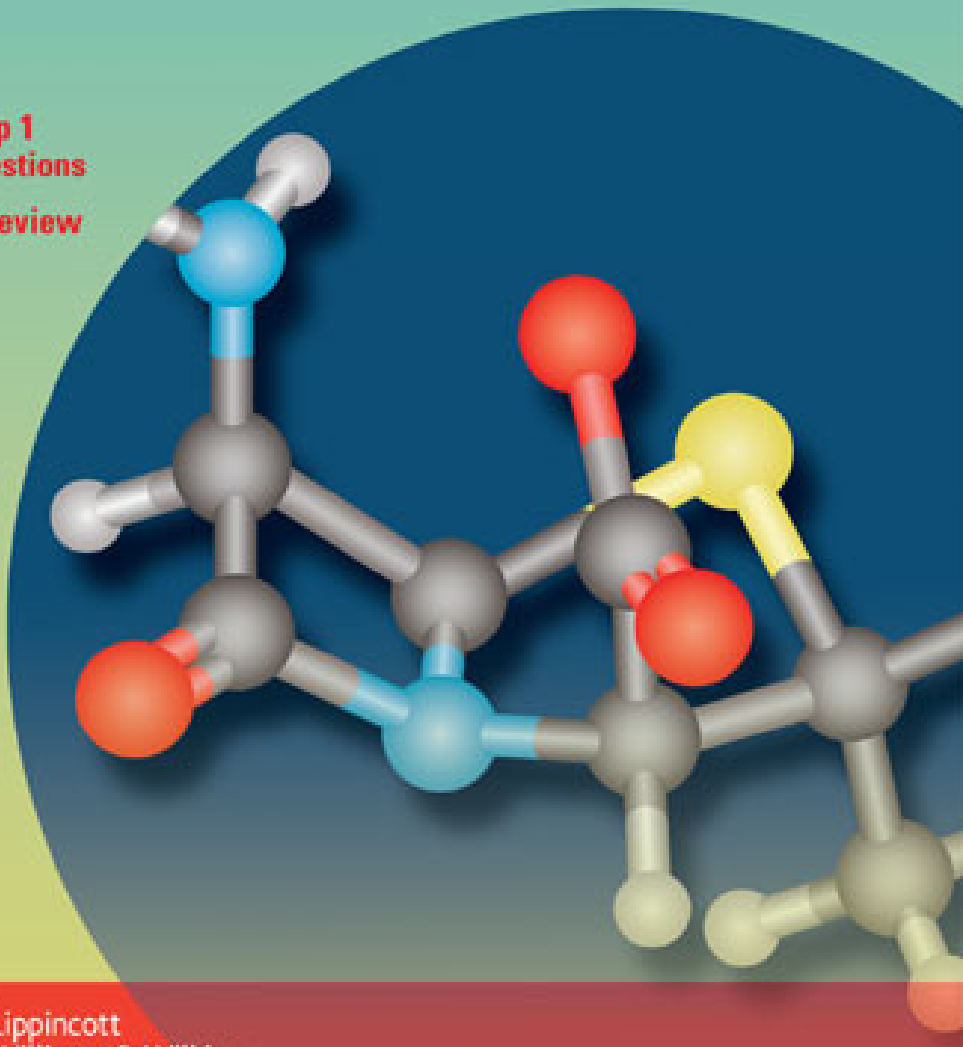

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High-Yield™

Pharmacology

THIRD EDITION

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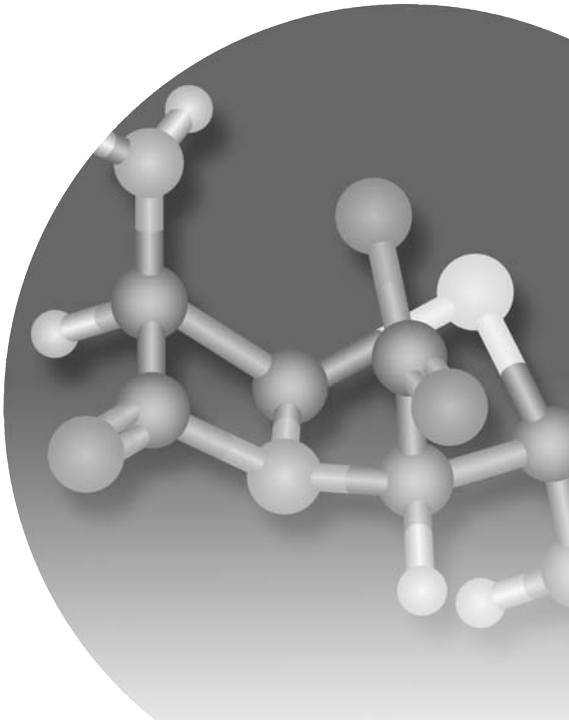

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Preface

The discipline of pharmacology encompasses both how drugs affect the body (pharmacodynamics), as well as how the body affects drugs (pharmacokinetics). Because it is such an interdisciplinary field, pharmacology necessarily is built upon a foundation consisting of nearly every other basic science discipline that is part of a medical school curriculum. You must have a good grasp of physiology, pathology, biochemistry, microbiology, and molecular biology in order to study pharmacology. Even many disciplines that people have not traditionally associated with pharmacology are turning out to be essential for understanding pharmacology, such as anatomy and genetics. In fact, one of the hottest areas in pharmacology right now is pharmacogenomics, where a patient's treatment is tailored based upon his or her unique genetic makeup.

This edition of *High-Yield Pharmacology* has been substantially updated and revised. Specifically, new sections on biologics have been added in the appropriate chapters, as well as several new figures and tables. In addition, the cardiovascular pharmacology chapter has been expanded and split in half, reflecting the rapid growth in the pharmacology of this area. Readers who desire a very brief review can read the bolded printed text, which highlights the most important concepts in each chapter. In addition, the index can be used to help you review the class of every drug in the book.

It is unfortunate that many medical students approach pharmacology as just a list of drug names and side effects that must be memorized for the United States Medical Licensing Examination. You may be using this book to review pharmacology for Step 1 of the USMLE, and I hope you will find it helpful as you prepare. But I also hope that it will give you at least an inkling of how interesting and dynamic the field of pharmacology is. Please feel free to contact me at weisss@ccf.org if you have any comments or suggestions about the book.

Stephanie T. Weiss

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Contents

Chapter **1**

General Principles

I Pharmacokinetics: General Principles

A. PHARMACOKINETICS is the study of the movement of drugs into and out of the body, including **absorption (bioavailability), distribution, metabolism (biotransformation),** and **elimination (ADME).**

B. Clinical pharmacokinetics, which involves the **mathematical description** of the **processes of ADME,** is useful to predict the serum drug concentrations under various conditions.

C. PHARMACOKINETICS can be thought of as **what the body does to the drug.**

II Pharmacokinetics: Administration and Absorption of Drugs

A. Many routes of drug administration can be used.

1. The oral route (PO) is usually preferred**.**

a. **Advantages** include:

i. **Convenience**

ii. A **large surface area** for absorption

iii. Fewer **abrupt changes of serum drug concentrations** than with parenteral administration

b. **Disadvantages** include:

i. **First-pass metabolism** by the liver

(a) All the blood flow from the intestinal tract goes initially to the liver through the portal vein; therefore the **drug may be metabolized before being distributed** to the other tissues in the body

(b) First-pass metabolism of a drug can be **avoided by parenteral administration of the drug** and partially avoided by rectal administration.

ii. **Systemic exposure to the drug**

2. The parenteral routes of administration are technically more difficult and usually must be performed by a health care professional. Common methods are **inhalation, sublingual, intravenous (IV), intramuscular (IM), and subcutaneous (SQ) administration.**

a. **Advantages** include:

i. A **faster onset** (usually)

ii. **More reliable** absorption

iii. **No first-pass metabolism**

b. **Disadvantages** include:

i. **More difficult** administration

ii. **Pain or necrosis** at the site of infection
iii. Possibility of **infection**
iv. **Toxicity from a bolus intravenous (IV) injection**
v. **Necessity of dissolving the drug if given intravenously**

B. Some drugs are actively or passively transported by carrier proteins, but the movement of drugs across cell membranes usually occurs passively by **diffusion.**

C. THE RATE OF DIFFUSION IS HIGH IF:

1. The unionized form of a drug has a high lipid solubility.

a. Lipid solubility is related to the oil-water partition coefficient.
b. Cell membranes are basically lipoidal in nature, and only lipid soluble substances will diffuse through them.

2. A large proportion of the drug is present in the unionized form.

a. **Only the unionized form can cross cell membranes,** because the ionized form will have a very low solubility in lipids.
b. The equilibrium between the ionized (A^-) and unionized (HA) forms of a weak acid is:

$$\mathbf{HA \leftrightarrow H^+ + A^-}$$

c. The equilibrium constant (K_a) for the dissociation of an acid is defined as:

$$\mathbf{K_a = \frac{[A^-][H^+]}{[HA]}}$$

d. By taking the negative log (–log) of both sides of the K_a expression and rearranging, we can get the Henderson–Hasselbalch equation for a weak acid:

$$\mathbf{pH = pK_a + \log \frac{[A^-]}{[HA]}}$$

e. The proportion of unionized drug will depend on the pH and can be determined with the Henderson–Hasselbalch equation.
f. Weak bases also dissociate, and the equation for dissociation of the conjugate acid of a weak base is:

$$\mathbf{HB^+ \leftrightarrow H^+ + B}$$

g. The equilibrium constant (K_a) for the dissociation of the conjugate acid of a weak base is defined as:

$$\mathbf{K_a = \frac{[B][H^+]}{[HB^+]}}$$

h. By taking the negative log (–log) of both sides of the K_a expression and rearranging, we can get the Henderson–Hasselbalch equation for a weak base:

$$\mathbf{pH = pK_a + \log \frac{[B]}{[HB^+]}}$$

i. Note that the conjugate base should always go in the numerator, while the conjugate acid belongs in the denominator.
j. When the pH equals the pK_a, 50% of a drug will be ionized and 50% will be unionized.
k. The most dramatic changes in the amounts of ionized and unionized drug occur with pH changes near the pK_a.

3. **The membrane is thin.**
4. **The membrane is porous.** Porosity is especially important for water-soluble drugs.
5. **The surface area of the membrane is large.**
6. **The difference in concentrations on the two sides of the membrane is large.**
7. **The diffusion constant, based on molecular size, molecular shape, and temperature, is large.**

D. At the **basic pH** in the small intestine
1. **Weak bases are well absorbed** because most of the drug is unionized.
2. **Weak acids are poorly absorbed** because most of the drug is ionized.
3. The opposite scenario occurs in the acidic environment of the stomach; however, the stomach does not have a very large absorptive capability.

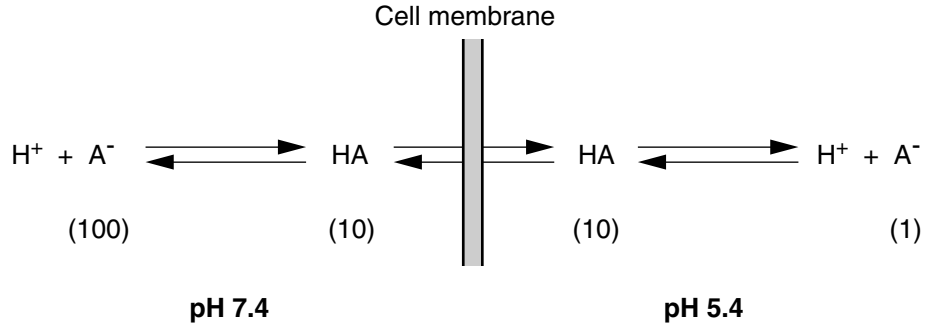
E. ION TRAPPING occurs with weak acids and weak bases if there is a difference in pH on the two sides of a membrane.
1. **The ionized form of the drug will be trapped on one side.**
   a. The ionized form of a **weak base** will be protonated and trapped on the side with the **lower pH.**
   b. The ionized form of a **weak acid** will be deprotonated and trapped on the side with the **higher pH.**
2. Figure 1-1 illustrates ion trapping for a weak acid with a pK_a of 6.4. At equilibrium, the unionized concentrations on either side of the membrane will be equal, but 91% of the drug will be in the compartment at pH 7.4.

F. STRONG BASES AND STRONG ACIDS are **totally dissociated** or ionized in solution; thus, they are **poorly absorbed at any pH.** Quaternary ammonium compounds are completely ionized at physiological pHs and therefore are also poorly absorbed.

G. ABSORPTION OF A DRUG IS USUALLY FAST, as compared to the elimination; thus, it is often ignored in kinetic calculations. The rate of gastric emptying can affect the absorption and bioavailability of a drug.

H. BIOAVAILABILITY is the **fraction of drug administered that reaches the systemic circulation without being metabolized.**
1. **Bioavailability *(F)* equation:**

$$F = \frac{\text{[drug] in the systemic circulation after oral administration}}{\text{[drug] in the systemic circulation after IV administration}}$$



● **Figure 1-1** Ion trapping of a weak acid (pK_a 6.4) on the side of the cell membrane with the higher pH. The numbers in parentheses represent the relative concentrations of each form of the weak acid under steady-state conditions.

a. The **bioavailability** after oral administration depends on
   i. The **disintegration** of a tablet
   ii. The **dissolution** of the drug in the intestinal contents
   iii. Gastrointestinal and **first-pass metabolism**

b. **A drug that is administered by IV will be 100% bioavailable.**

2. **Bioequivalence** occurs when drugs with equal *F* have the same drug concentration versus time relationship (i.e., similar rate and extent of drug absorption).
3. **Therapeutic equivalence** (TE) is commonly said to occur when two drugs have the same maximal response; it may be different than bioequivalence. (Note that the FDA defines TE as having the same ingredients, dosage form, route of administration, and concentration.)

III Pharmacokinetics: Distribution of Drugs

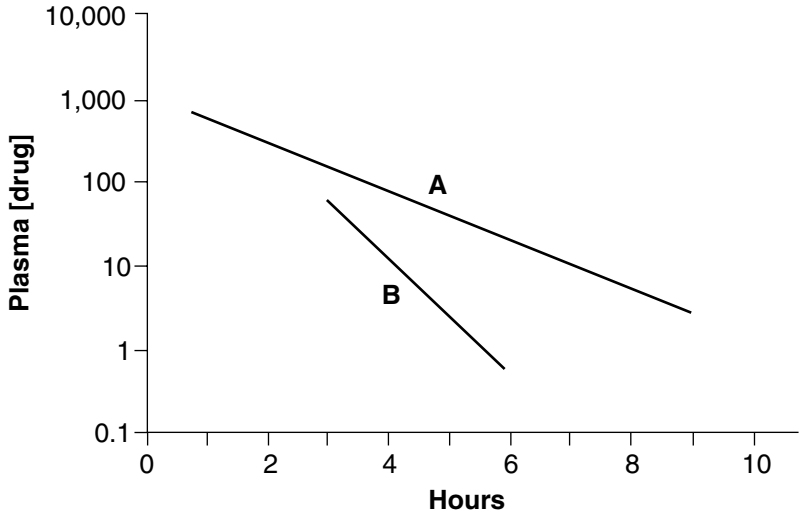
A. THE INITIAL DISTRIBUTION of a drug to the tissues is determined by the **relative blood flows** to the tissues. Sites with high blood flows will initially receive more of the drug.

B. THE VOLUME OF DISTRIBUTION V_d is an approximation of the hypothetical fluid volume that a drug appears to distribute in.

1. It can be very large, even larger than the total body volume, if a drug is highly bound to tissues. This makes the serum drug concentration very low and the V_d very large.
2. The V_d must be calculated at the time of administration.
   a. **Apparent volume of distribution equation:**

$$V_d = \frac{\text{amount of drug administered}}{\text{serum [drug]}}$$

   b. For the drugs illustrated in Figure 1-2, if the same amount of each was administered, the concentration of drug A at time 0 will be lower; thus, it will have the larger V_d (the numerator is constant, but the denominator is smaller for A than for B). This occurs because more of drug A than drug B is distributed in extravascular tissue.



● **Figure 1-2** Relationship of plasma drug concentration versus time for two drugs. Drug A has the larger apparent volume of distribution.

3. **The loading dose** for a drug is based on the $\mathbf{V_d}$.

$$\textbf{Oral loading dose} = \frac{\mathbf{V_d \times C}}{\boldsymbol{F}}$$

where *C* is the desired or target serum drug concentration and *F* is the bioavailability (fraction of administered drug in the blood).

C. The final **apparent volume of distribution ($\mathbf{V_d}$)** will be affected by
1. **The lipid solubility** of a drug, which, if high, will result in good penetration into cells and a high V_d
2. **Plasma protein binding and tissue binding**
   a. **Plasma protein binding, especially to albumin,** will reduce the V_d.
   b. **Tissue binding** will increase the V_d.
   c. Both types of binding act as **reservoirs** for the drug, as only the unbound drug can activate pharmacological receptors. Thus binding will
      i. **Slow the onset** of drug action
      ii. **Prolong the duration** of drug action, if the drug is eliminated by glomerular filtration in the kidney
3. **Competition** for binding sites on albumin between two drugs A and B **can raise free levels** of A in the blood if
   a. The concentration of B exceeds the number of albumin binding sites
   b. B is able to displace A from the albumin binding sites

IV Pharmacokinetics: Metabolism of Drugs

A. The **liver** is the **primary site of drug metabolism.**

B. Metabolism can change a drug in several ways.
1. The **polarity is usually increased,** enhancing the water solubility and renal excretion of the drug metabolite.
2. The **activity of the drug is reduced. Exceptions** are the **prodrugs,** which are drugs that are inactive in the form administered but are metabolized to their active forms.
3. A drug metabolite usually has a **smaller $\mathbf{V_d}$** due to its increased water solubility.

C. PHASE 1 metabolic reactions usually lead to the **alteration or inactivation** of the drug's activity. Often, new functional groups are introduced that make further metabolism possible.
1. **Oxidation by cytochrome P450 (CYP)** enzymes (also known as **mixed function oxidases [MFO],** microsomal enzymes, mono-oxygenases) **occurs** in the **smooth endoplasmic reticulum (ER).**
   a. Nicotinamide adenine dinucleotide phosphate **(NADPH), cytochrome P450 reductase,** and elemental oxygen **($\mathbf{O_2}$)** are required.
   b. Many reactions can be produced, including:
      i. **Hydroxylation**
      ii. **Dealkylation**
      iii. **Deamination**
      iv. **Sulfoxidation**
      v. **Oxidation**
   c. Highly lipid soluble drugs are more readily metabolized by CYPs.
2. **Reductive reactions** can occur in the ER or the cytosol.
3. **Hydrolytic reactions** do not occur in the ER.

D. **PHASE 2** metabolic reactions are **conjugative,** adding highly polar groups to the drug to increase renal elimination.
1. **Glucuronidation** occurs in the **ER.** Glucose is used to form uridine diphosphate glucuronic acid (UDPGA), which then transfers a glucuronide to the drug in the presence of glucuronyl transferase.
2. Other substances can be conjugated (by transferases primarily in the cytosol) to drugs. These conjugates generally reduce the drug's activity and increase its polarity, including:
   a. Sulfate
   b. Acetyl
   c. Methyl
   d. Glutathione
   e. Amino acids, especially glycine

E. Many drug **interactions** are due to changes in CYP activity in the liver.
1. **Induction** of CYPs results from increased levels of CYPs in the ER.
   a. The onset of induction is **slow** (days) and the duration is **long** (taking a week or more for recovery after the drug is withdrawn).
   b. Many drugs that are metabolized by the CYPs also induce the CYPs, including:
      i. **Barbiturates, phenytoin, rifampin**
      ii. **Alcohol**
      iii. **Cigarette smoke**
   c. This induction hastens the metabolism of the inducing drug along with other drugs metabolized by the same CYPs.
2. **Inhibition** of drug metabolism occurs if there is **competition** between drugs at the CYP, or if a drug tightly binds to the CYP.
   a. Potent CYP inhibitors include **cimetidine, ritonavir,** and **azole antifungals.**
   b. Grapefruit juice has a similar inhibitory effect.

F. Liver enzymes are polymorphic in the population, such that individuals with different enzyme forms may metabolize a drug at different rates.

G. The rate of metabolism is first order for most drugs
1. **First-order** metabolism is **proportional** to the **concentration** of **free drug.**
2. A constant fraction of drug is metabolized per unit of time (i.e., the metabolism of the drug has a half-life.)

V Pharmacokinetics: Elimination of Drugs and Drug Metabolites

A. The **kidney** is the primary organ that excretes drugs and drug metabolites.
1. If the drug is excreted in the unmetabolized form, the kidney also decreases that drug's pharmacological activity.
2. **Polar drugs and drug metabolites** are readily eliminated by the kidney.

B. **GLOMERULAR FILTRATION** of the unbound molecule accounts for the excretion of most drugs.
1. **Drug molecules bound by plasma proteins will not be filtered** by the glomerulus.
2. **Hydrophilic** substances are most **efficiently eliminated** by the kidney, because they are not readily reabsorbed across the nephron tubule after they are filtered.
3. If a drug is a **weak base,** administration of ammonium chloride will **acidify the urine** and increase the amount of the base that is in the ionized form.

a. The **excretion of the weak base will be increased.**
b. This will be most effective if the pK_a of the drug is near the physiological pH.

4. The **excretion of a weak acid can be increased by alkalinizing the urine** with sodium bicarbonate.

C. ACTIVE TRANSPORT of a few drugs occurs in the **proximal tubule.**

1. It usually involves **secretion of strong acids or strong bases.**
2. P-glycoprotein is an important **transporter** in renal and other cells.
3. Characteristics of active transport are
   a. **Competition** between substrates for the carrier
   b. **Saturability** of the carrier
   c. **Being unaffected by plasma protein binding**
4. Active reabsorption can also occur.
5. A few substances are both actively secreted and actively reabsorbed (e.g., uric acid, aspirin).

D. BILIARY EXCRETION occurs in the liver.

1. Large polar compounds, often conjugated metabolites, are actively excreted into the bile.
2. Enterohepatic cycling occurs with a few drugs that are eliminated in the bile, reabsorbed from the intestine, returned to the liver and again eliminated in the bile.
   a. **Glucuronidase** in the intestine can cleave off the glucuronide, so the free drug can be reabsorbed (Figure 1-3).
   b. **Digitoxin,** a cardiac glycoside, undergoes enterohepatic cycling.
   c. This **may increase the half-life** of the drug.

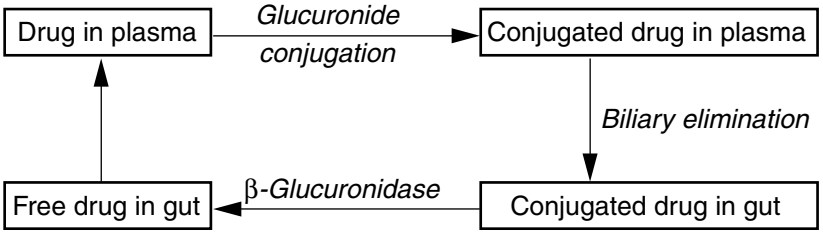
E. ELIMINATION usually follows the principles of **first-order kinetics,** which means that a constant fraction of the drug is eliminated per unit of time (k_e).

1. Clearance (Cl) equals $V_d \times k_e$
   a. Clearance is measured as a volume per unit of time.
   b. The rate of drug elimination equals Cl $\times$ C_{ss}, where C_{ss} is the drug concentration at steady state.
   c. The **oral maintenance dose** simply involves the replacement of the amount of drug that has been eliminated in the dosage time interval (T).

$$\textbf{Oral maintenance dose} = \frac{\text{Cl} \times C_{ss} \times T}{F}$$

2. The half-life ($t_{1/2}$) of a drug is the time required for the serum drug concentration to be reduced by 50%.

a. $$t_{1/2} = \frac{0.69}{k_e} = \frac{0.69 \times V_d}{\text{Cl}}$$



● **Figure 1-3** Enterohepatic cycling of a conjugated drug.

b. If the $t_{1/2}$ of a drug is 5 hours, then the serum drug concentration will be reduced by 75% in 10 hours (50% after the first 5 hours, then 25% after the second 5 hours).
c. During repeated administrations, it takes **four to five half-lives to attain a steady-state drug concentration.**
d. When the dosage interval (T) is reduced with the same total amount of drug being administered (i.e., more frequent administration of smaller aliquots that sum to the same net dose), the $t_{1/2}$ is not changed.
   i. The fluctuations of the drug concentration become smaller.
   ii. This is a useful approach when a drug has a very narrow therapeutic window between the effective drug concentration and the toxic drug concentration.
   iii. Continuous infusion is administration in infinitely small aliquots.

3. With **reduced kidney function,** the maintenance dose should be reduced if the drug is cleared from the body by the kidney because Cl is smaller.

a. **Oral maintenance dose** $= \dfrac{(Cl_{hepatic} + Cl_{renal} + Cl_{others}) \times C_{ss} \times T}{F}$

b. **Creatinine clearance** is a good quantitative **indicator of glomerular filtration rate.** Serum creatinine may also serve as a useful index of glomerular filtration rate.

4. With **reduced liver function,** there is **no good predictor** of the oral maintenance dose for drugs that are cleared by the liver.
a. If the **extraction ratio** for a drug passing through the liver **approaches 1,** then Cl equals hepatic blood flow (BF).
   i. **Reduced hepatic BF or reduced cardiac output (CO) will reduce the hepatic Cl of a drug with a high hepatic extraction ratio.**
   ii. An example is **lidocaine,** which has a lower $Cl_{hepatic}$ in patients with congestive heart failure. As a result, the maintenance dose of lidocaine should be reduced in these patients.
b. If the hepatic extraction ratio is near 0, hepatic BF is unimportant. Intrinsic metabolic rate and the amount of plasma protein binding become important factors.

5. If a drug follows first-order elimination kinetics, **doubling the dose will double the C_{ss},** but it does not change the amount of time need to reach C_{ss} (i.e., it does not affect $t_{1/2}$).

F. The above equations **do not apply** to drugs that have **zero-order** elimination kinetics (i.e., those for which a constant *amount* of drug is eliminated per unit of time rather than a certain *fraction* of drug per unit of time).
1. It is very difficult to predict and control the C_{ss} for these drugs because the fraction of drug being eliminated does change with the concentration of drug present.
2. Drugs which follow zero-order kinetics include:
a. Ethanol
b. Heparin
c. Phenytoin
d. Aspirin at high concentrations

VI Pharmacodynamics

A. PHARMACODYNAMICS is a description of the properties of **drug-receptor interactions** and can be thought of as **what the drug does to the body.**

B. DRUGS BIND to specific receptors with

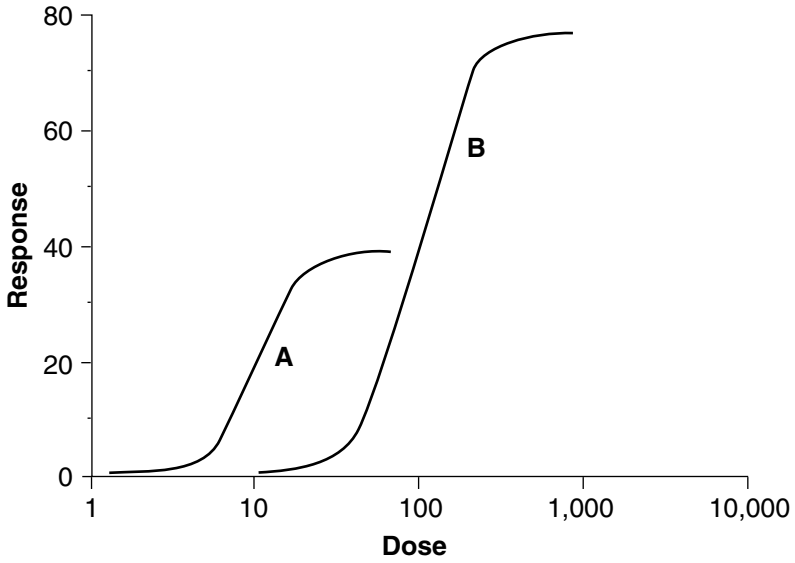
1. Ionic bonds (electrostatic attractions)
2. Hydrogen bonds
3. Van der Waals forces, which are weak but necessary for a good fit
4. Covalent bonds, which are uncommon and are usually irreversible

C. DOSE–RESPONSE CURVES show the **relationship** between the **concentration of a drug** and the **magnitude of its effect.**

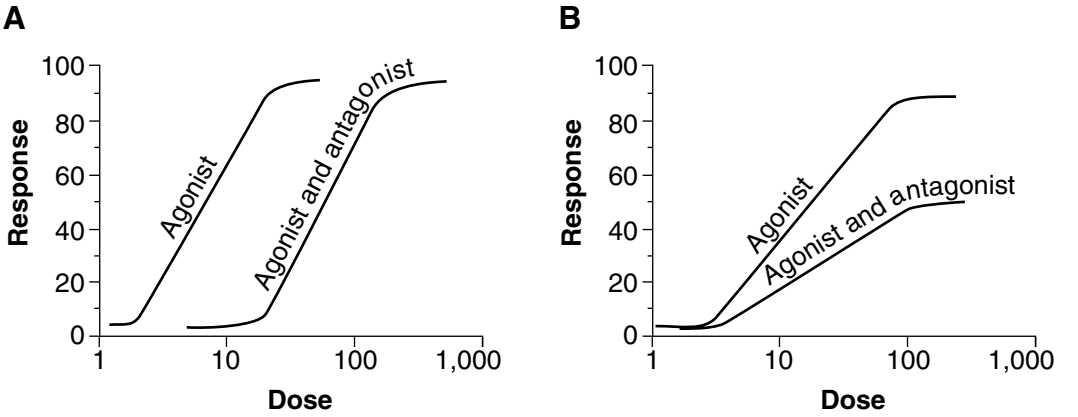
1. **The potency** (affinity) of a drug is inversely related to the **median effective dose** (**ED_{50}**), where ED_{50} is the **dose that produces the desired effect in 50% of the subjects.**
2. **The efficacy (intrinsic activity)** is equivalent to the **maximal effect** of the drug.
3. The potency and intrinsic activity are independent.
   a. In Figure 1-4, drug B has a higher efficacy than drug A (80 vs. 40 read off the *Y*-axis).
   b. Drug A is approximately 10 times more potent than drug B, because the ED_{50} of drug A is 10% the ED_{50} of drug B (10 vs. 100 read off the *X*-axis).
4. Drug A is a partial agonist (or a partial antagonist), because the maximal response is smaller compared to drug B (40 versus 80).

D. AGONISTS change the effector site and **lead to biological responses that mimic the responses of the natural ligand.**

1. The drug–receptor interaction follows the **laws of mass action.**
   a. Drug molecules bind to receptors at a rate that is dependent on the drug concentration.
   b. The number of drug–receptor interactions determines the magnitude of the drug effect.
   c. Types of receptors include **ligand-gated ion channels, G protein-coupled receptors, kinase-linked receptors,** and **intracellular receptors.**
2. This leads to **dose–response** curves, which can be
   a. **Quantal** (all or none [e.g., death])
   b. **Graded** (e.g., blood pressure)



● **Figure 1-4** Dose-response relationships for two drugs. Drug B has twice the efficacy of drug A. However, drug A is approximately 10 times more potent than drug B.



● **Figure 1-5** Dose-response relationships for an agonist alone and for an agonist in the presence of (A) a competitive surmountable antagonist and (B) a competitive insurmountable or noncompetitive antagonist.

3. As seen in Figure 1-4, agonists can be **full agonists** (have the same maximal effect as the natural ligand-curve B) or **partial agonists** (have a lower maximal effect compared to the natural ligand-curve A)

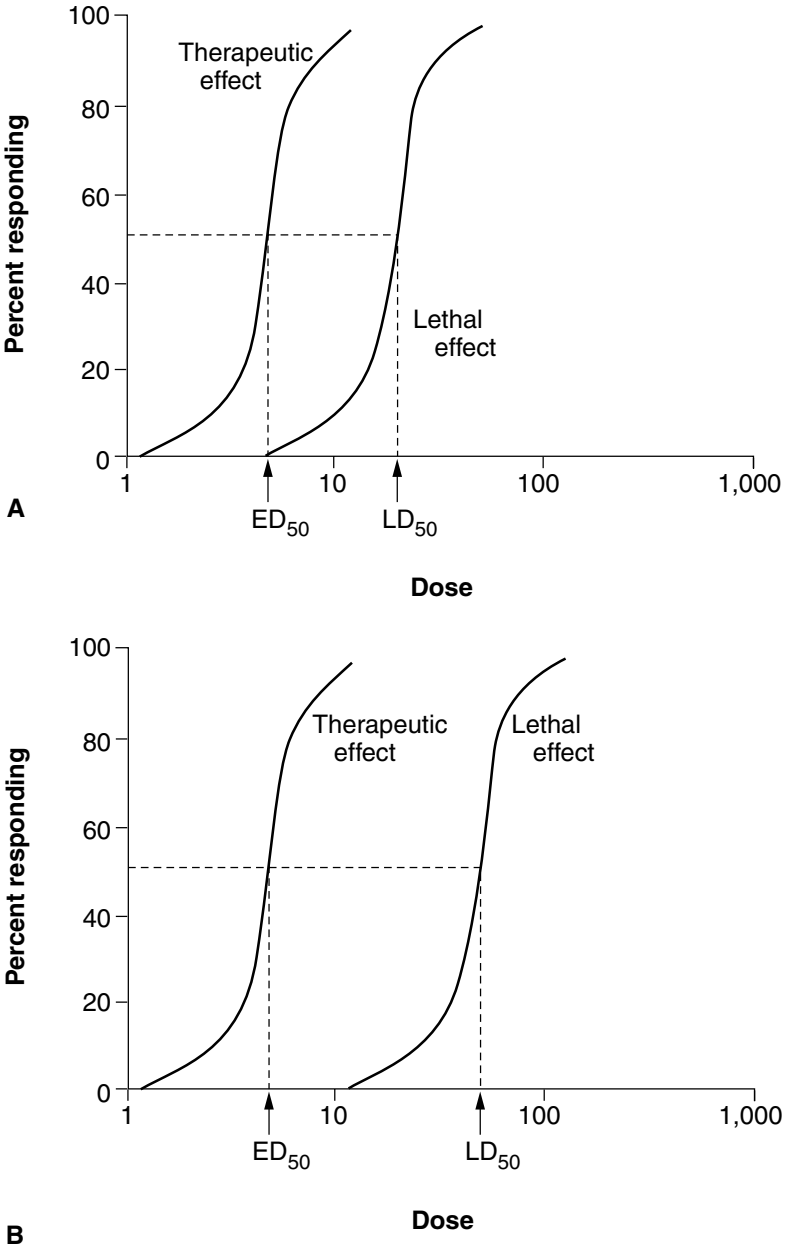
E. ANTAGONISTS are drugs with a high affinity for a receptor and **no intrinsic activity**. They alter the dose-response curves for the agonists.

1. **Competitive surmountable** (reversible) antagonists induce a **parallel shift** of the agonist dose-response curve to the right with no change in intrinsic activity (Figure 1-5A). The effect of the antagonist can be surmounted by increasing the concentration of the agonist.
2. **The maximal effect** of a specific agonist **is reduced** (increasing the concentration of the agonist will not surmount the effect of the antagonist) with little or no change in the ED_{50} of the agonist (Figure 1-5B) by
   a. **Competitive insurmountable (irreversible) antagonists,** which often bind covalently to a receptor
   b. **Noncompetitive antagonists,** which often act at a site other than the receptor for the agonist
3. **Other types of antagonism** can occur.
   a. **Functional** (physiological) antagonism involves the opposing actions of **two agonists** at different receptors (e.g., acetylcholine [ACh] and norepinephrine [NE] on heart rate).
   b. **Chemical antagonism** involves the **direct binding** of a drug by another drug without the involvement of a receptor (e.g., heavy metal chelators).
   c. Partial agonists will act as antagonists in the presence of a full agonist, since the intrinsic activity of the partial agonist is lower than the intrinsic activity of the full agonist.

F. THE THERAPEUTIC INDEX (TI [**therapeutic window**]) measures the **relationship between the efficacy and safety** of a drug (Figure 1-6).

$$TI = \frac{LD_{50}}{ED_{50}} \text{ or } \frac{TD_{50}}{ED_{50}}$$

1. **LD_{50}** is the dose that kills 50% of the subjects.
2. **TD_{50}** is the dose that induces a toxic effect in 50% of the subjects.
3. A large TI is desirable in order to avoid overlap between the toxic and therapeutic ranges of the drug. (See Figure 1-6A versus Figure 1-6 B.)



● **Figure 1-6** Dose–response relationships for a therapeutic effect and the lethal effect of a drug. The distance between these curves is indicative of the safety of the drug. (A) shows a drug with a narrow therapeutic window (overlap between the curves) and (B) shows the graph for a drug with a wider therapeutic index. ED_{50} = effective dose in 50% of patients; LD_{50} = lethal dose in 50% of patients.

VII Age-Dependent Pharmacology

A. PEDIATRIC PHARMACOLOGY

1. Newborns have **a greater percentage of weight from body water and less body fat** than adults.

a. A **water-soluble drug will have a higher V_d** (relative to body size) in children than in adults.
b. A **lipid-soluble drug will have a lower V_d** (relative to body size) in children than in adults.

2. **Plasma protein binding is reduced** for approximately the first year.
3. **Metabolism,** especially oxidation and glucuronidation, is also **reduced**.
4. **Glomerular filtration rate (GFR) and renal tubular function** are **reduced** in newborns.

B. GERIATRIC PHARMACOLOGY

1. The **elderly** generally have
   a. A **smaller overall** body mass and less lean body mass
   b. **A higher percentage of body fat** and less body water
      i. A **water soluble drug will have a lower V_d** than in a person of average age.
      ii. A **lipid soluble drug will have a higher V_d.**
   c. **Reduced plasma albumin,** which will reduce the amount of bound drug in the plasma
   d. **Reduced renal excretion**
   e. **Reduced hepatic metabolism** of some drugs, especially Phase I reactions.
   f. Other nonpharmacokinetic changes
      i. Central nervous system (CNS) drugs often produce confusion.
      ii. Cardiovascular drugs often have greater effects in the elderly patient because the homeostatic mechanisms (e.g., baroreceptor reflexes) are sluggish.
2. Special care must be taken when prescribing drugs for the elderly.
   a. Overall, elderly patients require **smaller dosages of most drugs** than young adults.
   b. **Compliance issues** (e.g., cost, complex dosage regimens, childproof packaging that is difficult to open) are common in the elderly.
   c. Drug safety is of particular concern due to the fact that elderly patients tend to have reduced drug metabolizing capability, take multiple drugs, and have comorbidities. This increases the risk of problems due to drug-drug interactions and side effects.

VIII Regulations Governing the Development of New Drugs

A. In 1962, Congress passed the **Kefauver–Harris Amendment** (which requires proof of drug efficacy) **to the Food, Drug, and Cosmetic Act of 1938** as a result of thalidomide toxicity that occurred in Europe.

1. The 1938 Food, Drug, and Cosmetic Act required that drugs be safe and pure, but it did not require that they be effective.
2. **The Food and Drug Administration (FDA)** was charged with regulating drugs.
3. **Procedures** were developed **for testing** new drugs. The procedures include animal studies, an Investigational New Drug (IND) application for permission to test the drug in humans, human studies, and a New Drug Application (NDA) for permission to market the drug (Table 1-1).

B. THE ANDA (Abbreviated New Drug Application) was established so that it is only necessary to demonstrate bioequivalence for a generic form of an approved drug.

C. PRESCRIPTIONS are required to dispense drugs that are:

1. **In the NDA Phase** of development
2. **Toxic**

TABLE 1-1 PROCEDURES FOR DEVELOPMENT OF NEW DRUGS (ESTABLISHED BY THE KEFAUVER–HARRIS AMENDMENT, 1962)

1. **Animal studies** are initially performed to determine the activity and toxicity in more than one species.
2. An **IND application** is submitted to the FDA.
3. **Clinical phases** are begun.
   - **Phase 1** involves studies of kinetics in approximately 10 healthy volunteers.
   - **Phase 2** involves studies of the dosage range, effectiveness, and toxicity in approximately 100 patients, utilizing single- or double-blind methods.
   - **Phase 3** involves studies of the same parameters in approximately 1000 patients. Special attention is paid to toxicities with low frequencies.
   - The **NDA** must be approved by the FDA.
   - **Phase 4** (NDA Phase) is a monitored release of the new drug after FDA approval to many physicians to detect rare toxicities.

FDA = Food and Drug Administration; IND = Investigational New Drug; NDA = New Drug Application

3. **Habit forming.** These drugs are divided into schedules based on their **potential for abuse,** as required by the Controlled Substances Act of 1970.
   a. **Schedule C-I drugs** are drugs of abuse with **no clinical use.**
   b. The others are **clinically useful.**
      i. **Schedule C-II** drugs are highly abused.
      ii. **Schedule C-III** drugs are less commonly abused.
      iii. **Schedule C-IV** drugs are even less commonly abused.
      iv. **Schedule C-V** drugs have minor potential for abuse and may even be available over the counter.

Chapter **2**

Peripheral Neuropharmacology

I Overview of the Autonomic Nervous System

A. This part of the peripheral nervous system **regulates the activity of cardiac muscle, smooth muscle,** and **exocrine glands.** It has two major divisions.

1. The parasympathetic nervous system refers to the division of the autonomic nervous system arising from the **brainstem** and the **sacral region** of the spinal cord.

a. **Acetylcholine (ACh)** is the neurotransmitter at **both the ganglionic and neuroeffector synapses** (Figure 2-1).

b. The **receptors** activated by ACh in the ganglion are **nicotinic (N) cholinoceptors,** and those in the neuroeffector junction are **muscarinic (M) cholinoceptors.**

2. The sympathetic nervous system refers to the division of the autonomic nervous system arising from the **thoracic and lumbar** regions of the spinal cord.

a. **ACh** is the neurotransmitter in the **ganglionic synapse; norepinephrine (NE)** is the neurotransmitter at the **neuroeffector synapse. Exceptions** include:

i. N-cholinergic innervation of the **adrenal medulla,** which has no postganglionic cell. NE and epinephrine are released directly into the bloodstream.

ii. Sympathetic dopaminergic innervation of **renal blood vessels.**

iii. Sympathetic M-cholinergic innervation of some **sweat glands** and some **muscle blood vessels.** These cells lack parasympathetic innervation.

b. The **receptors** in the ganglion are **N-cholinoceptors** and those at the neuroeffector junction are **α- and β-adrenoceptors.**

B. The **synthesis and breakdown** of **neurotransmitters** in the autonomic nervous system have been studied in detail.

1. ACh is synthesized in the nerve terminal from **choline and acetyl coenzyme A by choline acetyltransferase.**

a. It is then **stored in vesicles** with peptides and ATP.

b. In response to depolarization of the neuron, **calcium-induced membrane-vesicle fusion** leads to **ACh release into the synapse.**

c. After it is released, ACh is broken down to choline and acetate by cholinesterases.

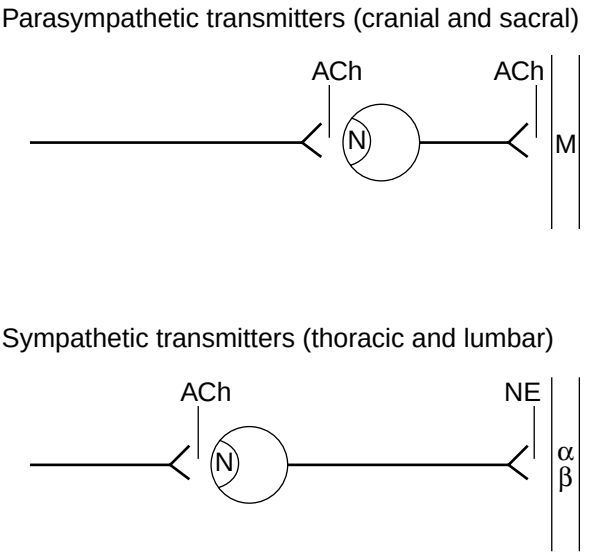
2. NE synthesis involves multiple steps (Figure 2-2).

a. **Tyrosine hydroxylase** is the **rate-limiting step** in the synthesis; it is also the site **for negative feedback inhibition** by NE.

b. **Dopamine (DA)** is taken up into the granule and **metabolized to NE by the granular enzyme DA β-hydroxylase.**

c. NE is complexed to ATP and chromogranins in the granule.

d. Released **NE** can be **taken back up into the nerve ending (reuptake);** it can be **metabolized;** or it can **diffuse away from the synapse.**



● **Figure 2-1** Neurotransmitters in the parasympathetic and sympathetic nervous systems. Important exceptions in the sympathetic nervous system include (1) sweat glands, which have M receptors; (2) renal vascular smooth muscle, which has D_1 dopamine receptors; and (3) the adrenal medulla, which has no postganglionic cell. N = nicotinic cholinoceptors, M = muscarinic cholinoceptors, α = α-adrenoceptors, β = β-adrenoceptors. ACh = acetylcholine; NE = norepinephrine

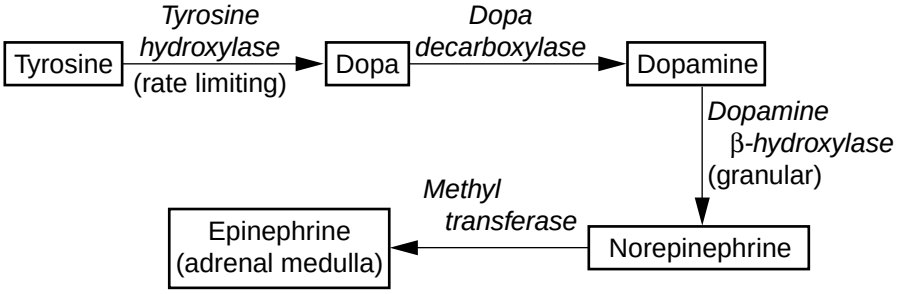
i. **Reuptake** is the most important mechanism for termination of NE action.
ii. **Cocaine** or **tricyclic antidepressants block reuptake** of NE, thereby enhancing the neurotransmitter effects.

e. **Catechol-O-methyltransferase (COMT)** and **monoamine oxidase (MAO) convert NE to methoxyhydroxymandelic acid (vanillylmandelic acid, VMA).** VMA accounts for 90% of the NE and NE metabolites found in the urine (Figure 2-3).

f. **Cells that produce epinephrine (EPI) have a methyltransferase** that **converts NE to EPI.**

C. The **effects of sympathetic and parasympathetic nerve stimulation** are listed in Table 2-1. Many of the effects of the autonomic drugs can be predicted from a thorough understanding of this table.

1. Parasympathetic and sympathetic responses are coordinated; one is generally decreased when the other is increased.

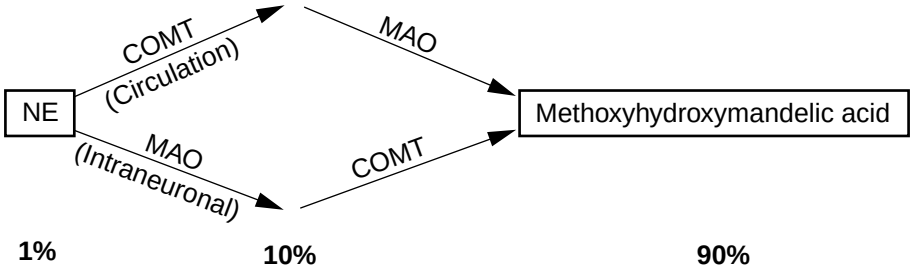


● **Figure 2-2** Synthesis of norepinephrine.

TABLE 2-1 EFFECTS OF AUTONOMIC NERVE ACTIVITY ON ORGAN FUNCTION

Organ	Sympathetic Nerve Activity	Parasympathetic Nerve Activity
Eye		
Radial muscle	α_1-contracts (mydriasis)	—
Circular muscle	—	M-contracts (miosis)
Ciliary muscle	—	M-contracts
Heart		
SA node	β_1-accelerates	M-decelerates
Conduction	β_1-accelerates	M-decelerates
Contractility	β_1-increases	M-decreases
Blood Vessels		
Skin, splanchnic vessels	α-constricts	—
Skeletal muscle	α-constricts	—
	β_2-dilates	—
	M-dilates	—
	DA-dilates	—
Renal, mesenteric vessels Endothelium	—	M*-releases EDRF
Bronchioles		
Smooth muscle	β_2-dilates	M-constricts
Gastrointestinal tract		
Gut contractility	β_2-reduces	M-increases
Sphincters	α_1-contracts	M-relaxes
Secretion	—	M-increases
Genitourinary tract		
Bladder motility	β_2-reduces	M-increases
Sphincter	α_1-contracts	M-relaxes
Pregnant uterus	β_2-relaxes	—
	α-contracts	M-contracts
Penis[+]	α-ejaculation	M-erection
Skin		
Pilomotor smooth muscle	α-contracts	—
Sweat glands	M-increases	—
Metabolic functions		
Hepatic gluconeogenesis	α,β_2-increases	—
Hepatic glycogenesis	α,β_2-increases	—
Lipolysis	β_3-increases	—
Glands		
Salivary secretions	α_1-thick	M-thin
Lacrimal, respiratory secretions	—	M-increases
Adrenal gland		
EPI and NE secretion	N-increases	—
Kidney		
Renin release	β_1-increases	—

*Most blood vessels have uninnervated muscarinic cholinoceptors. Relaxation involves release of endothelium-derived relaxing factor (EDRF) from the endothelium in response to circulating muscarinic agonists.
[+]A mnemonic for remembering that erection is parasympathetic and ejaculation is sympathetic is "point and shoot."
α = α-adrenoceptors; β = β-adrenoceptors; DA = dopamine; EPI = epinephrine; M = muscarinic cholinoceptors; N = nicotinic cholinoceptors; NE = norepinephrine; SA = sinoatrial; — = no effect



● **Figure 2-3** Metabolism of norepinephrine by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). The percentages represent the proportions of each form found in the urine. NE = norepinephrine

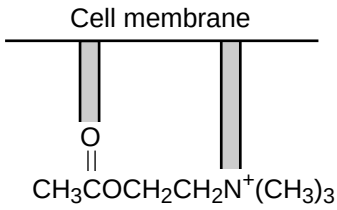
2. **Presynaptic receptors can modulate neurotransmitter release** (e.g., autoreceptors that decrease transmitter release in response to binding that same transmitter).
3. **Postsynaptic receptors can be up- or down-regulated** in response to previous decreases or increases in neurotransmitter release, respectively.

II Parasympathomimetics

A. Drugs in this class produce effects similar to activation of the parasympathetic nervous system.

B. SPECIFIC DRUGS

1. **ACh** acts at **N-cholinoceptors** and **M-cholinoceptors.**
   a. There are **two binding sites** for ACh on the ACh receptors. One site binds the **quaternary nitrogen** of ACh, and the second site binds the **carbonyl oxygen** (Figure 2-4).
   b. ACh has some major **disadvantages** as a drug.
      i. It **activates all cholinoceptors in most internal organs,** leading to **many side effects** from administration.
      ii. It has a **short duration of action** due to rapid metabolism by cholinesterases.
2. **Quaternary ammonium analogs of ACh** are available that have slightly different properties than ACh (Table 2-2).
   a. **Methacholine** is a hindered acetylmethylcholine ester that is hydrolyzed more slowly by acetylcholinesterase compared to ACh. It is used for diagnosing bronchial airway hyperactivity in asthma.



● **Figure 2-4** Binding of acetylcholine to the cholinoceptor. The two bars represent the binding sites on the receptor.

TABLE 2-2 PROPERTIES OF ACh AND ACh ANALOGUES

	Metabolized by Cholinesterases	Nicotinic Activity	GI Activity	CV Activity
ACh	+++	+	++	+++
Methacholine	+	–	+	+++
Carbachol	–	+	+++	+
Bethanechol (*Urecholine*)	–	–	+++	+

ACh = acetylcholine; CV = cardiovascular; GI = gastrointestinal

b. **Carbachol** and **bethanechol** are choline carbamates that have **longer durations of action** than ACh and methacholine.
   i. Bethanechol **(***Urecholine***)** is used to treat **gastrointestinal (GI) atony** and **urinary retention** due to **bladder atony.**
   ii. Carbachol is used topically to treat **glaucoma.**

3. Two alkaloids have parasympathomimetic activity; they are stable to hydrolysis by acetylcholinesterase.
   a. **Muscarine** is a **quaternary amine** that acts only on muscarinic receptors.
   b. **Pilocarpine** is a **tertiary amine** that acts only on muscarinic receptors.
      i. As a tertiary amine, it is **more readily absorbed,** and it **penetrates the blood–brain barrier to** reach the CNS.
      ii. Its main use is to **treat glaucoma** (*Pilocar*).
      iii. **Pupillary constriction** can be induced with pilocarpine.
      iv. It is very effective at **enhancing salivary secretions** in **xerostomia** (*Salagen*).

C. The effects of all parasympathomimetics are **similar to the effects of parasympathetic nerve stimulation** (see Table 2-1).

1. Parasympathomimetics also **activate uninnervated cholinoceptors** (e.g., M-cholinoceptors in blood vessels to lower blood pressure) and M-cholinoceptors at sympathetic cholinergic synapses.

2. The dilating effect of parasympathomimetics **on blood vessels is mediated by the release of endothelium-derived relaxing factor (EDRF),** which is probably nitric oxide, from the endothelium. An intact endothelium is required for these effects to occur.

3. An **overdose** of a parasympathomimetic leads to
   a. **A marked fall in blood pressure**
   b. **An increase in heart rate,** mediated via **reflexes** induced by the fall in blood pressure. The fall in blood pressure reduces afferent baroreceptor activity, which leads to an increase in efferent sympathetic tone to the heart.
   c. Activation of M-cholinoceptors at many sites, which induces a **DUMBELS syndrome** composed of
      i. ***D*efecation, diarrhea**
      ii. ***U*rination**
      iii. ***M*iosis, muscle weakness**
      iv. ***B*ronchoconstriction**
      v. ***E*mesis**
      vi. ***L*acrimation**
      vii. ***S*alivation, seizures, sweating**

III Cholinesterase Inhibitors

A. These drugs bind to and **inhibit acetylcholinesterases,** thereby **increasing ACh concentration** in the cholinergic synapses.

1. Cholinesterase inhibitors are **indirect parasympathomimetics** because they **do not bind to ACh receptors.**
2. **Butyrylcholinesterases (pseudocholinesterases) are also inhibited by cholinesterase inhibitors,** but the function of these cholinesterases is unknown.
3. The mechanism of binding to cholinesterase varies; some cholinesterase inhibitors **bind both the esteratic (E) and anionic (A) sites,** and **some bind only to one site** (see Figure 2–4).
4. The quaternary amines (e.g., neostigmine) will not induce CNS effects because the quaternary structure precludes passage across the blood–brain barrier. However, tertiary amines (e.g., physostigmine) are able to enter the CNS.
5. Characteristics of the important cholinesterase inhibitors are summarized in Table 2-3.

B. THE CARBAMATES (e.g., physostigmine, neostigmine) and the noncarbonate compound **edrophonium** are **reversible inhibitors** of cholinesterases.

1. **Edrophonium** can be used to **diagnose myasthenia gravis** or to **differentiate** a **myasthenic crisis** from a **cholinergic crisis.** Edrophonium is very short acting, so myasthenia gravis is treated long term with pyridostigmine or neostigmine.
2. **Competitive neuromuscular blockade** can be reversed with neostigmine.
   a. To **reduce the parasympathetic side effects of the cholinesterase inhibitors, atropine** should also be administered.
   b. Atropine has no effect on the skeletal neuromuscular junction, because there are no M-cholinoceptors at this site.
3. **Intestinal and bladder atony** can be treated with physostigmine or neostigmine.
4. **Alzheimer's disease** can be somewhat reduced with **tacrine** (*Cognex*) or **donepezil** (*Aricept*). Tacrine was the prototype drug of this class used in Alzheimer's, but newer drugs like donepezil are preferred due to the hepatotoxicity of tacrine.
5. **Paroxysmal supraventricular tachycardia (PSVT)** can be terminated with edrophonium.
6. **Anticholinergic poisoning** can be diagnosed and treated with cholinesterase inhibitors.

C. ORGANOPHOSPHATES are **very lipid soluble.** They **irreversibly inhibit cholinesterases** by covalently binding to a serine residue in the active site of these enzymes. This group includes:

1. **Diisopropyl phosphorofluoridate (DFP, isofluorphate),** the prototype.
2. **Echothiophate** (*Phospholine*), which can decrease ocular pressure due to **glaucoma.**

TABLE 2-3 PROPERTIES OF VARIOUS CHOLINESTERASE INHIBITORS

Inhibitor	Binding Sites	Chemical Properties
Physostigmine (*Antilirium*)	E & A	Tertiary carbamate
Neostigmine (*Prostigmin*)	E & A	Quaternary carbamate
Pyridostigmine (*Mestinon*)	E & A	Quaternary carbamate
Edrophonium (*Tensilon*)	A	Quaternary (noncarbamate), short duration
Organophosphates	E	Irreversible

A = anionic; E = esteratic

3. **Malathion and parathion**
   a. They must be metabolized to their active forms, **malaoxon** and **paraoxon.**
   b. They are more toxic to insects than to humans because humans detoxify them more rapidly; thus they are effective as **insecticides.**

D. EFFECTS

1. The effects of the cholinesterase inhibitors are primarily **muscarinic** in nature.
   a. A **DUMBELS** syndrome is induced. (See Section II.)
   b. **Nicotinic effects** occur **only at high doses.**
2. **An overdose of cholinesterase inhibitors** causes **death** from **respiratory insufficiency.**
   a. Reduced respiratory function is due to
      i. **Increased bronchial secretions**
      ii. **Bronchoconstriction**
      iii. **Central respiratory depression**
      iv. **Depolarizing neuromuscular blockade**
   b. **Specific antidotes** used for poisoning by the cholinesterase inhibitors are
      i. **Atropine at high dosages,** which blocks the muscarinic effects of the accumulated ACh
      ii. **Pralidoxime (2-PAM)** (*Protopam*), which can **reactivate the cholinesterases** that have been inhibited by an organophosphate
         (a) It **must be administered within a few hours after the exposure,** because an "aging" process occurs, and the organophosphate–cholinesterase complex becomes insensitive to 2-PAM.
         (b) Pralidoxime will have **no effect on poisoning from the carbamates.**
3. **Chronic exposure** to the organophosphates leads to **delayed neurotoxicity** due to **demyelination of motor neurons.**
4. **Contraindications** for the use of cholinesterase inhibitors include:
   a. **Asthma**
   b. **Peptic ulcers**

IV Parasympathetic Blocking Drugs (Antimuscarinics)

A. Drugs in this class **block the effects of the parasympathetic nervous system.**

1. The **effects of ACh are reversed** (ACh reversal) by muscarinic antagonists.
   a. The **muscarinic vasodilating actions** of ACh are **blocked.**
   b. The **nicotinic (ganglion) vasoconstricting actions** from high doses of ACh are **unmasked.**
2. **Atropine** is a **competitive, surmountable antagonist.** It blocks M_1-, M_2-, and M_3-cholinoreceptors.
3. **Scopolamine** is similar to atropine except there are more CNS effects, which may occur even at therapeutic doses.
4. Both are **tertiary amines,** so they will penetrate into the CNS.

B. The **effects, uses,** and **side effects** are summarized in Table 2-4. Note that atropine will not increase blood pressure because there is no parasympathetic tone to the blood vessels.

C. Both anticholinergics and phenylephrine, an α_1-adrenoceptor agonist, induce mydriasis, but **phenylephrine will not induce cycloplegia** (loss of accommodation).

D. These drugs have a **large therapeutic index.**

TABLE 2-4 EFFECTS, USES, AND SIDE EFFECTS OF THE PARASYMPATHETIC BLOCKING DRUGS

Effects	Uses	Side Effects
Increase heart rate (may be an initial decrease due to vagal nuclei activity)	Bradycardia that is vagally mediated (e.g., digoxin therapy)	Tachycardia
Pupillary dilation and cycloplegia	Eye exam (tropicamide [*Mydriacyl*])	Blurred vision Photophobia Angle closure glaucoma
Bronchodilation	COPD, asthma (quaternary: ipratropium [*Atrovent*])	
Decrease gut motility	Antispasmodic [propantheline (*Pro-Banthine*)]	Constipation
Decrease bladder contractions	Urge incontinence (tolterodine [*Detrol*])	Urinary retention
Decrease secretions	Preanesthetic medication	Dry mouth
Sedative	Preanesthetic medication	
Other	Reduce motion sickness (scopolamine) Parkinson's disease (trihexyphenidyl [*Artane*]) Antagonize poisoning from cholinesterase inhibitors and muscarine	Drowsiness (scopolamine)

1. **Side effects** include the following:
   a. **Flushing** (red as a beet)
   b. **Blurred vision, cycloplegia** (blind as a bat)
   c. **Xerostomia, anhydrosis** (dry as a bone)
   d. **Hyperthermia** (hot as a hare)
   e. **Confusion, delirium, hallucinations** (mad as a hatter)
2. High doses produce **life-threatening toxicity only in children,** who seem to be more sensitive to the drugs.
   a. The side effects in Table 2-4 will be accentuated.
   b. **Hot skin and fever** occur, due to direct vasodilation.
3. **Adult anticholinergic poisoning** is more common with H_1 antihistamines, tricyclic antidepressants, and phenothiazines.
4. The antidote for anticholinergic poisoning is a **cholinesterase inhibitor** (e.g., physostigmine).

V Ganglionic Blocking Drugs

A. Drugs in this class **competitively inhibit nicotinic cholinoceptors in the ganglion,** which leads to ganglionic blockade. These drugs have no effect on the neuromuscular nicotinic cholinoceptors.

1. **Hexamethonium and trimethaphan (***Arfonad***)** are **polar amines.**
2. Trimethaphan has a very short duration of action and is thus useful to treat hypertensive crises. Blockade of sympathetic ganglia by trimethaphan reduces peripheral vascular resistance and lowers blood pressure.

B. THE MAJOR LIMITATION of the ganglionic blocking drugs is that they **inhibit both sympathetic and parasympathetic ganglia.**

1. This results in **many autonomic side effects.**
2. **Less toxic drugs are available** for the treatment of **essential hypertension.**

C. When both sympathetic and parasympathetic ganglia are blocked by hexamethonium, the net effect will be equivalent to blockade of the dominant autonomic system for each tissue.

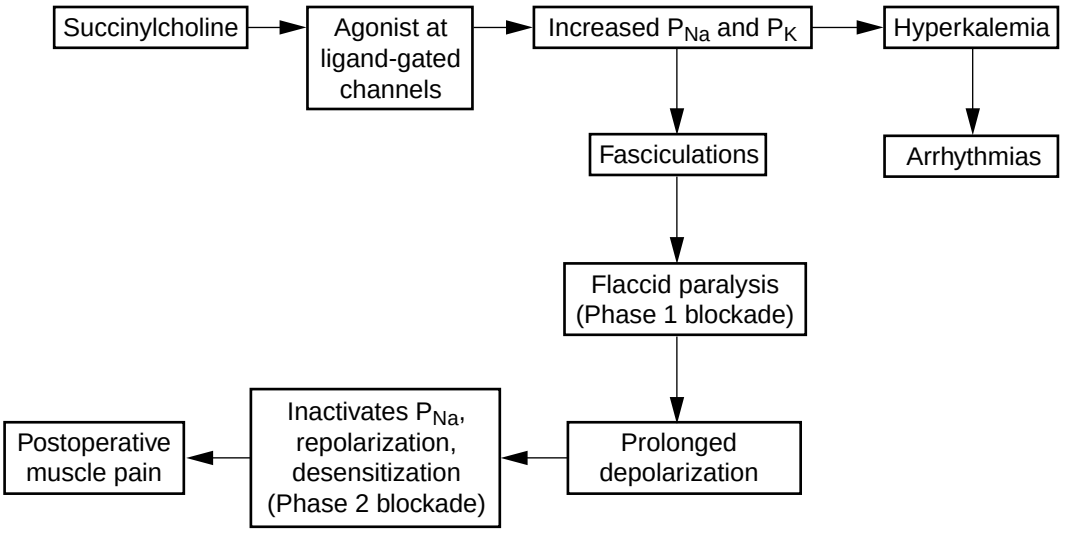
D. There is no therapeutic use for **nicotine** except in **smoking cessation products.** Nicotine activates **nicotinic receptors** in the
1. **Sensory nerve endings**
2. **Ganglia**
3. **Adrenal medulla**
4. **Neuromuscular junction,** leading to depolarization block

VI Neuromuscular Blocking Drugs

A. In somatic nerves, there are no ganglia, and acetylcholine binds to nicotinic receptors. These drugs **block skeletal neuromuscular transmission, thereby inducing paralysis.**

B. **COMPETITIVE NICOTINIC ANTAGONISTS** are **quaternary amines** that bind nicotinic cholinoceptors in the muscle end-plate region.
1. **The end-plate potential (EPP) is reduced** below the threshold for the muscle action potential.
2. The EPP must be reduced to 20% of the normal amplitude for muscle paralysis to occur.
   a. A **reduction of the safety factor** and an increase in the sensitivity to competitive neuromuscular blocking drugs occurs with
      i. **Myasthenia gravis**
      ii. **General anesthetics,** which reduce the sodium and potassium permeability changes at the end-plate
      iii. **Aminoglycoside antibiotics,** which reduce the release of ACh
      iv. **Calcium channel blockers**
   b. When given at low doses, an **increase in the safety factor** and a reversal of competitive neuromuscular blockade can be induced with the **cholinesterase inhibitors** (e.g., neostigmine). However, at high doses, cholinesterase inhibitors cause a depolarizing blockade due to increased concentrations of ACh in the end-plate, similar to succinylcholine.
3. All the competitive neuromuscular blocking drugs act by the same mechanism (blocking ACh binding), but they do have other properties that are different
   a. ***d*-Tubocurarine**
      i. **Releases histamine,** which can lead to bronchospasm and lower blood pressure
      ii. **Blocks ganglionic nicotinic receptors,** which can also lower blood pressure
   b. **Pancuronium** (*Pavulon*) induces a vagal blockade, which can increase heart rate and increase blood pressure.
   c. **Atracurium** (*Tracrium*) is very short acting.
   d. **Vecuronium** (*Norcuron*) has no cardiovascular side effects.

C. **DEPOLARIZING** neuromuscular blocking drugs act like ACh but are not broken down as quickly. **Succinylcholine** (*Anectine*) is a quaternary amine.



● **Figure 2-5** Effects of depolarizing neuromuscular blocking drugs (e.g., succinylcholine). P_{Na} = sodium permeability. P_K = potassium permeability

1. It binds to and **activates the nicotinic cholinoceptors.**
   a. **Phase 1 depolarization block** is the major initiator of muscle paralysis (Figure 2–5). It involves **opening of sodium channels, depolarization, and fasiculations,** followed by **flaccid paralysis.**
   b. With long periods of paralysis, **Phase 2 block** characterized by **receptor desensitization** develops. **Sodium channels close and are refractory to further stimulation.**
2. Succinylcholine is **metabolized by butyrylcholinesterases** in the serum.
   a. **Succinylcholine apnea** can occur if a patient has a **genetic** defect that results in low butyrylcholinesterase activity.
      i. **Excessive paralysis will be induced by a standard dose,** because less of the drug is metabolized before reaching the end-plate region.
      ii. **Paralysis of the respiratory muscles** (apnea) occurs with an overdose.
   b. There is **no antidote** for succinylcholine paralysis.
      i. Cholinesterase inhibitors will increase the paralysis by slowing the breakdown of succinylcholine and ACh.
      ii. Patients should be **ventilated** until their respiratory function returns.
3. The major advantage of succinylcholine is its **rapid onset and short duration** of paralysis.

D. The primary **uses** of neuromuscular blocking drugs are as an adjunct during **intubation** and for **muscle relaxation during surgery.**

E. Other drugs can affect muscle function by various mechanisms.
1. **Hemicholinium** blocks the uptake of choline and leads to depletion of ACh in the motor nerve terminal.
2. **Botulinum toxin** (*Botox*) **blocks the release of ACh, which induces muscle paralysis.** It is used to reduce motor unit activity in eye and facial muscles.
3. **α-Bungarotoxin** binds irreversibly to the neuromuscular nicotinic cholinoceptor.
4. **Dantrolene** (*Dantrium*) **reduces calcium release from the sarcoplasmic reticulum** in skeletal muscle. This reduces the spasticity from **malignant hyperthermia** (e.g., as induced by inhalation anesthetics and neuromuscular blocking drugs).

5. **Baclofen** (*Lioresal*) is **a central muscle relaxant that activates $GABA_B$ receptors** and thereby decreases spasticity.

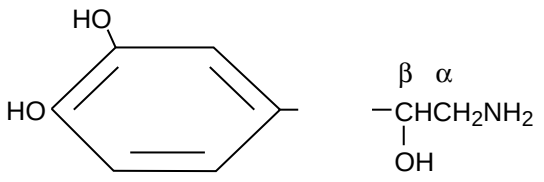
VII Sympathomimetics

A. Drugs in this class **mimic the effects of the sympathetic nervous system** by activating adrenoceptors or inducing the release of endogenous NE.

1. **α-Receptors** preferentially bind **epinephrine ≥ norepinephrine >> isoproterenol.**
   a. **α_1 Receptors** are present on many target organs. Binding of ligand to these receptors activates a G_q protein, resulting in formation of IP_3 and DAG.
   b. **α_2-Receptors** are present on **presynaptic adrenergic neurons** and **beta islet cells** in the pancreas. Binding of ligand to α_2-receptors activates a G_i protein, decreasing the intracellular concentration of cAMP.
2. **β-Receptors** preferentially bind **isoproterenol > epinephrine ≥ norepinephrine.** Ligand binding to β-receptors activates a G_s protein, increasing the intracellular concentration of cAMP.

B. There are two groups of sympathomimetics.

1. **Catecholamines are direct sympathetomimetics** (norepinephrine agonists) that have a **catechol** (3,4-dihydroxybenzene) in their structure (Figure 2-6).
   a. Important **catecholamines** are
      i. **Norepinephrine (NE),** an **α- and β_1-agonist**
      ii. **Epinephrine (EPI),** an **α-, β_1- and β_2-agonist**
      iii. **Isoproterenol (ISO),** a **β_1- and β_2-agonist**
      iv. **Dobutamine** (*Dobutrex*), a **β_1-agonist**
      v. **Dopamine (DA),** an **α-, β_1-, and D-receptor agonist**
   b. **Increased alkyl substitution** on the **ethylamine nitrogen increases selectivity for beta receptors** over alpha receptors **(ISO > EPI > NE).**
   c. The ***l*-form** of the catecholamine is active.
   d. **Administration by parenteral injection or inhalation** is used because of rapid metabolism in the gut and first-pass metabolism.
2. **Phenylethylamines** do not have the catechol structure, and thus they are **less readily metabolized** by COMT and MAO. They are also **more effective when given orally.**
   a. **Phenylephrine** (*Neo-Synephrine*) and **methoxamine** (*Vasoxyl*) are direct sympathomimetic **α_1-agonists.**
   b. **Clonidine** (*Catapres*) is a direct **α_2-agonist.**
   c. **Terbutaline** (*Bricanyl, Brethine*), **albuterol** (*Proventil, Ventolin*), **salmeterol** (*Serevent*), and **ritodrine** (*Yutopar*) are direct **β_2-agonists.**



3,4-Dihydroxybenzene (catechol) **Ethylamine**

● **Figure 2-6** General structure of catecholamines, as illustrated with NE.

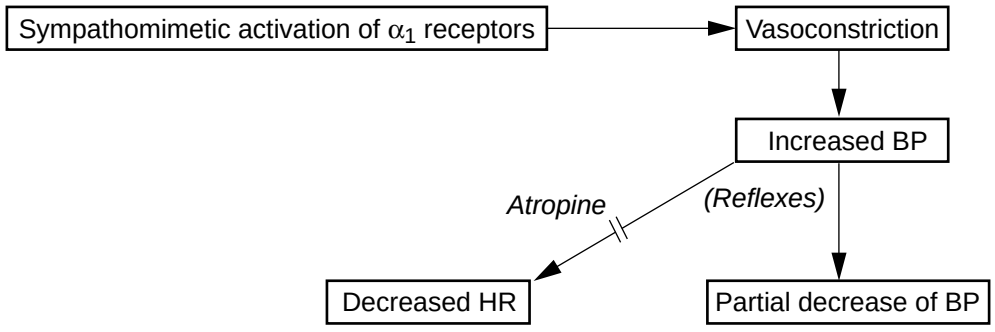
d. **Tyramine** and the **amphetamines** are **indirect** sympathomimetics.
   i. This means that they induce the release of endogenous NE, and it is the NE that activates the α- and β-adrenoceptors.
   ii. Amphetamine has a CNS stimulatory effect and increases blood pressure.
   iii. Tyramine is a byproduct of tyrosine metabolism and can cause dangerous increases in blood pressure in patients who are taking MAO inhibitors.
   iv. **Effects** of indirect sympathomimetics will be **reduced** by the following procedures, which will not affect or will even increase the effects of direct sympathomimetics.
      (a) **Cocaine and tricyclic antidepressants** block the uptake of tyramine and NE into the adrenergic nerve ending, an action that reduces the effect of tyramine and augments the effects of exogenously administered NE.
      (b) **Denervation, reserpine, and guanethidine** deplete the endogenous catecholamines; thus, the indirect agonists become ineffective, and the effects of exogenous NE will be unchanged or enhanced.

e. **Ephedrine** is a **mixed adrenergic agonist** that has **both direct and indirect sympathomimetic properties.**
   i. Ephedrine has similar effects as EPI.
   ii. Abuse of ephedrine can cause life-threatening cardiovascular effects.

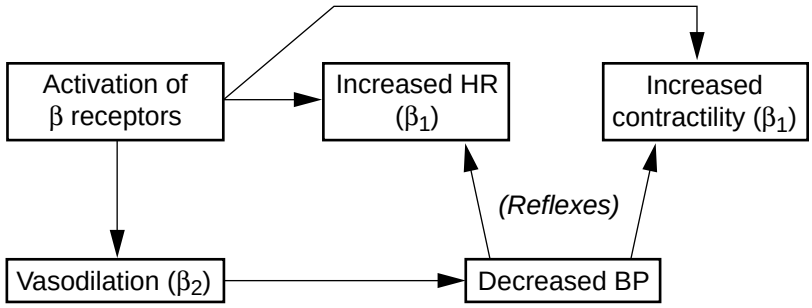
C. The effects of each agonist will depend on the types of receptors that are activated.

1. NE (levarterenol), an α_1- and β-agonist, will induce (Figure 2-7):
   a. An **increase in blood pressure** due to **α_1**-stimulation without a **β**-agonist effect, making it useful for treating shock.
   b. A **reflex reduction in heart rate.** This indicates that the reflex baroreceptor effects are more important than the direct effects of NE on the heart. The reduction of heart rate can be blocked by atropine.

2. EPI is an agonist at **α-, β_1-, and β_2-adrenoceptors.**
   a. **At low doses** it induces **little change of mean blood pressure** (α_1-vasoconstricting and β_2-vasodilating effects balance out); thus **heart rate will be increased due to direct β_1 effects on the heart.**
   b. **At high doses, the α_1-vasoconstricting effect will predominate,** mean blood pressure will increase, and heart rate will be reflexly reduced.
   c. **Bronchodilation** occurs due to binding of EPI to β_2-receptors on bronchial smooth muscle. EPI can thus be used to treat **asthmatic emergencies** and **anaphylactic shock.**
   d. EPI **increases blood glucose concentration** and **lipolysis** by increasing glucagon release, gluconeogenesis, and glycogenolysis.



● **Figure 2-7** Effects of α-adrenoceptor activation on blood pressure and heart rate. The reflex effects on the heart (blocked by atropine) will predominate over the direct β effects, if norepinephrine is the agonist.



● **Figure 2-8** Effects of β-adrenoceptor activation on blood pressure and heart rate. Both the reflex and direct effects result in an increase in heart rate and contractility. BP = blood pressure; HR = heart rate

3. **ISO, a β-agonist,** will induce (Figure 2-8):
   a. A **decrease in blood pressure (β_2)** due to dilation of skeletal muscle arterioles.
   b. **Large increases in heart rate and contractility,** due to both direct (β_1) and reflex effects.
   c. **Bronchodilation** due to β_2-receptor agonism.
4. **DA, an agonist at α-, β_1-, and D-receptors,** will induce:
   a. **Increased cardiac contractility and heart rate** due to stimulation of **β_1-receptors** at intermediate doses**.**
   b. **Vasoconstriction of skeletal muscle blood vessels** and **increased blood pressure** due to stimulation of **α receptors** at high doses
   c. **Vasodilation of renal and mesenteric blood vessels** due to stimulation of **D receptors,** making it useful for treating shock

E. The **effects, uses,** and **side effects** for the various sympathomimetics are summarized in Table 2–5.

VIII α-Adrenoceptor Antagonists

A. Drugs in this class **inhibit α-adrenoceptors,** thereby **reducing the α-effects of endogenously released NE.**

B. **NONSELECTIVE** antagonists block both α_1- and α_2-adrenoceptors.
1. The properties of the various α-antagonists are quite different.
   a. **Phenoxybenzamine** (*Dibenzyline*) is an **alkylating agent** that forms a reactive intermediate.
      i. A **covalent** (irreversible) interaction with α-receptors results in **competitive, insurmountable antagonism.**
      ii. Phenoxybenzamine is very irritating when given subcutaneously or intramuscularly, and therefore **can only be given orally or intravenously.**
      iii. Although it blocks alpha receptors, phenoxybenzamine is not useful as an antihypertensive due to induction of reflex tachycardia and increased cardiac output.
   b. **Phentolamine** (*Regitine*) is a **competitive, surmountable antagonist.**
      i. The **duration of action is short.**
      ii. It is effective after oral or parenteral administration.
   c. **Ergot alkaloids** are α-antagonists, vasoconstrictors, and oxytocics.
      i. **Ergotoxine** is the most potent **α-antagonist.**
      ii. **Ergotamine** is the most potent **vasoconstrictor.** The vasoconstriction is unrelated to autonomic receptor actions.
      iii. **Ergonovine** is the most potent **oxytocic.**

TABLE 2-5 EFFECTS, USES, AND SIDE EFFECTS FROM ACTIVATION OF ADRENERGIC RECEPTORS

Drug	Receptor Specificity	Effects	Uses	Side Effects
Epinephrine (EPI)	α_1, α_2, β_1, β_2	Vasoconstriction (α) Reduce intraocular pressure (α) Bronchodilation (β_2)	Prolong local anesthesia (α) Glaucoma(α) Anaphylactic shock (β_2)	Anxiety, Arrhythmias, Hypertension
Norepinephrine (NE)	α_1, α_2, β_1	Vasoconstriction (α)	Treatment of shock (α)	Hypertension, Reflex bradycardia
Isoproterenol (ISO)	β_1, β_2	Increased myocardial contractility (β_1)	Acute heart failure (β_1)	Arrhythmias, Tachycardia
Dopamine (DA)	α_1, β_1, D	Dilated renal and mesenteric vessels (D) Vasoconstriction at high doses (α_1) Increased myocardial contractility (β_1)	Treatment of shock (α_1, D) Congestive heart failure (β_1)	Arrhythmias, Hypertension, Nausea
Dobutamine	β_1	Increased myocardial contractility (β_1)	Congestive heart failure (β_1)	Arrhythmias, Tachycardia
Phenylephrine Methoxamine	α_1	Vasoconstriction (α_1) Mydriasis without cycloplegia (phenylephrine-α_1)	PSVT (α_1) Eye exam (phenylephrine-α_1)	Headache Reflex bradycardia
Clonidine	α_2	Inhibits sympathetic vasomotor centers (α_2)	Hypertension (α_2)	Xerostomia, Constipation
Terbutaline Albuterol Salmeterol Ritodrine	β_2	Bronchodilation (β_2) (short acting: terbutaline, albuterol; long acting: salmeterol) Uterine relaxation (ritodrine-β_2)	Bronchospasm, asthma (β_2) Premature labor (ritodrine-β_2)	Muscle tremor Angina
Amphetamine Ephedrine	α, β, CNS	CNS stimulant (CNS) Vasoconstriction (α_1)	ADHD Hypotension, Nasal decongestant	Arrhythmias Hypertension, Tachycardia (α, β)

DA = dopamine; EPI = epinephrine; ISO = isoproterenol; PVST = paroxysmal supraventricular tachycardia

2. When EPI is administered IV in the presence of an α-antagonist, the **normal pressor effect of EPI is reversed to a depressor effect.**
   a. α-Receptor activation by EPI, which normally increases blood pressure, is blocked.
   b. β_2-Receptor activation by EPI leads to a drop of blood pressure.
3. The effect of NE on blood pressure is decreased but not reversed by α-antagonists, because NE has much weaker β-agonistic effects than EPI.

4. Alpha antagonists have no effect on ISO, which is primarily a β-agonist.
5. The clinical **uses** of phenoxybenzamine and phentolamine are limited.
   a. **Pheochromocytoma** can be diagnosed and treated.
   b. **Peripheral vascular disease** can be treated.
   c. Blood pressure is reduced, but not by very much; thus, they are not used to treat essential hypertension. Also, **side effects** are more common than with other antihypertensive drugs.
      i. **Postural hypotension** results from
         (a) **Venule dilation**
         (b) **Impaired sympathetic reflexes** to the blood vessels
      ii. **Tachycardia** results from increased sympathetic reflexes to the heart. This effect is enhanced by the α_2-blockade (blockade of presynaptic inhibitory sites), which leads to increased NE release and increased NE effects at sites where β-receptors predominate (e.g., myocardium).
      iii. **Renin release is increased.**

C. The newer drugs are **selective α-antagonists.**

1. **Prazosin** (*Minipress*), **doxazosin** (*Cardura*), **tamsulosin** (*Flomax*), and **terazosin** (*Hytrin*) are selective **α_1-antagonists.**
   a. **Both arterioles and venules are dilated,** leading to reduced preload and afterload on the heart.
   b. Blood pressure is reduced with less tachycardia and less renin release than with nonselective antagonists.
   c. **Clinical indications** include
      i. **Essential hypertension** (prazosin, doxazosin, terazosin)
      ii. **Prostatic hypertrophy** (tamsulosin, doxazosin, terazosin)
   d. An important **side effect** is **first-dose syncope.**
2. **Yohimbine** is a selective **α_2-antagonist** with no demonstrated clinical usefulness.

IX β-Adrenoceptor Antagonists

A. Drugs in this class **inhibit β-adrenoceptors,** thereby **reducing the β-effects of endogenously released NE.**

B. β-Blockers are **structurally similar to catecholamines.**

1. They have **bulky alkyl** substitutions on the nitrogen and an **oxymethylene bridge** near the aromatic ring.
2. The ***l*-isomers** are the active forms.

C. THE NONSELECTIVE β-blockers inhibit both β_1- and β_2-adrenoceptors.

1. **Propranolol** (*Inderal*) is 90% bound to plasma proteins and is **rapidly metabolized** by the liver.
   a. The bioavailability is low ($F = 0.3$) due to first-pass metabolism.
   b. The IV dose is one third of the oral dose.
   c. The half-life is short, approximately 3 hours.
   d. An active metabolite, hydroxypropranolol, is formed.
2. The **effects, uses, side effects,** and **contraindications** of the β-blockers (e.g., propranolol) are listed in Table 2-6.
3. Other **nonselective β-blockers** have important differences from propranolol.
   a. **Nadolol** (*Corgard*) is nonselective, water soluble, and not metabolized, so the **half-life is long** (15 hours).

TABLE 2-6 EFFECTS, USES, SIDE EFFECTS, AND CONTRAINDICATIONS OF BETA-BLOCKERS

Effects	Uses	Side Effects	Contraindications
Decreased heart rate	Tachycardia Angina Hyperthyroid crisis	Bradycardia	
Prolonged AV conduction time	Arrhythmias (e.g. PSVT)	Slow AV conduction	Heart block
Decreased myocardial contractility	Angina Mild heart failure	Heart failure	Severe heart failure
Bronchoconstriction		Bronchospasm	Asthma
Decreased glycogenolysis		Hypoglycemia	Diabetes
Peripheral vasoconstriction		Vasoconstriction	Peripheral vascular disease Angina at rest
Decreased blood pressure	Hypertension Glaucoma Migraine	CNS depression Insomnia Nightmares Sudden withdrawal can increase BP and induce arrhythmias Sexual dysfunction	

AV = atrioventricular; BP = blood pressure; CNS = central nervous system; PSVT = paroxysmal supraventricular tachycardia

b. **Pindolol** (*Visken*) is nonselective with **intrinsic sympathomimetic activity (ISA).**
   i. It is a partial antagonist with β-agonistic activity.
   ii. Drugs with ISA induce less bradycardia and less dysregulation of carbohydrate and lipid metabolism.

c. **Labetalol** (*Normodyne, Trandate*) and **carvedilol** (*Coreg*) are nonselective with **α_1-blocking activity**. They decrease blood pressure with less change of heart rate and contractility than other β-blockers; produce peripheral vasodilation; and do not alter glucose or lipid levels in the blood.

D. SELECTIVE β_1-blockers (cardioselective) have weaker actions on the bronchi, making them more useful in patients with **asthma.** The β_1-selectivity is relative, however, so these drugs can still be dangerous when administered to asthmatics.

1. **Metoprolol** (*Lopressor*) is β_1-selective.
2. **Atenolol** (*Tenormin*) is β_1-selective and **water soluble,** which results in **fewer CNS effects.**
3. **Acebutolol** (*Sectral*) is β_1-selective with **ISA.**
4. **Esmolol** (*Brevibloc*) is β_1-selective and is rapidly metabolized by esterases **($t_{1/2}$ = 9 minutes),** making it useful for emergency therapy.

X Adrenergic Neuron-Blocking Drugs

A. These drugs have **no effects on adrenergic receptors.** Instead, they **reduce the release of NE from the postganglionic adrenergic neuron.**

B. RESERPINE (*Serpasil*) **depletes monoamines** (NE, DA, and serotonin [5-HT]); depletion of NE results in sympathetic blockade (e.g., lowering of blood pressure).

1. It acts by blocking **granular catecholamine uptake into intracellular vesicles.** Neuronal catecholamine uptake from the synapse is unaffected.
2. **The side effects** are very marked, including:
   a. **Profound psychological depression and sedation.** It must be used with caution when treating patients with a history of depression.
   b. **Extrapyramidal symptoms** from DA depletion

C. GUANETHIDINE (*Ismelin*) is transported to the site of action in the nerve terminal via the neuronal catecholamine transport mechanism. The effects are **blocked by uptake inhibitors** (e.g., cocaine and tricyclic antidepressants).
1. There is an **initial release of NE** from vesicles and a transient increase in blood pressure.
2. The **release is subsequently reduced** and depletion also occurs as guanethidine replaces NE in the vesicles.
3. The drug is very effective but has **prominent side effects,** including:
   a. **Symptoms of severe sympathetic block**
   b. **Severe postural hypotension**
   c. **Marked impotence** in males
   d. **Severe diarrhea**

D. α-METHYLTYROSINE competitively **inhibits tyrosine hydroxylase,** and thereby depletes NE. It is used to treat **pheochromocytoma,** if surgery is not possible.

XI Drugs for Glaucoma

A. OPEN-ANGLE GLAUCOMA, a chronic condition, is the most common type. It is treated pharmacologically with five groups of drugs, with beta blockers and prostaglandin agonists being the most popular:
1. One general strategy is to **increase outflow of intraocular fluid.**
   a. **Cholinomimetics** and **cholinesterase inhibitors** (e.g., pilocarpine and physostigmine) are commonly used.
   b. **Prostaglandin $F_{2\alpha}$ agonists** include **latanoprost** (*Xalatan*) and **bimatoprost** (*Lumigan*).
2. The second general strategy is to **reduce the production of intraocular fluid.**
   a. **Beta-blockers** (e.g., **timolol** [*Timoptic*], **betaxolol** [*Betoptic*]) can be used.
   b. **Diuretics** include **dorzolamide** (*Trusopt*) and **acetazolamide** (*Diamox*).
3. **Alpha-agonists both increase outflow and reduce production** of intraocular fluid**. EPI** is a nonselective α-agonist, whereas **apraclonidine** (*Iopidine*) is an α_2-selective agonist.

B. CLOSED-ANGLE GLAUCOMA is induced when the iris dilates and obstructs the drainage of intraocular fluid; this is a medical emergency. **Antimuscarinics,** which are pupillary dilators, can induce this type of glaucoma. Drugs used include:
1. **Cholinomimetics: pilocarpine** will **constrict the pupil** and lower the intraocular pressure.
2. **Diuretics: acetazolamide** will **decrease secretion of intraocular fluid.**
3. **Osmotic agents** will draw fluid from the eye.
4. Other types of drugs (alpha agonists, beta blockers, prostaglandins) are too slow in onset to be used for treating acute glaucoma.
5. **Surgery** can correct the defect.

Chapter **3**

Central Neuropharmacology

I Principles of General Anesthesia

A. THE PRIMARY OBJECTIVES of general anesthesia are:
1. **Amnesia**
2. **Analgesia**
3. **Unconsciousness**
4. **Suppression of autonomic reflexes**
5. **Muscle relaxation**

B. Due to the blood–brain barrier, all central nervous system (CNS) drugs including the general anesthetics must either be **lipid soluble** or carried across the barrier by active transport (e.g., P-glycoproteins) in order to be effective.

C. The mechanism of action of general anesthetics has been difficult to determine.
1. Classical theories involve a **physical association** of anesthetics with cell membranes. This leads to several implications.
   a. The **potency** of inhaled anesthetics is defined in terms of the **minimal alveolar concentration (MAC).**
      i. MAC is the **anesthetic alveolar partial pressure required to prevent movement in 50% of patients** in response to a skin incision.
      ii. It is inversely related to the **oil–water partition coefficient** for that anesthetic.
   b. The association of the anesthetic with cell membranes **reduces the excitability** of the membranes.
   c. The important receptors for inhalation anesthetics are not known.
   d. There are **no specific antagonists** for the inhalation anesthetics.
2. Recent theories involve an **enhancement of the effects of inhibitory neurotransmitters (e.g., gamma-aminobutyric acid, GABA).**
3. At low concentrations of a general anesthetic, the CNS is depressed more than other tissues. But as the concentration is increased, all excitable cells are eventually depressed.

D. Several factors should be considered when selecting anesthetics:
1. **The patient's kidney and liver function**
2. **The patient's respiratory function,** since anesthetics are respiratory depressants
3. **Cardiac or CNS abnormalities**
4. **Family or personal history of malignant hyperthermia**
5. **The pregnancy status of the patient,** to avoid harm to the fetus
6. **Other drugs being taken by the patient,** both legal and illegal

E. Anesthetics induce characteristic stages of anesthesia. These were first described for anesthesia with diethyl ether, but they occur with other anesthetics as well.
1. **Stage 1** involves **analgesia.** The patient is conscious.
2. **Stage 2** involves **excitement,** due to **blockade of inhibitory pathways** in the brain. This can be a dangerous phase due to the vomiting, restlessness, delirium, and other hyperexcitable effects that may occur.
3. **Stage 3** is the stage at which **surgery is usually performed.** The patient is unconscious, and his or her skeletal muscles are relaxed.
4. **Stage 4** involves **respiratory and cardiovascular depression,** which, if pronounced, can lead to death.

F. The **three steps of anesthesia** are **induction, maintenance,** and **recovery.**
1. **Induction** describes the period from the beginning of anesthetic administration until effective surgical anesthesia is achieved.
2. **Maintenance** involves sustained surgical anesthesia, which is often performed with inhalation anesthetics because they provide a high degree of control.
3. **Recovery** describes the period from discontinuation of anesthesia until the patient has regained consciousness. The anesthesiologist continues to monitor the patient during this period.

G. The **rate of induction** of inhaled anesthesia is **dependent on the blood solubility of an anesthetic,** assuming that the anesthetic is being administered as the only agent. Note that this is generally not the case in most surgeries.
1. The blood solubility can be determined by measuring the blood–gas partition coefficient λ.
2. High blood solubility leads to a slow rise in the partial pressure of the anesthetic in the body and a slow induction.
   a. This is undesirable because it prolongs Stage 2 of anesthesia.
   b. **Halothane** has **high blood solubility,** whereas **nitrous oxide (N_2O)** has **low blood solubility.**
3. The induction of highly blood soluble anesthetics is most readily hastened by "overpressuring" (using a high concentration of anesthetic).

H. The factors affecting distribution vary with the phase.
1. **The initial distribution** of an anesthetic will depend on the relative **tissue blood flow;** more anesthetic will go to areas with higher blood flow (e.g., heart, brain, endocrine organs).
2. **The final distribution** will be dependent on the **tissue–blood partition coefficients,** although the tissue–blood partition coefficient for most anesthetics in most tissues is approximately 1.
   a. An exception is the fat–blood partition coefficient, which is usually high (25–60).
   b. Movement of an anesthetic into fat will be slow due to the low blood supply to fat. Only after long anesthesias will significant amounts of anesthetic be sequestered in fat.
   c. Recovery from long anesthesias may be slower than anticipated due to the slow elimination of anesthetic from fat.

II Inhalation Anesthetics

A. The inhalation anesthetics act as gases in the body and follow the **gas laws.**
1. **Dalton's Law.** An anesthetic exerts a partial pressure that is proportional to the percent of the anesthetic in the mixture.

2. **Fick's Law.** The anesthetic diffuses down its concentration gradient.
3. **Henry's Law.** The amount of anesthetic dissolved in a liquid is proportional to the partial pressure of the anesthetic in the gaseous mixture.

B. DIETHYL ETHER was the first useful anesthetic.

1. It has several major disadvantages, including:
   a. **Very slow induction** ($\lambda = 16$)
   b. **Flammability**
   c. **Respiratory irritation,** which frequently leads to enhanced secretions, nausea, and vomiting
2. It is, however, a complete anesthetic, meaning that it
   a. Induces muscle relaxation, due to actions on the spinal cord and neuromuscular junction
   b. Induces analgesia
   c. Induces unconsciousness

C. As compared to diethyl ether, the newer inhalation anesthetics, which are **halogenated hydrocarbons,** are

1. Less soluble in blood, resulting in **faster rates of induction and recovery**
2. **Nonflammable**
3. **Less irritating** to the respiratory tract

D. Common **disadvantages** of the newer inhalation anesthetics are that they

1. **Depress respiration**
2. **Decrease blood pressure** in a dose-related fashion
3. Dilate cerebral blood vessels, which can increase intracranial pressure
4. Relax the uterus during pregnancy
5. Induce a low incidence of malignant hyperthermia, which can be treated with dantrolene
6. Have weaker analgesic actions

E. Specific properties of the halogenated hydrocarbon inhalation anesthetics are shown in Table 3-1.

1. **Halothane** (*Fluothane*) was the first anesthetic in this group.
   a. It is a **poor skeletal muscle relaxant and a poor analgesic;** thus, it is usually combined with other drugs (e.g., muscle relaxants and analgesics). The combination is called balanced anesthesia.
   b. Halothane **sensitizes the myocardium to catecholamines;** thus, arrhythmias may occur when catecholamines are administered.

TABLE 3-1 PROPERTIES OF HALOGENATED INHALATION ANESTHETICS

	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane
Induction speed (λ)	2.3	1.8	1.4	0.7	0.4
% MAC (1 atm)	0.75	1.68	1.15	1.85	6.0
Irritation of respiratory tract	Low	Low	Moderate	Low	High
Muscle relaxation	Low	Moderate	Moderate	Moderate	Moderate
Myocardial depression	High	Moderate	High	Low	Low
Sensitization of myocardium	High	Moderate	Low	Low	Low
% Metabolized	20	2	0.2	5	0.02

c. **Metabolism of halothane** to halogenated products is high, which may account for the infrequent **hepatotoxicity.**
d. For these reasons, it is not commonly used in the United States any longer.

2. **Enflurane** (*Ethrane*) can induce **seizure patterns** during anesthesia and is also no longer used in the United States.
3. **Isoflurane** (*Forane*) has **respiratory irritant** effects.
4. **Sevoflurane** (*Ultane*) is partially metabolized by the liver and may be hepatotoxic.
5. **Desflurane** (*Suprane*) has the **fastest** onset of and recovery from anesthesia. It also has **respiratory irritant** effects.

F. NITROUS OXIDE is a gas with

1. **Rapid onset and recovery** ($\lambda = 0.4$)
2. **Excellent analgesic activity**
3. No effect on the function of most vital systems
4. **Inadequate potency,** leading to
   a. Unconsciousness only when used with other anesthetics
   b. **A second gas effect** during induction, which accelerates the onset of anesthesia by other inhalation anesthetics
   c. **Diffusion hypoxia** during recovery, due to the filling of the lungs with nitrous oxide so that inadequate oxygen is inhaled. This can be avoided by administering **100% oxygen** for a short time at the conclusion of the nitrous oxide anesthesia.
5. Note that nitrous oxide (N_2O) should not be confused with the vasodilator nitric oxide (NO).

G. Several **miscellaneous** anesthetics are of historical interest.

1. **Methoxyflurane** is
   a. **The most potent anesthetic** available for clinical use
   b. **The best analgesic** anesthetic
   c. **Nephrotoxic** and thus seldom used
2. **Cyclopropane** is an explosive gas.
3. **Chloroform** is
   a. A complete anesthetic
   b. Hepatotoxic

III Intravenous Anesthetics

A. BARBITURATES, such as **thiopental** (*Pentothal*), have a rapid onset of anesthesia due to **high lipid solubility.**

1. When administered they go primarily to areas of high blood flow, such as the brain.
2. The short duration of anesthesia is due to **redistribution** from the brain to more soluble peripheral tissues with less blood flow, such as skeletal muscle and fat.
3. Clearance from the body by metabolism is very slow.
4. The duration of anesthesia becomes longer with repeated administrations because less redistribution can occur. As a result, the primary **uses** of thiopental are for
   a. **Induction** of anesthesia
   b. **Procedures of short duration**
5. The anesthetic has the following **properties:**
   a. **Marked respiratory and cardiovascular depression,** especially with a rapid bolus injection
   b. Weak skeletal muscle relaxant activity

c. **Antianalgesic** activity (increases sensitivity to pain)
d. Pharyngeal stimulation
e. **Very alkaline** solution, which causes severe tissue injury if given through an infiltrated IV.

B. PROPOFOL (*Diprivan*) also has a rapid onset of action and recovery.
1. Although the anesthesia is terminated by redistribution, there are **fewer cumulative effects** compared with barbiturates, and it can be used for long anesthesias.
2. The **postoperative complications (e.g., nausea, vomiting, residual drowsiness) are less than with other IV anesthetics.**
3. It can markedly reduce blood pressure.

C. OPIOIDS, such as **fentanyl** (*Duragesic*), **sufentanil** (*Sufenta*), and **alfentanil** (*Alfenta*), are **narcotic analgesics.** They are often used with other anesthetics.
1. They have the following anesthetic properties:
   a. Good analgesia
   b. Euphoria
   c. Respiratory depression, which can be reversed by naloxone
   d. Muscle rigidity
   e. Nausea and vomiting
2. The anesthesia is very safe with little cardiovascular depression.
3. **Droperidol** (*Inapsine*), an **antipsychotic** (neuroleptic), can be combined with fentanyl (*Innovar*) to induce neuroleptanalgesia.
   a. The patient is sometimes conscious and can respond.
   b. It can be supplemented with nitrous oxide to induce unconsciousness (neuroleptanesthesia).

D. MIDAZOLAM (*Versed*) is a **water-soluble benzodiazepine** with a rapid onset of action and a shorter duration than other benzodiazepines. It is used for sedation.
1. The patient remains conscious at low doses, but experiences amnesia during the anesthesia.
2. At high doses, some loss of consciousness is induced.
3. It can induce respiratory depression that is reversible by administration of benzodiazepine antagonists, such as flumazenil (*Romazicon*).

E. KETAMINE (*Ketalar*) is an analog of phencyclidine, a hallucinogen.
1. It induces a **dissociative anesthesia.**
   a. The patient may look awake but is unresponsive.
   b. The analgesic effects are excellent.
   c. Muscle tone is either unchanged or increased.
   d. Blood pressure is often increased.
   e. Respiration is not affected.
2. Ketamine can be administered intravenously or intramuscularly.
3. **Side effects** are related to hallucinogenic activity, which leads to
   a. **Vivid dreams**
   b. **Hallucinations,** which can be reduced by diazepam

F. ETOMIDATE (*Amidate*) is a hypnotic that lacks analgesic activity.
1. It is used in patients with coronary artery disease (CAD) and other cardiac diseases.
2. Etomidate **inhibits** the enzyme **11β-hydroxylase,** which leads to **decreased synthesis of glucocorticoids and mineralocorticoids.**

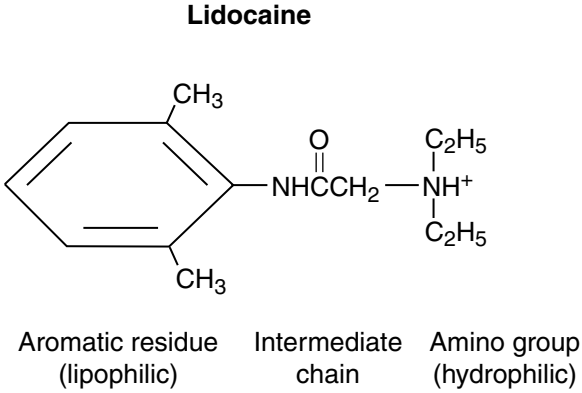
IV Local Anesthetics

A. REDUCTION OF SODIUM AND POTASSIUM ION PERMEABILITY (P_{Na} AND P_K) in activated nerve membranes leads to local anesthesia.

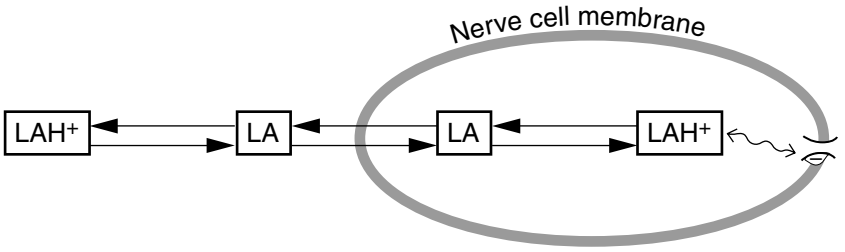
1. There are no effects on resting membranes.
2. The effects on the nerve action potential of both sensory and motor nerve fibers include:
   a. Reduction in the amplitude
   b. Reduction in the rate of rise
   c. Reduction in conduction velocity
   d. Blockade of axonal conduction
3. Sensory neurons are blocked before motor neurons because the sensory axons are usually smaller and have less myelin.

B. Local anesthetics, except for benzocaine, have three common **structural components** (Figure 3-1).

1. **The aromatic** residue is **lipophilic,** which is important for good membrane penetration.
2. **The amino** group is **hydrophilic.**
   a. It can become charged by picking up a proton.
   b. pH and pK_a determine whether the local anesthetic is present predominantly in the charged or uncharged forms.
      i. Only the uncharged form crosses the nerve cell membrane (Figure 3-2).
      ii. It is converted to the **charged form** inside the axon, which then interacts with binding sites within the ion channels.
      iii. Stock solutions of local anesthetics are acidic (local anesthetic is ionized). The acidity must be neutralized before anesthesia can occur.
      iv. Local anesthetics will be less effective for inducing anesthesia in areas of inflammation because:
         (a) The pH is low
         (b) Most of the anesthetic will be charged and unable to penetrate the nerve cell membrane
      v. Mucous membranes have a low buffering capacity and cannot readily neutralize the acidity of the local anesthetic solution. As a result, mucous membranes are relatively difficult to anesthetize.



● **Figure 3-1** General structure of local anesthetics, as illustrated by the amide, lidocaine. Some local anesthetics have an ester intermediate chain.



● **Figure 3-2** The unionized local anesthetic (LA) diffuses across the axon membrane and is converted to the ionized LA (LAH^+), which interacts with binding sites (−) in the sodium and potassium channels.

c. The pK_a must be between 7 and 9 so that some of the local anesthetic is in the charged form and some is in the uncharged form at physiological pH.

3. **The intermediate chain** determines how a local anesthetic is metabolized and can be either an ester or an amide.
   a. **Esters** are broken down by butyrylcholinesterases in the blood.
      i. **Cocaine** is only used for topical anesthesia.
      ii. **Procaine** (*Novocain*) is metabolized to para-aminobenzoic acid (PABA). It can induce an allergic reaction.
      iii. **Chloroprocaine** (*Nesacaine*) is metabolized most rapidly, has the shortest duration of action, and theoretically has the lowest risk of systemic toxicity.
      iv. **Tetracaine** (*Pontocaine*) is 10 times as potent as procaine and 10 times as toxic.
   b. The **amides,** which are metabolized by amidases in the liver, include:
      i. **Lidocaine** (*Xylocaine*)
      ii. **Mepivacaine** (*Carbocaine*)
      iii. **Bupivacaine** (*Marcaine*), which is cardiotoxic.

C. TOXIC EFFECTS are very uncommon but can be serious if the systemic absorption of the local anesthetic is excessive.
1. **Myocardial depression** is due to sodium channel blockade in myocardial muscle.
2. **Vasodilation** leads to a fall in blood pressure.
3. **Anxiety, depression, and convulsions** can occur due to **CNS neurotoxicity.**
4. **Hypersensitivity** reactions are rare and occur primarily with esters, which contain PABA derivatives.

D. EPINEPHRINE (EPI) IS FREQUENTLY COMBINED WITH LOCAL ANESTHETICS.
1. EPI reduces blood flow in the anesthetized area which
   a. **Reduces bleeding,** making it useful during some types of surgeries
   b. **Prolongs the anesthesia** by slowing the loss of anesthetic from the area of injection
   c. **Reduces the systemic concentration** of the anesthetic, thereby lowering the incidence of toxicity
2. EPI is not used with cocaine because cocaine by itself has vasoconstrictor activity, and it is not used on end-appendages where ischemia can be induced.

E. The symptoms of **local anesthetic toxicity must be treated** aggressively.
1. **Oxygen** reduces the hypoxia.
2. **Vasopressors or intravenous fluids** increase the blood pressure.
3. **Diazepam** reduces the convulsions.

F. During spinal anesthesia, blood pressure may fall due to blockade of sympathetic pathways in the spinal cord.

V Sedative–Hypnotic and Antianxiety Drugs

A. Hypnotics are medications that induce sleep, and antianxiety drugs are medications that reduce anxiety.
1. Many of these drugs have both hypnotic and antianxiety activity.
2. **The common mechanism of action is to enhance the inhibitory effects of GABA** in the CNS. This hyperpolarizes neurons by increasing the entry of chloride.

B. CLINICAL USES of sedative–hypnotic and antianxiety drugs include:
1. **Treatment of anxiety**
2. **Treatment of insomnia**
3. **Muscle relaxation**
4. **Treatment of seizures**
5 **Replacement therapy** during withdrawal from sedative–hypnotics (e.g., ethanol)
6. **IV anesthesia or sedation before surgical procedures**

C. SIDE EFFECTS common to these drugs include:
1. **Decreased REM sleep** with a rebound increase in REM sleep upon withdrawal
2. **Drowsiness**
3. **Hangover**
4. **Tolerance** with prolonged administration due to
   a. **Increased metabolism** from activation of mixed function oxidases (MFOs)
   b. **Reduced effects on the CNS**
5. **Respiratory depression.** These drugs reduce the sensitivity of the medullary respiratory centers to CO_2.
   a. Respiratory depression is increased when these drugs are combined with any other sedating drug.
   b. This is the **cause of death** from an overdose.
   c. **Tolerance does not develop to the depressant action on respiration.**
   d. Respiratory depression is very marked with barbiturates and very weak with benzodiazepines.
6. **Abuse potential. Physical dependence** occurs with all these drugs and results in an abstinence syndrome upon withdrawal.

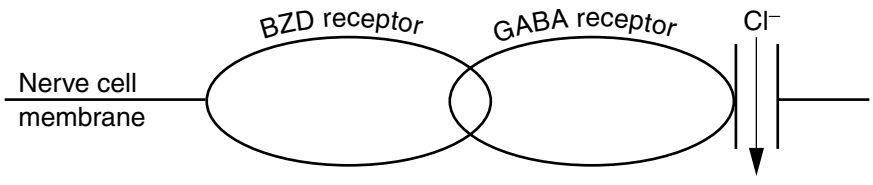
D. BARBITURATES are derived from **barbituric acid,** a combination of urea and malonic acid.
1. They are frequently provided as sodium salts (e.g., sodium pentobarbital) because the salt is more water soluble; however, it is very alkaline.
2. **The barbiturates are classified by duration of action**
   a. **Ultrashort-acting barbiturates (e.g., thiopental** [*Pentothal*]) have very high lipid solubilities due to sulfur in the structure. They are used as IV anesthetics.
   b. **Short- and intermediate-acting barbiturates (e.g., pentobarbital** [*Nembutal*]) have lower lipid solubilities and longer durations of action than are appropriate for sleeping pills.
   c. **Long-acting barbiturates (e.g., phenobarbital** [*Luminal*]) have the lowest lipid solubilities and the longest durations of action. They can be used as sedatives, anticonvulsants, or antianxiety drugs.
3. **Binding to plasma proteins** is highest for the highly lipid-soluble barbiturates.
4. **Metabolism by side chain oxidation** accounts for the clearance of all barbiturates from the body.

a. Only phenobarbital has some clearance (30%) by the kidney, and this can be increased by increasing the urinary pH.
b. Barbiturates greatly induce the cytochrome P450 enzymes in the liver, which decreases the activities of other drugs that are metabolized by these enzymes.

5. There are multiple **adverse effects:**
   a. **Drowsiness and impaired concentration**
   b. **Hangovers**
   c. **Dependence and severe withdrawal that can be lethal**
   d. **Overdoses** due to the **narrow therapeutic index** (e.g., patients who overdose on barbiturates develop **respiratory depression,** which is managed symptomatically by **assisting respiration** and stabilizing blood pressure)
   e. Due to an increase in porphyrin synthesis, **acute intermittent porphyria is an absolute contraindication** for the use of barbiturates.

E. BENZODIAZEPINE preparations differ primarily in their duration of action.

1. **Antianxiety preparations** usually have long durations of action ranging from 12 hours to several days. They include:
   a. **Chlordiazepoxide** (*Librium*), also used for alcohol withdrawal
   b. **Diazepam** (*Valium*), also used for skeletal muscle spasms and seizures
   c. **Alprazolam** (*Xanax*), used to treat panic disorders
2. **Hypnotic preparations** (sleeping pills) have shorter durations of action than the antianxiety drugs.
   a. **Flurazepam** (*Dalmane*) has a short half-life. However, its active metabolites give it a long clinical effect (up to 100 hours) and result in daytime drowsiness.
   b. **Temazepam** (*Restoril*) has a $t_{1/2}$ of 10 hours with no active metabolites.
   c. **Triazolam** (*Halcion*) has a short $t_{1/2}$ of 2.5 hours, which can result in early morning awakening.
3. **Benzodiazepines bind** to the **benzodiazepine site on $GABA_A$ receptors,** which leads to an enhancement of GABA inhibition (Figure 3-3).
4. **Effects** include:
   a. **Calming** of behavior
   b. **Reduction of anxiety**
   c. **Induction of sleep**
   d. **Anticonvulsant** actions
   e. **Muscle relaxation**
5. There are no autonomic effects.
6. **Side effects** include:
   a. **Drowsiness** and **confusion**
   b. **Dependence,** especially with quick onset agents (e.g., alprazolam, diazepam). Long-term use should be avoided.
   c. **Enhanced depression when combined with other CNS depressant drugs**
   d. **A prolonged withdrawal syndrome**



● **Figure 3-3** Relationship of the benzodiazepine (BZD) receptor to the gamma-aminobutyric acid (GABA) receptor. Enhanced chloride inflow will hyperpolarize (inhibit) CNS neurons, leading to sedative, antianxiety, and hypnotic effects.

7. Benzodiazepines have many **advantages over barbiturates.**
   a. They are **less likely to be abused,** although abuse still occurs.
   b. **Suicide potential is lower** due to the high therapeutic index (TI).
   c. **Less reduction of REM sleep** occurs.
   d. **Induction of MFOs is less pronounced.**
   e. **Flumazenil** (*Romazicon*), **a benzodiazepine antagonist,** will reverse the sedation effects of the benzodiazepines.

F. ZOLPIDEM (*Ambien*), **eszopiclone** (*Lunesta*), and **zaleplon** (*Sonata*) are hypnotics with little effect on the stages of sleep.
1. Although they are **not benzodiazepines,** they **bind to a subgroup of benzodiazepine receptors.**
2. They are **antagonized by flumazenil.**
3. They have little anxiolytic, anticonvulsant, or muscle relaxant activity.

G. BUSPIRONE (*BuSpar*) is an antianxiety drug that
1. **Is not a benzodiazepine**
2. **Is a partial agonist at $5HT_{1A}$ receptors**
3. **Does not have abuse potential**
4. **Has few CNS side effects (e.g., drowsiness is minimal)**
5. **Mildly increases respiratory drive**

H. ANTIHISTAMINES AND ETHANOL also have sedating properties
1. **Hydroxyzine** (*Atarax, Vistaril*) is an antihistamine with **antianxiety activity, low abuse potential,** and **marked sedative and anticholinergic effects.**
2. Other antihistamines (e.g., diphenhydramine) are found in many over-the-counter sleep preparations.
3. **Ethanol has both antianxiety and sedating effects.** However, it is not a therapeutically useful drug due to the high potential for abuse and dependence.

I. CHLORAL HYDRATE (*Noctec*) **is a hypnotic prodrug** that is metabolized by alcohol dehydrogenase to the active moiety, trichloroethanol.
1. **The unpleasant taste and odor** can reduce the potential for abuse.
2. **The TI is relatively low.**

VI Anticonvulsants

A. The anticonvulsants **act by reducing the excitability** of focal and **nonfocal neurons** (primarily) by
1. **Enhancing GABA inhibition,** which leads to an increased P_{Cl} and hyperpolarization of neuronal membranes
2. **Prolonging sodium permeability inactivation,** which enhances the effective refractory period of neurons
3. **Blocking T-type calcium channels**

B. ANIMAL MODELS are useful in the screening of potential drugs for the treatment of epilepsy.
1. **The convulsant pentylenetetrazol** induces convulsions that have drug sensitivities similar to absence seizures.
2. **Maximal electrical shock** induces convulsions with drug sensitivities similar to tonic–clonic seizures.

TABLE 3-2 ACTIVITIES OF ANTICONVULSANTS FOR SPECIFIC SEIZURE PATTERNS

	Tonic–Clonic	Partial	Absence	Akinetic and Atonic
Phenobarbital (*Luminal*)	+	+		
Primidone (*Mysoline*)	+	+		
Phenytoin (*Dilantin*)	++	++	–	
Carbamazepine (*Tegretol*)	++	++	–	
Valproic acid (*Depakene*)	+	+	++	
Ethosuximide (*Zarontin*)			++	+
Clonazepam (*Klonopin*)			+	+

Note: (–) means exacerbated

3. **Kindling** from weak, long-term stimulation of the cortex or amygdala induces generalized seizures.

C. All sedative–hypnotic and antianxiety drugs have anticonvulsant activity, but most produce too much drowsiness (sedation) to be clinically useful.

D. SELECTION of a specific drug for treatment depends on the **seizure type** (Table 3-2). Side effects should also be considered.

E. Many features are common to most antiepileptics.
1. None of these drugs are curative.
2. They tend to be **highly bound to plasma proteins.**
3. They are usually **cleared by hepatic metabolism.**
   a. They may **inhibit the metabolism** of other drugs (valproic acid).
   b. They may **induce the metabolism** of other drugs (e.g., the effectiveness of oral contraceptives can be reduced [phenobarbital, phenytoin, carbamazepine]).
   c. For older agents, it is important to measure the serum anticonvulsant concentration.
4. **Side effects** that usually occur include:
   a. **CNS depression** (Even phenytoin induces lethargy.)
   b. **Skin rashes** (Lamotrigine and carbamazepine can cause **Stevens–Johnson syndrome,** a life-threatening skin condition that is thought to be immune complex-mediated.)
   c. **Nystagmus**
   d. **Teratogenicity**
   e. **GI effects** (nausea, vomiting)

F. Each anticonvulsant has some unique features.
1. **Phenobarbital** (*Luminal*) has a half-life of 4 days. Patients develop some tolerance to the sedative–hypnotic effect, but not to the antiepileptic effect.
2. **Primidone** (*Mysoline*) is an active drug and is also partially metabolized to phenobarbital; thus, it has properties that are very similar to phenobarbital.
3. **Phenytoin** (*Dilantin*) is an effective antiepileptic with less sedative activity.
   a. **Elimination follows zero-order kinetics.** After saturation of hepatic enzymes, small increases in dose can lead to large increases in blood concentration.
   b. **Gingival hyperplasia, megaloblastic anemia,** and **cardiac arrhythmias** are important side effects.
   c. It is often used in new-onset status epilepticus.

4. **Carbamazepine** (*Tegretol*) is a tricyclic anticonvulsant that has **mood stabilization** activity. It is also used to treat restless leg syndrome and shingles.
   a. It induces MFOs in the liver.
   b. **Liver toxicity,** syndrome of inappropriate antidiuretic hormone (**SIADH),** and **aplastic anemia** are potential side effects**.**
   c. **Oxcarbazepine** (*Trileptal*) is an analog that has less toxicity.
5. **Valproic acid** (*Depakene*) is useful for **many types of seizures.** It can be **hepatotoxic,** but it does not induce cytochrome P450 enzymes.
6. **Ethosuximide** (*Zarontin*) is the drug of choice for **absence seizures.** It also does not induce cytochrome P450 enzymes.
7. **Clonazepam** (*Klonopin*) is a benzodiazepine, which produces considerable sedation. Tolerance can occur with long-term use.
8. **Tiagabine** (*Gabitril*), **levetiracetam** (*Keppra*), and **gabapentin** (*Neurontin*) are useful as adjunct therapies for partial seizures. Gabapentin and levetiracetam are also used to treat **neuropathic pain.**
9. **Topiramate** (*Topomax*) is useful as an adjunct in treating **refractory seizures. Felbamate** (*Felbatol*) and **lamotrigine** (*Lamictal*) can also be used to treat refractory seizures, but they are not first-line therapy due to severe side effects.

G. STATUS EPILEPTICUS is a life-threatening disorder that must be treated rapidly.
1. **An intravenous benzodiazepine,** such as diazepam (*Valium*) or lorazepam (*Ativan*), is the treatment of choice.
2. If the benzodiazepine is ineffective, other measures must be tried, including:
   a. **Phenytoin, given intravenously as fosphenytoin** (*Cerebyx*)
   b. **Phenobarbital, given intravenously**
   c. **General anesthesia**

VII Antipsychotic Drugs (Neuroleptics)

A. The typical antipsychotics **block D_2-dopamine receptors** in the limbic system, which probably accounts for the therapeutic effects of these drugs in reducing the symptoms of psychoses, hallucinations, and delusions.

B. BLOCKADE AT OTHER SITES LEADS TO SIDE EFFECTS.
1. **Blockade of D_2 receptors in the extrapyramidal system (basal ganglia) induces iatrogenic parkinsonism.** (See section XI-A on p. 47 for a description of parkinsonism.)
   a. **This complication can be reduced by anticholinergic drugs,** such as benztropine (*Cogentin*). This restores the dopamine–acetylcholine balance.
   b. L-Dopa should not be used to treat antipsychotic-induced extrapyramidal symptoms.
2. **Blockade of D_2 receptors in the pituitary** enhances the release of prolactin, which induces **galactorrhea** and **gynecomastia.**
3. **Blockade of histamine receptors** often leads to **sedation,** but these drugs have little abuse potential and display no tolerance.
4. **Blockade of M-cholinoceptors** leads to anticholinergic symptoms.
5. **Blockade of α-adrenoceptors induces hypotension and tachycardia.**
6. **Serotonin (5-HT) receptors are also blocked by newer atypical drugs.**
7. The effect on the **hypothalamus shifts body temperature** toward the **ambient temperature (poikilothermia).**

C. THE DRUGS CAN BE CLASSIFIED AS
1. **Typical drugs**

a. **Phenothiazines** include:
   i. **Chlorpromazine** (*Thorazine*) **and thioridazine** (*Mellaril*), which are low-potency phenothiazines.
   ii. **Fluphenazine** (*Prolixin*) which is a high-potency phenothiazine.
b. **Thiothixene** (*Navane*), **pimozide** (*Orap*), and **haloperidol** are also high-potency antipsychotics.

2. Atypical drugs

a. **Risperidone** (*Risperdal*) is a newer antipsychotic with $5HT_2$ receptor-blocking activity and fewer extrapyramidal symptoms than the typical antipsychotics.
b. **Clozapine** (*Clozaril*) also blocks $5HT_2$-receptors as well as D-receptors.
   i. It induces the fewest extrapyramidal symptoms
   ii. Is effective in some patients that are refractory to other antipsychotics
   iii. Can cause **agranulocytosis;** white blood cell counts must be monitored
c. **Olanzapine** (*Zyprexa*) is similar to clozapine but does not cause agranulocytosis. However, it leads to **metabolic syndrome, type 2 diabetes,** and **hyperlipidemia.**

D. The **side effects of the typical antipsychotics** are related to their potency.

1. High-potency typical antipsychotics induce the most extrapyramidal symptoms.
2. Low-potency typical antipsychotics induce fewer extrapyramidal symptoms, but they induce more anticholinergic effects, more hypotension, and more sedation than the high-potency typical antipsychotics.
3. The TI is very large. At high doses, convulsions can rarely occur.
4. Tardive dyskinesia is a major complication that can develop after long-term administration of typical antipsychotics.
   a. **Orofacial** symptoms predominate in adults.
   b. Withdrawal of the antipsychotic drug must be undertaken even though it will initially enhance the tardive dyskinesia.
   c. Anticholinergics do not reduce tardive dyskinesia.
   d. One proposed theory is that tardive dyskinesia is due to an **up-regulation of the D_2-receptors** in the basal ganglia.
5. Neuroleptic malignant syndrome is a rare but severe idiosyncratic reaction to antipsychotic medication. Treatment should be discontinued and supportive care given.
6. Weight gain is commonly seen with the **atypical antipsychotics.**

E. These drugs are **very long acting.**

1. Binding to many tissues results in a **large V_d.**
2. There are **many drug metabolites** due to extensive metabolism in the liver.

F. ANTIPSYCHOTIC DRUGS are also used

1. As **antiemetics** due to depression of the chemoreceptor trigger zone (the area postrema at the caudal end of the fourth ventricle).
2. To treat many less common neurological disorders (e.g., pimozide is used to treat Tourette's syndrome).
3. As sedatives, although this is inappropriate in view of the risk of tardive dyskinesia.

VIII Lithium Carbonate

A. The clinical indications for lithium are treatment of **manic depressive illness (bipolar disorder)** and **augmentation in unipolar depression,** including:

1. Acute treatment of the manic phase

2. Acute treatment of the depressive phase in combination with other agents
3. Prophylaxis

B. A **delay of 7–10 days** occurs before lithium has a clinical effect.

C. **SIDE EFFECTS** are common if the blood lithium concentration gets into the toxic range; thus, it is important to monitor the blood lithium concentrations to avoid toxicity.

1. **Tremor, ataxia, and confusion** can occur and occasionally lead to convulsions.
2. **Nephrogenic diabetes insipidus** can occur. It can be treated with the potassium-sparing diuretic amiloride or by switching the patient from lithium to an anticonvulsant.
3. **Hypothyroidism** can occur, and thyroid function must be monitored.
4. There is **no specific antidote** for lithium.
   a. Thiazide diuretics and calcium channel blockers will increase lithium retention and enhance toxicity; thus, they should be avoided in patients being treated with lithium.
   b. NSAIDs decrease lithium clearance and increase lithium blood levels.
   c. ACE inhibitors cause an increased lithium level due to sodium depletion.
   d. A high sodium diet will increase lithium excretion.

D. Alternate drugs for bipolar depression are the anticonvulsants carbamazepine (*Tegretol*), lamotrigine (*Lamictal*), and valproic acid (*Depakene*).

IX Antidepressants

A. The primary clinical indication for antidepressants is **major depression (unipolar disorder).**

1. The onset of the antidepressant effect is delayed, taking **2–3 weeks** to develop. This supports the hypothesis that down-regulation of presynaptic inhibitory NE or 5-HT receptors may be necessary for the clinical effect to occur.
2. These drugs **improve mood in depressed patients but not in normal subjects,** which is the basis of the term "antidepressant."

B. **TRICYCLIC ANTIDEPRESSANTS** have a structure that is similar to the phenothiazines (typical antipsychotics).

1. **Imipramine** (*Tofranil*), a tertiary amine that is the prototype tricyclic drug, has many effects that are similar to the phenothiazines. However, imipramine
   a. Produces very **little D_2-receptor antagonism**
   b. **Reduces amine reuptake,** which increases the concentration of NE and 5-HT in the CNS synapses
2. **Side effects** vary among specific drugs (Table 3-3), but are generally similar to the phenothiazines. They include:
   a. **Antihistaminergic effects** from blocking the H_1 receptors (e.g., **sedation)**
   b. **Anticholinergic effects,** such as tachycardia, arrhythmias, urinary retention, constipation, xerostomia, and blurred vision
   c. **Antiadrenergic effects,** such as orthostatic hypotension and reflex tachycardia due to blocking alpha adrenoceptors
   d. **Weight gain**
   e. **Anorgasmia and erectile dysfunction**
   f. **Drug interactions** (e.g., adrenergic agonists, ethanol, MAOIs)

TABLE 3-3 MAGNITUDE OF SIDE EFFECTS FROM TRICYCLIC ANTIDEPRESSANTS

	Sedation and Anticholinergic Activity
Doxepin (*Sinequan*)	High
Amitriptyline (*Elavil*)	High
Clomipramine (*Anafranil*)	High
Imipramine (*Tofranil*)	Moderate
Desipramine (*Norpramin*)	Low
Nortriptyline (*Aventyl, Pamelor*)	Low

3. Overdoses from tricyclics are common because depressed patients may ingest large amounts of the drug in an attempt to commit suicide, and these drugs have a narrow therapeutic index. Treatment of an overdose involves
   a. Supportive management
   b. Lidocaine to reduce arrhythmias
   c. Physostigmine to reverse anticholinergic effects
4. There are **other clinical uses** for the tricyclics.
   a. **Childhood enuresis** (bed-wetting) and **urinary incontinence** in the elderly can be reduced.
   b. Clomipramine (*Anafranil*) reduces **obsessive–compulsive behaviors.**
   c. Amitriptyline, doxepine, and nortriptyline can relieve **chronic pain.**

C. SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs) decrease the reuptake of both serotonin and norepinephrine.
1. They have similar actions as the tricyclics, but with fewer anticholinergic side effects.
2. **Venlafaxine** (*Effexor*) inhibits 5-HT reuptake at low doses and both 5-HT and NE reuptake at higher doses. It is associated with hypertension at higher doses.
3. **Duloxetine** (*Cymbalta*) inhibits 5-HT and NE reuptake at all doses.
   a. It is extensively metabolized and should be avoided in patients with severe liver or kidney disease.
   b. The major side effects are GI effects and sexual dysfunction.

D. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) inhibit serotonin reuptake but do not affect NE reuptake.
1. They include **fluoxetine** (*Prozac*), **sertraline** (*Zoloft*), **fluvoxamine** (*Luvox*), **citalopram** (*Celexa*), **escitalopram** (*Lexapro*), and **paroxetine** (*Paxil*).
2. They are similar in efficacy to the tricyclics for the treatment of major depression. Other uses include **panic disorder, anxiety,** and **obsessive–compulsive disorder** (fluvoxamine).
3. The main advantage is that they are **much safer** due to a lack of
   a. Sedation
   b. Orthostatic hypotension
   c. Anticholinergic effects
   d. Overdose potential when used alone
4. Side effects include:
   a. **Sexual dysfunction**
   b. **CNS stimulation,** leading to **insomnia** (fluoxetine)
   c. **Drowsiness** (paroxetine, fluvoxamine)

d. **Drug interactions** due to inhibition of CYP 450s (fluoxetine, paroxetine)
e. **Disinhibition,** possibly with bipolar underpinnings
f. **Increased suicidal ideation and attempts;** patients on SSRIs must be monitored for suicidal ideation.
g. **Weight gain** with prolonged use

E. MONOAMINE OXIDASE (MAO) INHIBITORS (e.g., tranylcypromine [*Parnat*] and phenelzine [*Nardil*]) are **competitive irreversible inhibitors of both MAO_A and MAO_B.**

1. This inhibition increases the concentrations of NE, DA, and 5-HT in the granules, which increases amine release.
2. MAO inhibitors **elevate mood in both normal and depressed people.**
3. **Side effects** can be severe, including:
   a. **Hepatotoxicity**
   b. **CNS stimulation**
   c. **Postural hypotension**
   d. **Hypertensive crisis** and **stroke when taken with**
      i. **Foods containing tyramine,** such as cheeses, beans, pickled herring, beer, and wine
      ii. **Sympathomimetics**
4. Combinations of tricyclics or SSRIs with MAOIs must be avoided because this can cause the **serotonin syndrome** (hyperthermia, clonus, CNS effects). A washout period of 2–6 weeks is needed before switching patients from other drug classes to MAOIs and vice versa.

F. ATYPICAL ANTIDEPRESSANTS affect mood by different mechanisms.

1. **Bupropion** (*Wellbutrin*) improves depression by an unknown mechanism.
   a. It is used for tobacco cessation (*Zyban*) as well as for depression.
   b. High doses may lead to **seizures.** However, it does not cause weight gain or sexual dysfunction.
2. **Mirtazapine** (*Remeron*) blocks the 5-HT and α_2 receptors. Side effects include **increased appetite, weight gain,** and **sedation.**
3. **Nefazodone and trazodone** (*Desyrel*) block 5-HT autoreceptors on presynaptic neurons. Both are sedating, and trazodone can cause **priapism.**

X CNS Stimulants

A. METHYLXANTHINES (e.g., caffeine, theophylline [aminophylline], theobromine) have mild CNS stimulant effects.

1. The primary **mechanism of action** is controversial.
   a. **Adenosine receptors are blocked,** thereby decreasing the inhibitory actions of adenosine.
   b. **Phosphodiesterases are inhibited at high concentrations,** which increases the concentration of intracellular cyclic adenosine monophosphate (cAMP).
2. **Many effects** are induced, including:
   a. **CNS stimulation**
   b. **Myocardial stimulation**
   c. **Bronchodilation**
   d. **Diuresis**
   e. **Constriction of cerebral vessels,** which reduces headache
3. Caffeine is more effective on the CNS, and theophylline and theobromine are more effective at peripheral sites.

B. AMPHETAMINES are phenylethylamines.
1. **Absence of a catechol** in the structure allows for good penetration into the CNS.
2. **The *d*-isomer** of amphetamine is more potent on the CNS than the *l*-isomer.
3. **Actions are mediated indirectly** through the release of endogenous catecholamines.
4. **Many effects** occur, including:
   a. **Improvement of mood**
   b. **Increase in motor activity** and **reduction of fatigue**
   c. **Dependence and tolerance**
   d. **Reduction of appetite,** which is temporary due to rapid development of tolerance
5. **Appropriate indications** include:
   a. **Hyperkinesis in children,** especially with **methylphenidate** (*Ritalin*) or **amphetamine salts** (*Adderall*). **Atomoxetine** (*Strattera*), not a stimulant, can also be used.
   b. **Narcolepsy** (**modafinil** [*Provigil*])
6. **An inappropriate indication is obesity.**
   a. Amphetaminelike drugs have been used as diet products; however, tolerance develops and **the reduction of appetite is temporary.**
   b. Side effects such as irritability, insomnia, vertigo, hypertension, confusion, GI effects, and peripheral sympathetic activation can occur.

XI Drugs for Movement Disorders

A. PARKINSON'S DISEASE is due to the **loss of dopamine (DA) neurons** in the **substantia nigra,** which leads to symptoms of:
1. **Tremor at rest**
2. **Cogwheel rigidity**
3. **Akinesia**
4. **Loss of postural reflexes**

B. METHYLPHENYLTETRAHYDROPYRIDINE (MPTP) destroys DA neurons and induces parkinsonian symptoms. It can be used to produce a valuable animal model.

C. TREATMENTS for Parkinson's disease either increase DA effects or block ACh in the basal ganglia. This relieves the symptoms temporarily but does not cure the disease.
1. **Levodopa** (L-dopa [*Dopar, Larodopa*]), the most effective treatment, is metabolized by dopa decarboxylase to DA, which increases the availability of DA, an inhibitory transmitter, in the basal ganglia.
   a. L-Dopa becomes effective in a few weeks, especially **for reducing rigidity and akinesia.**
   b. However, L-dopa is **rapidly metabolized** in peripheral tissues, so that only 1% of the administered dose reaches the CNS.
      i. **Pyridoxine (vitamin B_6) increases this metabolism** by activating dopa decarboxylase.
      ii. L-Dopa should be taken on an empty stomach because large, neutral amino acids will compete with it for absorption from the gut and transport across the blood–brain barrier.
      iii. **Carbidopa** (*Sinemet*), **a peripheral dopa decarboxylase inhibitor** that slows the metabolism of L-dopa, is usually combined with L-dopa.
         (a) The L-dopa dosage can then be reduced by 80% without changing the effectiveness.
         (b) The side effects from conversion of L-dopa to DA in the periphery are also reduced.

iv. **Catechol-O-methyltransferase (COMT)** inhibitors prevent methylation of L-dopa in a side pathway.
   (a) This side pathway becomes significant when dopa decarboxylase is inhibited by carbidopa.
   (b) **Entacapone** (*Comtan*) requires frequent dosing but is the least toxic COMT inhibitor.
   (c) **Tolcapone** (*Tasmar*) is longer acting but can cause fulminating hepatic necrosis.

c. **Side effects** from L-dopa include:
   i. **Nausea, vomiting, and anorexia** induced by stimulation of the chemoreceptor trigger zone. The severity of the nausea is reduced by gradually increasing the dose into the therapeutic range and by combining L-dopa with carbidopa.
   ii. **Postural hypotension**
   iii. **Arrhythmias** from actions of DA on the heart
   iv. **Choreiform movements** due to excessive actions of DA on the basal ganglion
   v. **Psychological disturbances** that can lead to insomnia and delirium

d. **ON–OFF effects** often develop after a year or more. These are indicative of the "wearing-off phenomena" at the end of dosage intervals and erratic effectiveness. Patients typically have a decline in response after a few years of therapy.

e. **Contraindications** for L-dopa include:
   i. **Treatment with MAO inhibitors,** because the combination can lead to a hypertensive crisis
   ii. **Glaucoma,** because L-dopa can induce mydriasis
   iii. **Psychiatric disorders (PD),** especially those disorders being treated with antipsychotic drugs, which are DA antagonists; however, SSRIs or mirtazapine can be tried in PD patients who are also depressed.

2. **DA receptor agonists** have effects and side effects that are similar to L-dopa. They are often used with L-dopa and carbidopa to reduce the ON–OFF effects. However, they are not active in patients who have no response to L-dopa.
   a. **Bromocriptine** (*Parlodel*) and **pergolide** (*Permax*) are **nonselective DA agonists.** Because they are ergot derivatives, they can cause pulmonary and retroperitoneal fibrosis.
   b. **Pramipexole** (*Mirapex*) and **ropinirole** (*Requip*) are **selective D_2-agonists,** which are very effective and have fewer side effects.
      i. These drugs are non-ergot derivatives and do not cause pulmonary or retroperitoneal fibrosis.
      ii. Pramipexole is cleared by renal tubular secretion. Its half life is increased by cimetidine, which interferes with the secretion of organic bases (cations).

3. **The anticholinergics** (e.g., trihexyphenidyl [*Artane*]), benztropine [*Cogentin*]) reduce the cholinergic excitatory tone in the basal ganglia.
   a. They are most frequently used in combination **with antipsychotic drugs** to reduce the extrapyramidal symptoms from the antipsychotic drugs.
   b. Side effects are due to central and peripheral cholinoceptor blockade.

4. **Amantadine** (*Symmetrel*) is an antiviral drug that reduces the symptoms of Parkinson's disease.
   a. It increases DA release, blocks ACh receptors, and inhibits N-methyl-D-aspartic acid (NMDA) glutamate receptors.
   b. Tolerance to this therapeutic effect often develops within 6 months.

5. **Selegiline** (*Eldepryl*) is an **inhibitor** of **MAO_B.** This enzyme metabolizes L-dopa, but not 5-HT or NE.
   a. The selective decrease of DA metabolism enhances the effectiveness of L-dopa with less risk of a hypertensive crisis.
   b. It can be used in combination with L-dopa, making it possible to lower the L-dopa dosage.
6. **Antihistamines,** such as diphenhydramine (*Benadryl*) have some weak therapeutic effects, which are probably due to the anticholinergic actions of these drugs.

D. The order of efficacies of the available drugs for this disease is the following:

L-dopa > bromocriptine > amantadine > anticholinergics

E. A common approach is to use the low-efficacy drugs (e.g., selegiline, amantadine, anticholinergics) during the early stages of Parkinson's disease and reserve L-dopa with carbidopa and dopaminergic agonists for the later stages.

F. **A LOSS OF GABA OR INCREASED DA** in the basal ganglia leads to the choreiform movements that are characteristic of **Huntington's disease.**
1. As a result, L-dopa and anticholinergics are an inappropriate combination.
2. Some reduction of symptoms can be induced by DA depleters, antipsychotics (DA blockers), or cholinesterase inhibitors. These treatments are largely palliative and do not cure the disease.

XII Drugs for Alzheimer's Disease

A. **ALZHEIMER'S DISEASE (AD)** is thought to be due to a **loss of cholinergic neurons** in the nucleus basalis of Meynert and **deposition of amyloid β-protein.**

B. As with the movement disorders, **treatment of AD is largely palliative.** The aim is to increase ACh or decrease NMDA glutamate receptors in the brain.
1. **Acetylcholinesterase inhibitors** (e.g., **donepezil** [*Aricept*], **rivastigmine** [*Exelon*], **galantamine** [*Razadyne*]) prevent ACh breakdown in the CNS.
2. **NMDA receptor partial antagonists** (e.g., **memantine** [*Namenda*]) are thought to be neuroprotective.

Chapter **4**

Substance Abuse and Pain

I General Features of Substance Abuse

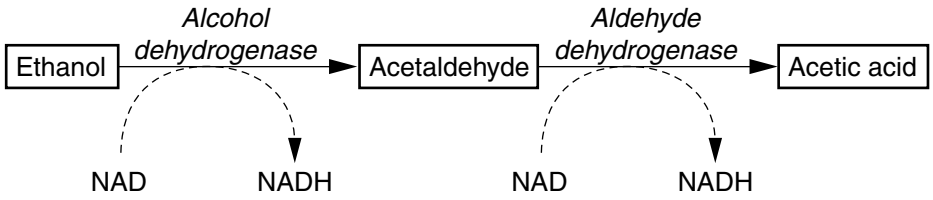
A. ABUSE is the misuse of a drug (e.g., taking it in ways not medically approved).
1. Abuse of a drug is often, but not always, associated with kinetic, dynamic, homeostatic, or learned **tolerance.**
   a. An **acute tolerance** (with first dose) has been described for ethanol.
   b. **Cross-tolerance** occurs between drugs with the same mechanism of action.
2. Drugs are abused for a variety of reasons:
   a. To induce a **feeling of euphoria**
   b. To **alter perception**
   c. As a **means of escape**
   d. Due to **peer pressure** in young people
3. Abusers of drugs usually derive more pleasure from a drug with a rapid onset of action than from a drug with a slow onset of action within the same class.

B. DEPENDENCE is the physical requirement for a drug due to adaptive physiologic changes (tolerance) after multiple exposures. If the drug is not available, **withdrawal** will occur.
1. The symptoms during withdrawal tend to be the opposite of the effects due to drug administration.
2. Withdrawal from a drug of abuse is usually less severe with long-acting drugs than with short-acting drugs within the same class. This is the theoretical basis for replacement therapy (e.g., methadone for heroin addicts).

C. ADDICTION is the psychological requirement for a drug.
1. It is characterized by **compulsive drug use in spite of associated negative consequences.**
2. An addicted person can crave a drug even in the absence of physical dependence.
3. Addiction is thought to be caused by an increase in central nervous system (CNS) dopamine release and/or a decrease in dopamine reuptake that occurs with use of the drug.

II Sedative-Hypnotics

A. ETHANOL is a commonly abused legal substance.
1. Due to **high lipid solubility and high water solubility,** ethanol distributes in total body water.
2. **Clearance** from the body occurs in the liver.



● **Figure 4-1** Metabolism of ethanol. NAD = nicotinamide adenine dinucleotide; NADH = reduced nicotinamide adenine dinucleotide

a. **Metabolism** by the **alcohol and aldehyde dehydrogenases** (Figure 4-1) follows zero-order kinetics.
   i. Products are acetaldehyde and acetic acid, respectively.
   ii. Two molecules of nicotinamide adenine dinucleotide hydrogenase (NADH) are produced for each molecule of ethanol.
b. An insignificant amount of ethanol is metabolized by mixed-function oxidases (MFOs), but this can induce the MFOs, particularly in alcoholics.

3. The effects of ethanol are related to the blood ethanol concentration.
a. **The legal limit** for driving in most states is a **0.08% (80 mg EtOH/100 ml blood) blood alcohol concentration (BAC).**
b. **Death** due to respiratory depression occurs in the range of **0.4–0.5% BAC,** although this is quite variable.
c. **Treatment** of an overdose of ethanol is **symptomatic.**

4. **Acute adverse effects** develop after a single exposure to ethanol.
a. **Behavior is changed** due to a loss of inhibitions.
b. The effects of other CNS depressants are enhanced.
c. **Hypothermia** results from peripheral vasodilation, which makes the person feel warm even though body heat is being lost.
d. **Hangovers** are common after drinking ethanol and may represent symptoms of an acute withdrawal.
e. Acute use of alcohol decreases metabolism of other CNS depressants.
f. **Panic attacks** may occur the day after alcohol is abused as blood alcohol levels drop.

5. A low intake of ethanol (one drink per day) is associated with increased high-density lipoprotein and decreased low-density lipoprotein cholesterol. This may reduce the risk of heart disease.

6. **Adverse effects from chronic (repeated) use** occur on almost every tissue in the body and include:
a. **Physical and psychological dependence**
b. **Activation of MFOs,** which increases the metabolism of many other drugs (e.g., phenytoin, warfarin)
c. **Edema** and **ascites**
d. **Hypertension**
e. **Cardiomyopathy** and **arrhythmias**
f. **Liver damage** (e.g., cirrhosis, fatty liver). **Acetaminophen combined with ethanol** can cause **severe acute liver damage** due to the production of hepatotoxic metabolites.
g. **Changes in blood glucose** due to **impaired gluconeogenesis**
h. **Damage to the gastrointestinal tract**
i. **Megaloblastic anemias** due to **folate** or **vitamin B_{12} deficiency,** or anemia due to **iron deficiency caused by GI bleeding**

j. **Malnutrition,** especially **thiamine deficiency,** which leads to **Wernicke–Korsakoff syndrome** (paralysis of extraocular muscles, ataxia, and confusion)
k. **Psychological sequelae. Depression** and **Korsakoff's psychosis** (long-term memory loss)
l. **Fetal alcohol syndrome.** Ethanol is a common cause of **birth defects** and **neurologic disorders.**
m. **Impaired visual acuity** (blurry vision)
n. **Immune system effects.** Increased **inflammation** of the liver and pancreas and increased risk for oropharynx and liver **cancers.**

7. **Withdrawal** from ethanol in someone who is dependent leads to a **stimulatory syndrome** that lasts about one week.
   a. **Tremor, hallucinations, convulsions, and delirium tremens** can occur during withdrawal.
   b. It is important to **replace thiamine** (vitamin B_1) and improve the diet.
   c. The severity of the withdrawal symptoms can be reduced by **replacement therapy with an antianxiety drug** (e.g., diazepam or chlordiazepoxide).
8. Long-term treatment of a recovering alcoholic requires counseling, group support therapy, and treatment for cravings.
   a. The opioid receptor antagonist **naltrexone** (*Revia, Vivitrol*) can reduce the craving for ethanol.
   b. **Acamprosate** (*Campral*) is a **weak NMDA receptor antagonist** and **$GABA_A$ receptor agonist** that is also used to treat alcohol cravings.
   c. **Disulfiram** (*Antabuse*) is occasionally useful to help alcoholics avoid the use of ethanol.
      i. It **inhibits the enzyme aldehyde dehydrogenase.**
      ii. **An accumulation of acetaldehyde** leads to a toxic syndrome (pain and retching) whenever ethanol is ingested.
      iii. Compliance with disulfiram treatment is generally poor.
9. **Methanol** has intoxicating effects similar to ethanol, except it is much more toxic.
   a. Metabolism by alcohol and aldehyde dehydrogenases results in the production of **formaldehyde and formic acid.**
      i. **Acidosis** and **sudden cessation of respiration** is the cause of death from acute ingestion.
      ii. **Retinal nerve damage** leads to blindness.
   b. **The specific antidote** for the treatment of methanol intoxication is **ethanol,** which competes with methanol for the metabolic enzymes and slows production of the toxic metabolites.
   c. Administration of bicarbonate and folate can be useful, as can dialysis.
10. **Ethylene glycol** is metabolized by the same pathway as ethanol and methanol to products that cause acidosis and renal failure.
    a. Acute intoxication is treated in a manner similar to methanol intoxication.
    b. **Fomepizole (***Antizol***)** is an **alcohol dehydrogenase inhibitor** that can prevent the formation of toxic metabolites.

B. BARBITURATES (e.g., pentobarbital and secobarbital) are very common drugs of abuse, although any sedative–hypnotic or antianxiety drug can be abused.

1. These drugs produce a **CNS depression with euphoria,** reduction of anxiety, and drowsiness, which is similar to the effects of ethanol.
   a. **Tolerance** occurs, but it is not large (5–10 times greater dose is needed to achieve the same effect).
   b. **Cross-tolerance** develops to alcohol, general anesthetics, benzodiazepines, and other sedative-hypnotics.

2. An overdose leads to **respiratory depression,** which should be treated symptomatically.
3. **Barbiturate withdrawal can be severe** and life-threatening with
   a. **Prolonged delirium**
   b. **Grand mal convulsions**
4. **Substitution therapy** (e.g., phenobarbital, given orally) can be used to reduce the withdrawal symptoms. The phenobarbital is then slowly withdrawn.

C. BENZODIAZEPINES have effects that are similar to other sedative–hypnotics.
1. They are commonly abused in ambulatory care settings; **alprazolam** (*Xanax*) is particularly prone to rapidly becoming abused by patients for whom it has been prescribed.
2. The withdrawal syndrome is similar to withdrawal from alcohol but is very long in duration (lasting from weeks to months)
   a. **Seizures** can occur and can result in **status epilepticus** and **death.**
   b. Treatment is similar to treatment for alcohol withdrawal, using a longer acting benzodiazepine such as **lorazepam** (*Ativan*) and then weaning the patient from it slowly.
3. An overdose of benzodiazepines can be reversed with **flumazenil;** however, this can induce withdrawal symptoms, and it may not restore normal respiratory function.

D. INHALANTS are most commonly used by very young abusers.
1. Inhalation of vapors from solvents, glue, gasoline, or anesthetics induces effects that are also very similar to ethanol.
2. As with other halogenated hydrocarbons, hepatotoxicity, cardiac toxicity, and carcinogenicity can occur.

III Cigarettes

A. NICOTINE is the active substance and is responsible for the addictive nature of cigarettes.
1. Nicotine binds to the nicotinic acetylcholine receptors, causing dopamine release in the ventral tegmental area of the brain.
2. **Stimulation of the CNS** induces arousal, relaxation, and mild euphoria.
3. **Activation of the sympathetic nervous system** induces vasoconstriction and an increase in blood pressure.

B. TARS AND CARBON MONOXIDE inhaled in cigarette smoke increase the risk of:
1. **Chronic obstructive pulmonary disease (COPD)**
2. **Cancer**
3. **Heart disease**

C. PHYSICAL AND PSYCHOLOGICAL DEPENDENCE occurs. Abstinence leads to anxiety, insomnia, and enhanced appetite that can last for several months.

D. Many approaches are available that increase the probability of successfully abstaining from cigarettes.
1. Physicians should follow the five As when counseling smokers
   a. **Ask** patients if they smoke.
   b. **Advise** patients to quit smoking.
   c. **Assess** patients' readiness to quit.

   d. **Assist** patients who would like to quit.
   e. **Arrange** for follow-up.
2. Nicotine is available in a patch, in gum, and in an inhaler. These devices release nicotine more slowly compared with smoking.
3. Other aids are available for smoking cessation.
   a. **Bupropion** (*Zyban*) is an antidepressant.
   b. **Varenicline** (*Chantix*) is a nicotinic receptor partial agonist.
4. Behavioral modification programs and telephone quit lines are also helpful.

IV CNS Stimulants

A. COCAINE AND AMPHETAMINES are the most commonly abused CNS stimulants.

B. The magnitude of the euphoria depends on the speed of onset.
1. **Amphetamines** can be taken **orally,** which results in a **slow onset.** They can also be **injected** or **crushed and snorted,** which results in a much **faster onset.**
2. Cocaine can be ingested, chewed, snorted, injected, or smoked.
   a. **Crack** is the free-base form of cocaine HCl. It is formed by heating cocaine HCl in an alkaline solution.
   b. **Smoked crack** has the most **rapid onset** and the most pleasurable effects.

C. Stimulants produce **euphoria** with:
1. Enhanced self-confidence and alertness
2. Increased motor activity
3. **Little physical dependence.** Fatigue is the primary physical symptom during withdrawal.
4. **Strong psychological dependence**

D. The period of euphoria varies depending on the half-life of the drug in the body.
1. **Cocaine induces a very short euphoria** (approximately 15 minutes), which is followed by a period of **marked dysphoria.**
2. The euphoria from amphetamines has a much longer duration.

E. Chronic abusers develop **paranoid, psychotic-like** symptoms.

F. OVERDOSES can be dangerous.
1. **Sympathomimetic actions** can lead to **tachycardia** and **arrhythmias.**
2. Abusers can become **aggressive** and experience **hallucinations.**
3. **Other dangerous effects** include **hypertension, hyperthermia, coma,** and **death.**
4. **Cocaine** can also induce
   a. **Gangrene,** due to peripheral vasoconstriction
   b. **Perforation of the nasal septum,** due to vasoconstriction in the nasal mucosa
   c. **Convulsions,** due to local anesthetic effects on the brain

V Anabolic Steroids

A. Steroids are often inappropriately used to enhance athletic performance and build muscle.

B. The Anabolic Steroid Control Act of 1990 made such use illegal.

C. SIDE EFFECTS include **increased blood pressure, heart disease, acne, baldness, hirsutism in women, impotence and gynecomastia in men, impulsivity, aggression, anger,** and **"'roid rage."**

VI Hallucinogens

A. These are drugs that **induce visual hallucinations.**

1. **Lysergic acid diethylamide (LSD),** psilocin, and harmaline are **indole** hallucinogens.
   a. The indole structure in these substances also occurs in serotonin, and these drugs are partial agonists of serotonin receptors.
   b. However, the colorful hallucinogenic effects and delusions are thought to be due to dopaminergic stimulation.
2. **Mescaline** and **MDMA** (methylenedioxymethamphetamine, **ecstasy)** are **phenylethylamine** hallucinogens.
   a. The phenylethylamines have more **sympathomimetic** effects than the indoles.
   b. MDMA is often used to decrease fatigue, enhance awareness, and give users a sense of closeness at rave parties.
      i. MDMA binds to the SERT transporter in neurons and increases serotonin levels in synapses by increasing serotonin release.
      ii. **Hyperthermia** is a dangerous adverse effect of MDMA.
3. **No physical dependence** occurs.
4. **Cross-tolerance** occurs between the indole and phenylethylamine hallucinogens.
5. Overdoses can result in a state of panic and psychotic behavior. These symptoms can be treated with diazepam.

B. PHENCYCLIDINE (PCP)

1. PCP, or "angel dust," is structurally similar to the anesthetic ketamine.
2. Although it produces hallucinations, there is **no cross-tolerance with LSD.** Chronic exposure can lead to **flashbacks** and a **schizophrenia-like psychosis.**
3. Low doses induce a **drunken-like state.**
4. High doses produce an **amphetamine-like state** in which the abuser can become very physically aggressive and difficult to control; thus, it is a very dangerous drug.

VII Marijuana

A. THE HEMP PLANT is the source of marijuana, which contains the active ingredient, **Δ^9tetrahydrocannabinol** (Δ^9THC). It is usually abused by smoking it.

1. Δ^9THC is **very lipid soluble,** and traces remain in the body for days after use.
2. **Metabolism** to an active product, 11-OH-Δ^9THC, occurs in the liver. This product is further hydroxylated to an inactive metabolite, 8,11-OH_2-Δ^9THC.

B. A VIVID DREAMLIKE STATE is induced with some **motor incoordination** and a **loss of sense of time.** Hallucinations and a sense of grandiosity can occur at high doses.

C. Chronic use leads to **some tolerance** for these effects, **apathy, and chronic bronchitis.** Long-term abusers are prone to developing **psychoses** (e.g., schizophrenia) and **paranoia**.

D. DRONABINOL (*Marinol*), which is Δ^9THC, has **antiemetic** and **appetite-stimulating** effects that are useful during cancer chemotherapy.

VIII Gamma-Hydroxybutyric Acid (GHB)

A. GHB inhibits the $GABA_B$ receptor in the ventral tegmental area of the brain at pharmacological doses.

B. GHB causes **euphoria, enhanced sensory perception, a feeling of social closeness, amnesia,** and **extreme thirst.**
1. It is a popular club drug, called "liquid ecstasy."
2. GHB has been used as a date rape drug because it is clear, odorless, colorless, and can easily be slipped into a drink.

IX Opioids

A. HEROIN, used intravenously, is the most popular opioid that is abused.
1. Physicians who abuse opioid drugs often choose potent ones like fentanyl.
2. Among health care providers, anesthesiologists and nurse–anesthetists are at particularly high risk for substance abuse.

B. The initial dose may be unpleasant with nausea, but subsequent doses induce a rush, euphoria, a reduction of anxiety, and contentment in the abuser.

C. MARKED TOLERANCE (up to 1000 times the original dose) to the desired effects occurs with repeated use of the opioids.

D. COMMON CAUSES OF DEATH in heroin addicts are
1. **Respiratory depression** from an overdose. This can be reversed with **naloxone** (*Narcan*) or **naltrexone** (*Revia*).
2. **Infections** from using unsterilized needles and syringes.

E. The withdrawal syndrome, which begins in 6 hours and peaks in 48 hours, includes:
1. Nausea, vomiting, diarrhea, and sweating.
2. Restlessness and tremor.
3. Dysphoria, lacrimation, rhinorrhea, piloerection, and fever.
4. Pupils are constricted while the drug is being used, and dilated during withdrawal.

F. WITHDRAWAL from heroin can be performed by
1. **Going "cold turkey"** (provide only symptomatic treatment)
2. **Replacement therapy with methadone,** a longer-acting opioid
3. **Treatment with clonidine** to reduce the symptoms

G. After withdrawal, abusers need long-term **rehabilitation** with
1. **Group therapy** (e.g., Narcotics Anonymous).
2. **Methadone maintenance,** which induces tolerance so that a lesser effect is obtained from heroin. However, methadone does not eliminate narcotic dependence; many patients will still have withdrawal symptoms after stopping use of methadone.
3. **Depot naltrexone.**

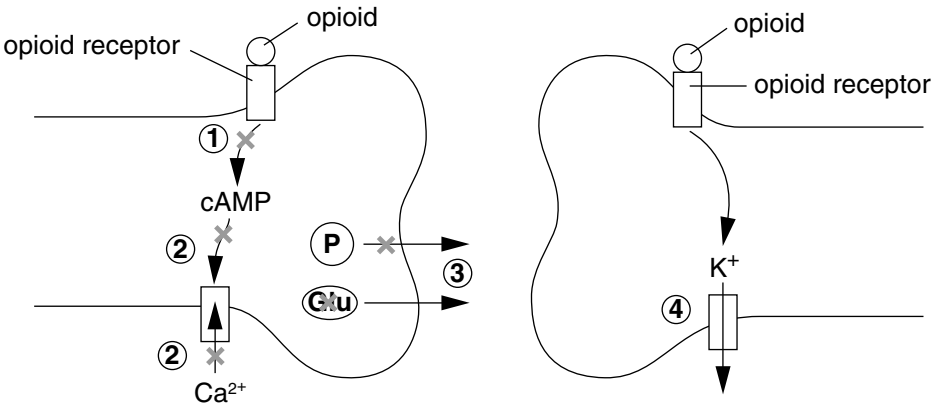
X Narcotic Analgesics

A. THE PROTOTYPE, MORPHINE, is extracted from the opium poppy in which 10% of the alkaloid content is morphine and 1% is codeine.

B. Morphine and codeine can be modified to form semisynthetic derivatives, including:
1. Heroin (diacetylmorphine), which is more lipid-soluble and has a more rapid onset of action
2. Oxycodone (*Roxicodone*)

C. Many synthetic narcotics have also been produced, such as
1. Meperidine (*Demerol*)
2. Levorphanol (*Levo-Dromoran*)
3. Methadone (*Dolophine*)
4. Fentanyl (*Duragesic*)
5. Propoxyphene (*Darvon, Dolene*)

D. THE PROPERTIES of morphine are representative of most of the drugs in this class.
1. Morphine is the least lipophilic opioid, but it can still cross the blood–brain barrier.
   a. **Absorption from the gut** is good, but serum morphine concentration is **variable** due to first-pass metabolism by the liver.
   b. The drug distributes in the total body water.
   c. It is **metabolized by glucuronide conjugation;** morphine-6-gluconoride is more active than the parent drug.
   d. Parenteral administration is commonly used to induce a rapid, predictable analgesic effect.
2. **The binding sites** for morphine are the endorphin, dynorphin, and enkephalin receptors. **μ-, κ,- and δ-receptor subtypes** have been identified; opioids act primarily on the **μ-receptors.**
   a. Opioid receptors are present in the pain-integrating areas of the CNS and PNS.
   b. Receptors are also present in the GI tract and brain stem, which leads to some undesirable effects of opioids (constipation, depression of respiration).
3. Opioids have multiple effects on pain pathway neurons, as shown in Figure 4-2.



● **Figure 4-2** Binding of opioids in the spinal pain pathway has several effects, including **(1)** decreasing presynaptic cAMP formation; **(2)** decreasing presynaptic calcium influx; **(3)** decreasing presynaptic glutamate and substance P release from vesicles; and **(4)** increasing postsynaptic hyperpolarization due to an increase in potassium efflux. (P) = substance P, Glu = glutamate, cAMP = cyclic AMP

a. **Analgesia** occurs due to a decrease of pain perception and a decrease in the psychological response to pain.
   i. An **inhibitory** action **on substance P release** in the spinal cord (see Figure 4-2) may account for some of the analgesic effects.
   ii. This is accompanied by a **mental clouding** or drowsiness.

b. Although the first dose can be dysphoric, subsequent doses produce euphoria.

4. Morphine induces many additional pharmacological **effects.**

a. **Respiratory depression** is induced by a reduction in the sensitivity of the medullary respiratory centers to CO_2. This occurs with all the narcotic analgesics and is the primary **cause of death** from an acute overdose.

b. **Physical dependence and tolerance** occur with long-term use, which means that a withdrawal syndrome will develop when the drug is discontinued. Cross-tolerance occurs with all other narcotic analgesics.

c. **Emesis** is often observed with the initial doses due to chemoreceptor stimulation in the area postrema in the medulla.

d. **Miosis** is induced by increased parasympathetic tone to the pupil via stimulation of the Edinger-Westphal nucleus. This is less pronounced with meperidine due to an anticholinergic effect.

e. **Constipation** results from decreased GI motility, even though there is increased tone of the GI smooth muscle.

f. **Histamine release** can be induced; thus, morphine can be dangerous to use in patients with asthma.

g. **Tone of the biliary tract and ureters** can be increased, causing urinary retention and inhibiting the voiding reflex.

h. **Antitussive** (cough suppressant) actions are prominent.

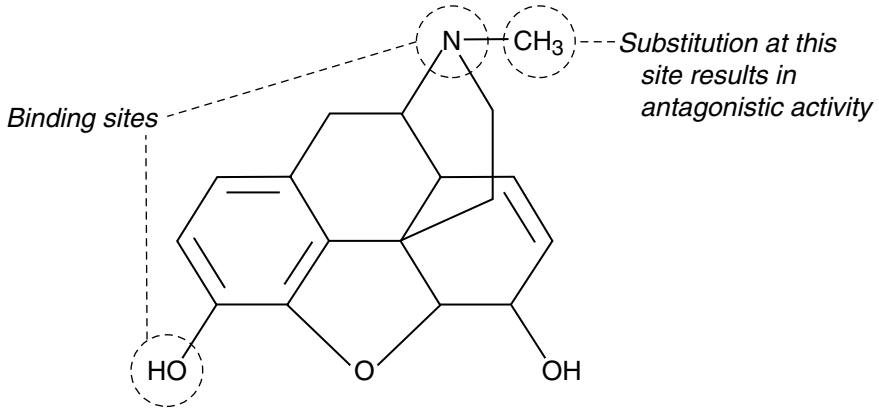
i. **Hyperthermia** can occur.

j. An **increase in intracranial pressure** can occur due to dilation of cerebral blood vessels.

E. NARCOTIC ANTAGONISTS have a structure that is very similar to morphine (Figure 4-3). A bulky substitution on the nitrogen results in antagonistic actions.

1. The pure antagonists have no analgesic activity.

a. **Naloxone** (*Narcan*) will
   i. **Reverse the respiratory depression** from an overdose of a narcotic.
   ii. Not affect the respiratory depression from a sedative-hypnotic.
   iii. **Induce a withdrawal syndrome in a narcotic addict.**



● **Figure 4-3** Modification of the narcotic structure (at N) results in narcotic antagonists. This diagram shows the structure of morphine.

   b. **Naltrexone** (*Revia*) **is more effective orally** and has a **longer duration of action** than naloxone.
2. **The weak agonist/antagonist analgesics,** such as **pentazocine** (*Talwin*), have analgesic activity in addition to antagonistic activity.
   a. They **will not reverse the respiratory depression** caused by a narcotic.
   b. They will **induce a withdrawal syndrome** in a narcotic addict.
   c. Most new narcotic analgesics are in this group. The rationale behind their use is that these analgesics should cause less respiratory depression and be less likely to be abused.

F. THERAPEUTIC USES of the narcotic analgesics include:
1. **Analgesia**
   a. Morphine is more potent than codeine, which is more potent than aspirin.
   b. Narcotics are used primarily for short term analgesia (e.g., myocardial infarction, surgery), except in terminally ill patients. The analgesic antipyretics are preferred to treat chronic pain.
2. **Diarrhea. Diphenoxylate** with atropine (*Lomotil*) or **loperamide** (*Imodium*) are preferred as they have few CNS effects.
3. **Neuroleptic anesthesia** (e.g., fentanyl).
4. **Antitussive** activity
   a. **Codeine** induces more cough suppression than morphine.
   b. **Dextromethorphan** (*Benylin DM*) has little narcotic activity, but it does have cough suppressant activity.
5. **Reduction of narcotic withdrawal symptoms.** This requires a drug, such as **methadone,** with a long duration of action.
6. **Maintenance of a narcotic addict** using methadone.

G. CLINICAL USES OF THE NARCOTIC ANTAGONISTS include:
1. **Analgesia** with the agonist/antagonist analgesics (pentazocine).
2. **Treatment of the respiratory depression from an acute narcotic overdose** using naloxone.
3. **Diagnosis of physical dependence** to a narcotic. Naloxone will precipitate withdrawal in narcotic addicts.
4. **Management of a narcotic addict.** Naltrexone will reduce the euphoric effects of the narcotics. **Buprenorphine** (*Suboxone, Subutex*), a partial agonist, is now available for outpatient treatment of opioid addicts.
5. **Management of an alcoholic.** Naltrexone reduces the craving for ethanol.

H. TRAMADOL (*Ultram*) is an atypical, narcoticlike analgesic that binds to μ-receptors and also inhibits reuptake of serotonin and norepinephrine.
1. It is indicated for **moderate to severe pain.**
2. **Seizures** are a serious potential side effect of tramadol; other side effects include **ulcers** and **GI bleeding.**
3. Although there is some potential for abuse, tramadol is currently not categorized as a controlled substance in the United States.

XI Analgesic Antipyretics

A. All analgesic antipyretics act by **inhibiting cyclooxygenase** (COX), thereby reducing prostaglandin synthesis.

B. ASPIRIN (acetylsalicylic acid) is a salicylate that acetylates and **irreversibly inhibits COX-1 and COX-2.** New COX must be synthesized to recover from the effects of aspirin.

1. The major **therapeutic effects** include:
   a. **Mild analgesia,** due to reduced prostaglandin synthesis at the sensory nerve endings
   b. **Antipyresis,** due to reduced prostaglandin synthesis in the hypothalamic temperature control center
   c. **Anti-inflammatory** actions at high doses, due to reduced prostaglandins at the sites of inflammation (See Chapter 7-VII.)
   d. At very low doses, **prophylaxis of MI** in older people at high risk

2. These effects occur without tolerance and without euphoria.

3. Side effects from aspirin include:
   a. **Gastric ulcerations** and gastric hemorrhaging, which can be **increased by ingesting ethanol** and **decreased by taking with food or misoprostol.**
   b. **Reducing platelet aggregation** by inhibiting formation of thromboxane A_2. This adverse effect is taken advantage of when managing patients
      i. After a myocardial infarction
      ii. With transient ischemic attacks
      iii. With angina, especially unstable angina
      iv. With atrial fibrillation
   c. **Hypersensitivity** reactions that
      i. Are not immunologically mediated
      ii. May be due to increased **leukotrienes**
   d. **Reduced renal uric acid secretion at low doses** and reduced uric acid reabsorption (uricosuria) at high doses.
   e. **Reye's syndrome,** which involves a fatal, fulminating hepatitis and cerebral edema, in children with chicken pox (varicella) or influenza viral infections. Thus, aspirin is best avoided in children.

4. Aspirin induces **acute toxic effects** in the following order as the dose is increased from the therapeutic to the toxic range.
   a. **Tinnitus** is an early indicator of toxicity.
   b. **Uncoupling of oxidative phosphorylation** increases CO_2 production, which increases respiration and can lead to hyperthermia at toxic doses.
   c. **Direct medullary stimulation** also enhances respiration, leading to **respiratory alkalosis** and HCO_3^- excretion (loss).
   d. At even higher doses, **metabolic acidosis** subsequently occurs due to
      i. **Direct respiratory depression**
      ii. **Acidic products** of aspirin metabolism, which leads to fluid and electrolyte loss
      iii. **Previous loss of HCO_3^-**

5. Management of aspirin overdoses involves
   a. **Emesis, lavage,** or **dialysis**
   b. **Fluids with HCO_3^-**
   c. **Monitoring blood aspirin concentration** beginning 6 hours after ingestion

C. IBUPROFEN (*Motrin, Nuprin, Advil*) and **naproxen** (*Aleve*) **reversibly inhibit COX** and have

1. Effects that are very **similar to aspirin,** including
   a. **Mild analgesic activity.** Ibuprofen is especially effective for dysmenorrhea.
   b. **Antipyretic activity.**
   c. **Anti-inflammatory activity.**

2. **Side effects** that are similar to, but milder than, the side effects for aspirin, including:
   a. **Gastrointestinal bleeding**
   b. **Increased bleeding times**
   c. **Overdose toxicity like that of aspirin**

D. KETOROLAC (*Toradol*) is an unusual NSAID in that it can be **given intramuscularly** as well as orally.
1. It is only used for the **treatment of acute pain.**
2. It has a clinical efficacy similar to morphine.

E. ACETAMINOPHEN (*Tylenol*) elevates the pain threshold, possibly by inhibiting the NO pathway.
1. The primary **effects** of acetaminophen are quite different from aspirin, and include:
   a. **Mild analgesic activity**
   b. **Antipyretic activity**
   c. **No anti-inflammatory activity**
   d. **None of the side effects of aspirin**
2. **The major adverse effect** from high doses is **delayed hepatic necrosis.**
   a. A toxic phase 1 metabolite builds up in the liver because of the **depletion of glutathione.**
   b. This toxicity is especially prominent in combination with ethanol.
   c. The hepatotoxicity can be avoided by early administration of **N-acetylcysteine,** which replenishes the stores of glutathione.

Chapter **5**

Cardiovascular Pharmacology

I Diuretics

A. Drugs in this class act on the kidney to **enhance the elimination of salt and water** from the body.

B. Increased intake of water does increase urine volume, due to decreased antidiuretic hormone (ADH) and decreased renin release. Water itself is not a diuretic, however, because there is no net loss of body fluids.

C. IN THE PROXIMAL CONVOLUTED TUBULE, CARBONIC ANHYDRASE INHIBITORS (e.g., **acetazolamide** [*Diamox*]) **induce bicarbonate loss,** which leads to alkaline diuresis.

D. IN THE DESCENDING LOOP OF HENLE, OSMOTIC DIURETICS (e.g., **mannitol** [*Osmitrol*], glycerol, and urea) are **filtered by the kidney and are not reabsorbed.**

1. These diuretics osmotically hold water in the tubules and increase urine flow.
2. However, they can increase extracellular volume, resulting in edema.

E. THE LOOP DIURETICS (**furosemide** [*Lasix*], **ethacrynic acid** [*Edecrin*], and **bumetanide** [*Bumex*]) act at the **thick, ascending limb of the loop of Henle,** which is **impermeable to water.**

1. **Sodium and chloride cotransport is blocked** due to **inhibition of the $Na^+/K^+/2Cl^-$ transporter.**
2. **A marked diuresis is produced** because large amounts of sodium are normally reabsorbed at this site.
3. Loop diuretics are effective when taken orally and are **eliminated by active proximal tubular secretion.**
   a. This secretion is important for the drugs to reach their intratubular site of action.
   b. Competition with the transport of uric acid at the same site can lead to hyperuricemia.
   c. Loop diuretics have much shorter durations of action than the thiazides.
4. **Side effects** are more common than with thiazides and include:
   a. **Hypovolemia,** due to rapid, large decrease in blood volume.
   b. **Hyponatremia.**
   c. **Hypokalemia,** which increases the risk of atrial and ventricular arrhythmias.
   d. **Hyperuricemia,** which can cause or exacerbate attacks of gout.
   e. **Hyperglycemia.**
   f. **Hypocalcemia,** which is the opposite of the effect of thiazides.
   g. **Ototoxicity,** especially with ethacrynic acid. Loop diuretics should not be combined with other ototoxic drugs (e.g., aminoglycosides).

5. **Loop diuretics have a greater diuretic efficacy than the thiazides, which have a greater efficacy than the potassium-sparing diuretics.**

F. THIAZIDE (e.g., **hydrochlorothiazide** [*Esidrix, HydroDIURIL*]) and thiazide-like (e.g. **chlorthalidone** [*Hygroton, Thalitone*]) **diuretics** are the most commonly used class of diuretic drugs. They **impair sodium and chloride cotransport** in the **initial part of the distal tubule.**

1. The distal convoluted tubule is also impermeable to water; thus, the increased sodium in the tubular fluid holds water in the nephron, leading to diuresis.
2. The increased sodium in the tubular fluid also enhances Na^+/K^+ exchange, leading to **hypokalemia.**
3. Thiazides **increase calcium reabsorption,** which can **decrease the risk of hip fracture due to osteoporosis.**
4. Thiazide diuretics also **decrease peripheral vascular resistance in arterioles.**
5. The thiazides are effective when taken orally and are **eliminated by active proximal tubular secretion.**
   a. Secretion into the lumen is important for the drugs to reach their intratubular site of action.
   b. Competition with the transport of uric acid at the same site can lead to hyperuricemia.
6. **Side effects** from the thiazides include:
   a. **Hypokalemia,** which is the most common side effect. This can increase the risk of arrhythmias.
   b. **Hyperuricemia,** which may precipitate or exacerbate gout attacks.
   c. **Hyperglycemia** in diabetics due to decreased insulin release.
   d. **Small increases in low-density lipoprotein (LDL) cholesterol.**
   e. **Hypercalcemia.**
   f. **Hyponatremia,** due to increased ADH levels secondary to hypovolemia.
   g. **Orthostatic hypotension,** due to volume depletion.

G. POTASSIUM-SPARING DIURETICS induce a weak diuresis by **reducing sodium–potassium exchange** in the **late portion of the distal tubule and collecting ducts.** The serum potassium is elevated as a result of this action.

1. **Spironolactone** (*Aldactone*) is a **competitive aldosterone antagonist;** thus it is effective only when aldosterone is present.
2. **Triamterene** (*Dyrenium*) and **amiloride** (*Midamor*) directly block ENaC sodium channels in the collecting duct. Thus, they are effective even after an adrenalectomy and loss of endogenous aldosterone.
3. These drugs cause
   a. **Potassium retention**
   b. **Small sodium loss**
   c. **Weak diuresis**
4. **Side effects**
   a. **Hyperkalemia**
      i. Potassium-sparing diuretics are frequently combined with thiazide and loop diuretics to counteract the hypokalemia from those diuretics.
      ii. If the acute risk of cardiac arrhythmias from hyperkalemia is high, administration of insulin will reduce the hyperkalemia by enhancing potassium uptake into cells.
   b. **Gynecomastia** can be induced in men by spironolactone, which is a steroid antagonist.
   c. **Menstrual irregularities** in women can also result from spironolactone use.

H. CONIVAPTAN (*Vaprisol*) is an **ADH (vasopressin) antagonist** that **blocks the V_2 receptors in the collecting duct.** This may cause nephrogenic diabetes insipidus.

I. Other drugs have diuretic side effects.
1. The **xanthines** (e.g., caffeine, theophylline, theobromine) produce a weak diuresis by increasing the glomerular filtration rate.
2. **Lithium** is not used primarily as a diuretic, but it has anti-ADH activity.

J. Diuretics are useful to **mobilize edematous fluid** from many sites in the body. Important **clinical indications for administration of diuretics** include:
1. **Congestive heart failure.** Diuretics will reduce the preload on the heart and improve heart function.
2. **Hypertension.**
3. **Hepatic ascites,** which commonly occurs due to cirrhosis of the liver.
4. **Acute pulmonary edema,** because of the rapid, massive effect of loop diuretics.
5. **Renal failure** due to damage to glomeruli, which causes a **nephrotic syndrome.**
6. **Hypercalcemia.** Can be treated with a loop diuretic such as furosemide.
7. **Hypocalcemia.** Can be treated with a thiazide.
8. **Nephrogenic diabetes insipidus.** Can be treated with a thiazide because thiazides produce hyperosmolar urine.
9. **Inappropriate ADH secretion.** Can be treated with furosemide and hypertonic saline or conivaptan.
10. **Increased intracranial pressure.** Can be treated with an osmotic agent.
11. **Hyperaldosteronism.** Can be treated with spironolactone.

II Calcium Channel Blockers

A. Drugs in this class **block the slow calcium channels,** especially the voltage-sensitive L-type calcium channels. Calcium channel blockade primarily affects the cardiovascular system.
1. Reduced calcium entry **reduces the plateau phase** (phase 2) of the action potential in the sinoatrial (SA) and atrioventricular (AV) nodes of the heart. There is little effect on the ventricular action potential, where calcium currents are less important.
2. Reduced calcium entry into vascular smooth muscle leads to **vasodilation** and a fall in blood pressure.

B. VERAPAMIL (*Calan, Isoptin*), a diphenylalkylamine; and **diltiazem** (*Cardizem*), a benzothiazepine, have the following actions:
1. **Reduce heart rate**
2. **Prolong AV conduction time**
3. **Dilate coronary vessels**
4. **Dilate peripheral arterioles,** without affecting venules
5. **Reduce myocardial contractility**

C. The dihydropyridines **nifedipine** (*Procardia*) and **nicardipine** (*Cardene*) are much **more potent arterial vasodilators,** and the fall in blood pressure activates baroreceptor reflexes. As a result, the myocardial depressant effects from calcium channel blockade are counteracted, and
1. **Heart rate is increased.**
2. **AV conduction time is reduced.**
3. **Myocardial contractility is increased.**

D. AMLODIPINE (*Norvasc*) is a long-acting dihydropyridine calcium channel blocker with properties similar to nifedipine.

E. THE CLINICAL INDICATIONS for the calcium channel blockers are

1. **Supraventricular arrhythmias**
   a. **Paroxysmal supraventricular tachycardia (PSVT) can be acutely terminated.**
   b. **Atrial flutter and fibrillation are effectively treated,** because reduced AV conduction due to the calcium channel blockade reduces the ventricular rate.
2. **Angina,** because calcium channel blockers dilate coronary and other vascular smooth muscle.
3. **Hypertension.**
4. **Cerebral vasospasm.** The dihydropyridine **nimodipine** (*Nimotop*) has high lipid solubility and is particularly effective for this purpose.
5. **Vascular disease.**
6. **Migraine headaches.** Verapamil is commonly used for this purpose.

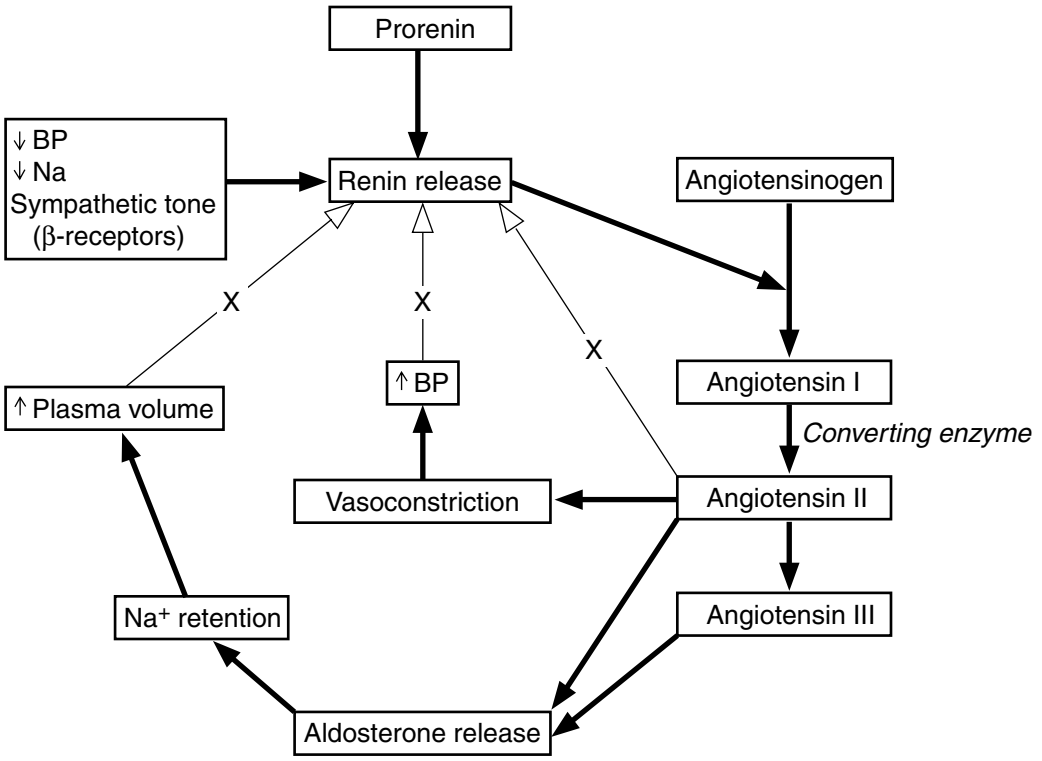
F. SIDE EFFECTS of calcium channel blockers include the following:

1. **Constipation**
2. **Hypotension and dizziness**
3. **Exacerbation of preexisting heart failure,** especially with verapamil
4. **Flushing**
5. **AV block and bradyarrhythmias**

III Antihypertensives

A. Treatment with antihypertensives is usually **initiated if the patient's blood pressure (BP) is greater than 140/90 mm Hg.**

1. **Essential hypertension** is of **multifactorial origin** (genetic plus environmental). It disproportionately affects **older people**, **men**, and **blacks.**
2. **Arterial blood pressure = cardiac output (CO) × peripheral resistance.** CO depends on **heart rate** and **stroke volume (**which depends on **contractility, preload**, and **afterload).**
3. There are **two interconnected BP control systems** in the body:
   a. **Baroreceptors,** which **increase sympathomimetic stimulation** and **decrease parasympathomimetic stimulation in response to a decrease in BP (rapid response).**
   b. **Renin–Angiotensin–Aldosterone System (RAAS).** The **kidney releases renin in response to decreased perfusion.**
      i. Renin cleaves **angiotensinogen** to **angiotensin I (AT I),** which is in turn cleaved to **angiotensin II (AT II)** by **the angiotensin-converting enzyme (ACE).**
      ii. **AT II** is a potent **vasoconstrictor.** It also **reduces renin release** and **stimulates release of aldosterone.** Increased aldosterone leads to **sodium and water retention** and an **increase in BP (**Figure 5-1).
      iii. The primary clinical use of angiotensin is to **increase blood pressure.** It induces fewer cardiac arrhythmias than the catecholamines.
4. Treatment of hypertension has been demonstrated to **decrease the incidence of**
   a. **Stroke**
   b. **Heart failure**
   c. **Myocardial infarction**
   d. **Coronary artery disease**



● **Figure 5-1** Renin–angiotensin aldosterone system.

e. **Renal failure**
f. **Arterial dissections**

B. **TREATMENT** for hypertension is initiated with **lifestyle changes** (e.g., weight loss, decreased consumption of salt).

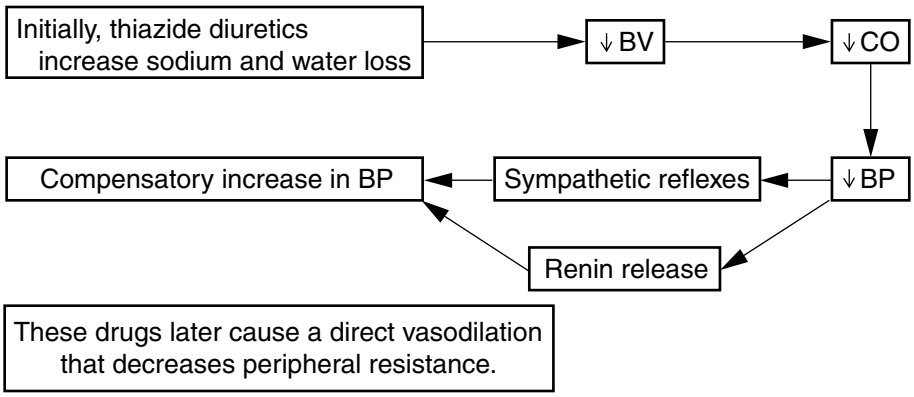
C. If this is insufficient to control blood pressure, a **thiazide diuretic** (e.g., **hydrochlorothiazide** [*Esidrix, HydroDIURIL*]) can be given.

1. Thiazides are useful in hypertension because they are **cheap, convenient,** and have **few side effects.**

2. **Thiazides initially increase sodium and water loss.**

a. This effect is compensated for by the mechanisms illustrated in Figure 5-2.
b. **Later,** the blood pressure is reduced as a result of **direct vasodilation,** which decreases peripheral resistance.
c. **High salt intake** leads to **water retention,** which will **reduce the effectiveness of the thiazides.**
d. The **onset of the antihypertensive action is slow,** taking 2–4 weeks to develop.
e. **Side effects** can occur, including:
   i. **Hypokalemia.** To avoid hypokalemia, combine thiazide diuretics with potassium supplements or potassium-sparing diuretics (e.g., spironolactone).
   ii. **Hyperglycemia.**
   iii. **Small increases of LDL and small decreases of HDL cholesterol.**

3. Loop diuretics should only be used if the thiazides do not induce diuresis.



● **Figure 5-2** Effects of the thiazides that reduce blood pressure and activate homeostatic mechanisms. BV = blood volume. CO = cardiac output. BP = blood pressure.

D. BETA-BLOCKERS (e.g., **propranolol** [*Inderal*]) can be given as a first-line alternative to thiazide diuretics.

1. **β-Blockers** have many effects on blood pressure. The **mechanism** may be related to
   a. **Decreased heart rate and contractility**
   b. **Decreased renin release**
   c. **Decreased CNS sympathetic output**
   d. **Blockade of presynaptic β-adrenoceptors,** resulting in decreased norepinephrine (NE) release
2. **The side effects** are described in Table 2-6. Additional concerns include increased LDL cholesterol, increased triglycerides, and reduced high-density lipoprotein (HDL) cholesterol; however, these changes are small.
3. When combined with other antihypertensives, propranolol decreases the reflex sympathetic activation of the heart and the reflex sympathetic activation of renin release.
4. **Metoprolol is cardioselective;** thus, it induces less bronchoconstriction in asthmatics and less masking of hypoglycemia in diabetics than propranolol. The β-selectivity is relative, however, and tends to disappear at high dosages.

E. ANGIOTENSIN-CONVERTING ENZYME (ACE) can be inhibited by several drugs.

1. **The effects** of ACE inhibition include:
   a. **Reduced conversion of angiotensin I to angiotensin II**
   b. **Reduced blood pressure**
   c. **Reduced aldosterone levels,** which increases sodium and water excretion
   d. **Increased plasma renin levels,** due to reduced feedback inhibition on renin release
   e. **Dilation of efferent renal arterioles,** which are regulated by angiotensin II, thus reducing renal perfusion pressure
   f. **Decreased vasoconstriction**
   g. **Increased bradykinin levels** due to decreased breakdown of bradykinin by ACE, which leads to additional vasodilation
2. **The indications** for ACE inhibitors are
   a. **Hypertension.**
   b. **Congestive heart failure.** ACE inhibitors have been shown to decrease mortality in CHF patients.
   c. Prevention and treatment of **diabetic nephropathy.**
   d. Patients who have had a **recent MI.**

3. **The side effects** include:
   a. **Hyperkalemia,** due to reduced aldosterone levels.
   b. **Hypotension.**
   c. **Coughing,** due to **increased bradykinin.**
   d. **Skin rashes and angioedema.**
   e. **Fetal toxicity.** ACE inhibitors should not be used during pregnancy.
   f. **Excessive reduction of pressure in the glomerulus** due to dilation of the efferent renal arterioles**.** ACE inhibitors should be avoided in patients with renal artery stenosis.
4. **Captopril** (*Capoten*) is the prototype ACE inhibitor.
   a. It **reduces angiotensin synthesis** and **lowers blood pressure** by
      i. **Vasodilation**
      ii. **Reduction of aldosterone release,** which increases the loss of water
   b. There are no autonomic effects and no changes in LDL cholesterol.
5. **Enalapril** (*Vasotec*) and **lisinopril** (*Prinivil, Zestril*) have the same effects as captopril, but they have **longer durations of action.**

F. AT1 ANGIOTENSIN II RECEPTORS can be **inhibited** by **angiotensin II receptor blockers (ARBs)** such as **losartan** (*Cozaar*) and **candesartan** (*Atacand*).
1. Effects are similar to those from ACE inhibitors. ARBs can therefore be used to treat CHF or hypertensive patients who cannot tolerate ACE inhibitors.
2. **Coughing is less common** because ACE is not inhibited and bradykinin levels do not rise.
3. However, ARBs are also **fetotoxic** and should not be used in pregnancy.

G. CALCIUM CHANNEL BLOCKERS (e.g., amlodipine [*Norvasc*]) vasodilate arterioles and reduce blood pressure.
1. They have no autonomic side effects and do not change LDL cholesterol.
2. There is an increased risk of heart attack or stroke with the short-acting dihydropyridines such as nifedipine.

H. THE SECOND LINE of drugs includes the **sympathetic blockers.** These drugs can be used alone but are usually combined with a first line drug.
1. **Peripheral sympathetic blockers** that can be used in hypertension include:
   a. **Prazosin** (*Minipress*), an α_1-blocker
   b. **Labetalol** (*Trandate, Normodyne*), an α_1- and β-blocker
2. Several drugs **act on the CNS** to reduce the efferent sympathetic tone (output) to the cardiovascular system.
   a. **Methyldopa** (*Aldomet*) is metabolized in CNS adrenergic neurons to **α-methyldopamine** and **α-methylnorepinephrine (α-methylNE).**
      i. **α-MethylNE** acts on α_2-adrenoceptors and decreases the sympathetic outflow from the medulla.
      ii. The site of action appears to be the **nucleus tractus solitarius.**
   b. **Clonidine** (*Catapres*) and **guanabenz** (*Wytensin*) are **α_2-adrenoceptor agonists** that act like α-methylNE in the medulla.
   c. **Side effects** from the CNS active sympathetic blockers include:
      i. **Drowsiness.**
      ii. **Sodium and water retention.** This can be decreased by coadministration of a diuretic.
      iii. **Positive Coombs' test** (increased risk for hemolytic anemia) with **methyldopa.**

iv. **Acute rebound hypertension with clonidine.** Clonidine should be withdrawn slowly.

I. DIRECT VASODILATORS (e.g., **hydralazine** [*Apresoline*], **minoxidil** [*Loniten*]) are useful in combination regimens for severe hypertension.

1. **Vasodilation of arterioles** leads to a fall in blood pressure.
2. **Homeostatic mechanisms** (e.g., sympathetic reflexes) are induced, which compensate for the fall in blood pressure and make the arteriolar vasodilators **ineffective when used alone.** The homeostatic mechanisms include increases in
   a. Sympathetic vasoconstrictor tone to blood vessels
   b. Heart rate
   c. Myocardial contractility
   d. Renin release, leading to increased fluid retention
3. The vasodilators are usually **combined with diuretics and sympathetic blockers,** which will dampen homeostatic compensatory mechanisms.
4. **Side effects** of these drugs include:
   a. **Palpitations.**
   b. **Flushing.**
   c. **Headache.**
   d. **Lupus-like syndrome with hydralazine,** especially in patients who are slow acetylators. This effect is reversible if the drug is discontinued.
   e. **Hirsutism with minoxidil.** In fact, minoxidil is used topically (as *Rogaine*) to treat baldness.
   f. **Pericardial effusion with minoxidil.**

J. HYPERTENSIVE CRISIS is a **severe rise in blood pressure** that has either already caused organ damage (**hypertensive emergency**) or has the potential to cause organ damage (**hypertensive urgency**).

1. Hypertensive crisis may be caused by secondary mechanisms. If hypertension is due to **elevated catecholamines,** a **phentolamine test** can be used for diagnosis.
   a. **Phentolamine** (*Regitine*) is an α-antagonist. It will **rapidly reduce blood pressure that has been elevated** due to
      i. Pheochromocytoma
      ii. Monoamine oxidase inhibitors
      iii. Sympathomimetics or cocaine
      iv. Clonidine withdrawal
   b. **Measurement of urinary catecholamine metabolites** is also diagnostic.
   c. **Treatment of hypertensive crisis due to elevated catecholamines** involves the administration of
      i. **α- and β-blockers**
      ii. Labetalol
      iii. Metyrosine, an inhibitor of tyrosine hydroxylase
2. **Hypertensive crises due to other causes** will not respond as dramatically to phentolamine and are treated with rapid-acting antihypertensives, usually administered intravenously.
   a. **Sodium nitroprusside** (*Nitropress*), like the nitrates, **dilates venules** and **arterioles.**
      i. The onset of action is **very rapid,** within minutes.
      ii. The half-life is **very short,** which makes the antihypertensive effect **very controllable,** but requires regular monitoring and administration by continuous infusion.

iii. **Side effects** include:
(a) **Hypotension.**
(b) **Toxicity from thiocyanate and cyanide,** which are by-products of nitroprusside metabolism. Cyanide toxicity can be treated with sodium thiosulfate.

b. **Fenoldopam** (*Corlopam*), is a **D_1-dopamine receptor agonist** that
i. **Dilates** peripheral arterioles, especially **renal and mesenteric arterioles**
ii. Has a **rapid onset** after IV infusion
iii. Has a **very short half-life**

c. **Nitroglycerin IV** has actions similar to nitroprusside, although venous dilation is more pronounced than arterial dilation.

d. **Diazoxide** (*Hyperstat IV*), like hydralazine, **dilates only arterioles.**
i. **Side effects** include:
(a) **Palpitations**
(b) **Hyperglycemia**
ii. Can **aggravate angina.**

e. **Labetalol** (*Normodyne, Trandate*), when administered intravenously, has a rapid antihypertensive action.

IV Drugs for Angina Pectoris

A. Patients with angina (stable, variant, or unstable) develop **ST segment elevation or depression** on the electrocardiogram (EKG) during myocardial hypoxia. This can be induced diagnostically by
1. Treadmill stress testing
2. Ergonovine, which induces coronary vasoconstriction
3. Dobutamine, which increases heart rate and contractility

B. TREATMENT of angina is oriented to reducing oxygen demand or increasing oxygen supply to the heart.

1. Nitric oxide (*INOmax*) is a gaseous signaling molecule that **dilates blood vessels** and **protects them against thrombosis and atherogenesis**.
a. Note that **nitric oxide (NO),** the vasodilator, should not be confused with **nitrous oxide (N_2O),** the anesthetic.
b. There are **three nitric oxide synthase enzymes** that produce NO: **nNOS (neural), eNOS (endothelial),** and **iNOS (inducible).**
i. **nNOS** and **eNOS** are **constitutively active** and regulated by **calcium.**
ii. **iNOS** is activated in **macrophages** in response to **inflammatory mediators.** It is not regulated by calcium.
c. NO binds to **guanylyl cyclase,** leading to an increase in **cGMP** and **protein kinase G (PKG).** This pathway leads to vasodilation.
d. NO can also be toxic to cells. The **antioxidant glutathione** protects cells from the oxidative effects of NO.
e. Currently, it is believed that selective iNOS inhibition would permit the positive effects of NO while preventing the negative effects. However, there is no iNOS-specific inhibitor on the market at this time.

2. Nitrates, which are useful for all types of angina, act directly on vascular smooth muscle cells.
a. They dilate vessels in a manner similar to nitric oxide. Endothelium-derived relaxing factor (EDRF) is probably nitric oxide.

i. The primary effect is a **reduction in venous tone,** which leads to venous pooling and reduced venous return (reduced preload).
ii. Arteriolar tone is less effectively reduced, and leads to reduced peripheral resistance (reduced afterload) and reduced blood pressure.
iii. Both effects reduce the myocardial wall stress and thereby **reduce oxygen consumption** of the heart.
iv. Dilation of collateral coronary vessels and coronary vessels in spasm are additional minor effects.

b. Short- and long-acting **preparations** are available.
i. **Nitroglycerin** (*Nitrostat*) is administered **sublingually** or as a **spray** to terminate an acute anginal attack.
(a) Onset is very rapid and half–life is short (1–3 minutes).
(b) Oral administration is ineffective for the treatment of an acute attack due to a high first–pass metabolism.
ii. High doses of nitroglycerin (*Nitro-Bid*) which saturate the metabolic enzymes, can be administered orally or topically as a patch for prophylaxis.
iii. **Isosorbide dinitrate** (*Isordil*) and **isosorbide mononitrate** (*Imdur*) are long-acting nitrates that are also useful for prophylaxis.

c. **Side effects** from nitrates include:
i. **Headache** from vascular dilation, the most common side effect
ii. **Syncope** from **postural hypotension**
iii. **Reflex tachycardia,** which may occasionally induce an anginal attack
iv. **Methemoglobinemia,** which can be reversed by methylene blue
v. **Tolerance and withdrawal symptoms,** such as anginal attacks during withdrawal from high-dose, long-term therapy

d. **Erectile dysfunction** can also be treated with nitrates**.**
i. **Sildenafil** (*Viagra*) is an oral drug that **prolongs penile erections** by **inhibiting phosphodiesterase type 5 (PDE-5),** an enzyme that metabolizes **cGMP.**
(a) Increased cGMP concentrations lead to decreased intracellular calcium levels. This causes relaxation of the corpus cavernosum and an erection.
(b) Sildenafil should be administered at least 1 hour before intercourse. Its effects last for up to 6 hours.
(c) **Side effects** of sildenafil include **interfering with blue-green vision.** In addition, sildenafil should not be used with other nitrates.
ii. **Tadalafil (***Cialis*) is another PDE-5 inhibitor that has a much **longer duration of action** than sildenafil (up to 36 hours).

3. **Amyl nitrite** is an inhaled vasodilator that is used for rapid relief of angina.
4. **β-Blockers** produce several beneficial effects.
a. β-Blockade of the heart is the primary mode of action.
i. Exercise-induced tachycardia and exercise-induced increases in myocardial contractility are reduced.
ii. Blood pressure is decreased (decreased afterload).
iii. Heart rate is reduced, which increases endocardial perfusion time.
iv. Reflex tachycardia from the nitrates is reduced, making the combination of nitrates and β-blockers quite useful.

b. Propranolol should be used with caution in patients with
i. **Variant (Prinzmetal's) angina,** as blockade of β-adrenoceptors (dilatory) in the coronary vessels may increase the coronary spasm
ii. **Asthma,** due to a bronchoconstricting effect

iii. **Calcium channel blockers,** as both classes of drugs depress myocardial contractility

c. **Propranolol is used prophylactically for 1.5 to 3 years after an acute MI to decrease ischemic damage.**

d. The side effects of β-blockers have been previously described (See Table 2-6). It is important to **avoid rapid withdrawal** from treatment, which can induce anginal attacks and rebound hypertension.

5. **Calcium channel blockers** (e.g., verapamil [*Calan, Isoptin*]) are effective for the treatment of all types of angina and may be used in combination with nitrates, β-blockers, or both. Calcium channel blockers:
   a. **Decrease heart rate**
   b. **Decrease myocardial contractility**
   c. **Vasodilate arterioles** (decrease afterload)
   d. **Dilate coronary vessels,** which reduces coronary spasm

V Drugs for Congestive Heart Failure

A. HEART FAILURE occurs when the **heart cannot pump enough blood to meet the body's needs.**

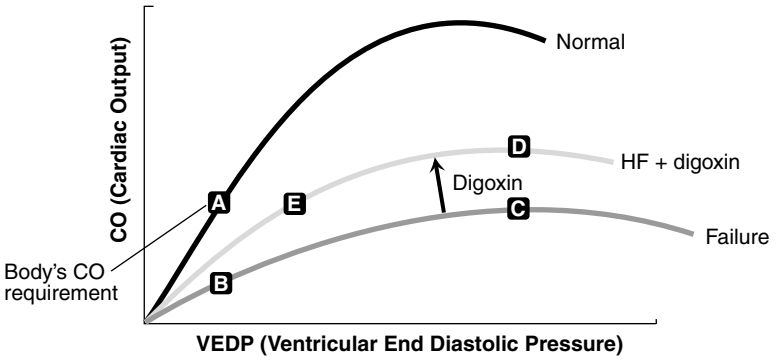
1. The body uses several physiologic mechanisms to compensate for heart failure:
   a. **An increase in sympathetic activity,** which leads to increased heart rate, contractility, afterload, and preload
   b. **Stimulation of the RAAS due to decreased kidney perfusion,** which increases the work done by the heart
   c. **Hypertrophy and dilation of the heart's chambers,** which can lead to systolic and/or diastolic dysfunction
2. If these mechanisms are not able to compensate for the heart failure, then the patient is said to have decompensated heart failure.

B. MILD CHRONIC CONGESTIVE HEART FAILURE CAN BE TREATED WITH drugs that reduce the preload and/or afterload on the heart, such as

1. **ACE inhibitors,** the drugs of choice, cause vasodilation and improve blood flow. This decreases the work of the heart. ARBs can also be used.
2. **β-blockers** (e.g., carvedilol) block sympathetic effects on the heart and vasculature.
3. **Aldosterone-inhibiting diuretics,** e.g. spironolactone, block the effects of aldosterone.
4. **Other diuretics (**e.g., loop diuretics or thiazides) eliminate excess water from the body and decrease the work of the heart.
5. **Vasodilators** (e.g., hydralazine), if ACE inhibitors are contraindicated or not tolerated.
6. Several other positive inotropes can be used, including **β-adrenergic agonists** (e.g., dobutamine) and **PDE inhibitors** (e.g., milrinone, amrinone). **These drugs may increase mortality in heart failure patients.**

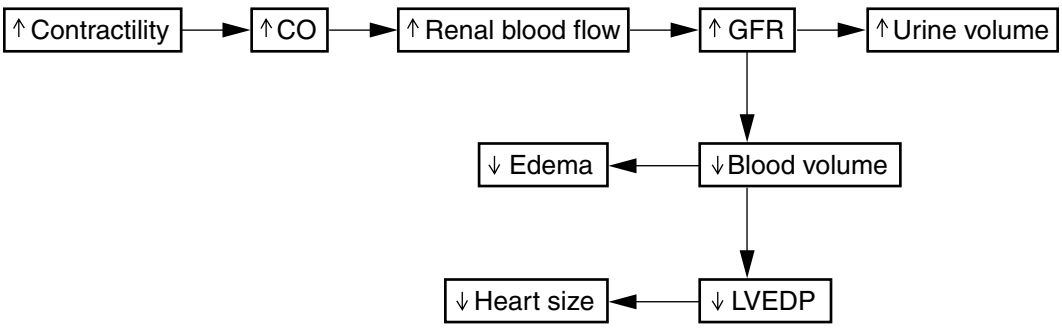
C. Historically, heart failure was treated with **cardiac glycosides,** which are derived from the foxglove (*Digitalis*) plant.

1. **The glycosides inhibit** the **Na^+/K^+ ATPase,** which **reduces active Na^+/K^+ transport.** This increases the intracellular concentration of sodium.
2. It also increases intracellular **calcium** by dissipating the sodium gradient required by the sodium–calcium antiport pump.



● **Figure 5-3** Effect of digoxin on myocardial contractility. A. Normal patient, with CO on the steep part of the Frank–Starling curve. B. Decompensated heart failure, accompanied by dyspnea, fatigue, and edema. C. In the decompensated patient, VEDP cannot increase sufficiently to increase CO above the body's minimum requirement. D. Digoxin or digitalis increases inotropy to a steeper curve so that an increase in VEDP leads to compensation. E. VEDP can decrease back toward the steeper part of the Frank–Starling curve with treatment, giving the patient a cardiac reserve. However, the curve is still flatter than normal.

3. The elevated free calcium ion concentration enhances myocardial contractility.
4. The effect on ventricular performance is shown in Figure 5-3.
   a. No net change of oxygen consumption occurs.
   b. The efficiency of myocardial contractions is improved.
5. The increased contractility leads to a cascade of events shown in Figure 5-4.
6. Two glycosides are used clinically:
   a. **Digoxin** (*Lanoxin*)
   b. **Digitoxin** (*Crystodigin*)
7. Glycosides are used as third-line drugs behind beta blockers and calcium channel blockers to treat **supraventricular arrhythmias** (e.g., atrial flutter and atrial fibrillation). The glycosides reduce ventricular rate by inducing partial AV nodal block.
8. **Side effects** are very common because there is considerable overlap between therapeutic and toxic serum concentration ranges.
   a. Most importantly, **glycosides cause arrhythmias that are accentuated by hypokalemia** (e.g., from diuretics) or **hypercalcemia.**
   b. If toxicity is life threatening, administer digoxin immune Fab (*Digibind*).
   c. **Drug interactions** leading to increased toxicity are common.



● **Figure 5-4** Effects resulting from the increase in myocardial contractility induced by digoxin. CO = cardiac output; GFR = glomerular filtration rate; LVEDP = left ventricular end-diastolic pressure

D. Uncompensated heart failure can ultimately lead to cardiogenic shock. The treatment for each type of shock (e.g., hypovolemic, cardiac insufficiency, altered vascular resistance) will be quite different.
1. **The goal is to optimize tissue perfusion,** not blood pressure (BP).
2. **Volume replacement** and **treatment of the cause of the shock** are the first steps.
3. **Sympathomimetics** can be used to increase BP. However, vasoconstrictors should be avoided if blood flow to the peripheral tissues is already compromised.
   a. **Dopamine** and **metaraminol** (*Aramine*) **increase BP without decreasing renal blood flow.**
   b. **Norepinephrine** can also be used, but it does **decrease renal blood flow.**
   c. **Epinephrine** is the drug of choice for **anaphylactic shock.**
   d. **Isoproterenol** can be used to stimulate the heart, but it increases cardiac work and heart rate more than the other sympathomimetics.
   e. **Dobutamine** increases cardiac output **without increasing heart rate or oxygen demand.**

VI Antiarrhythmics

A. There are five phases in the cardiac action potential:
1. Phase 0—upstroke due to the sodium current
2. Phase 1—peak due to inactivation of sodium channels and activation of potassium channels
3. Phase 2—plateau due to the inward calcium current balancing the outward potassium current
4. Phase 3—repolarization due to the potassium current after calcium channels close
5. Phase 4—diastolic depolarization due to gradual increase in sodium permeability

B. **BRADYARRHYTHMIAS** can be treated with **atropine or β-agonists.**

C. **TACHYARRHYTHMIAS** can be treated with the **antiarrhythmics,** which depress the electrical activity of the myocardial cells. The antiarrhythmics reduce tachyarrhythmias by
1. **Decreasing ectopic automaticity**
2. **Enhancing or depressing conduction** to reduce reentry

D. There are **four primary mechanisms** of **antiarrhythmic action,** which correspond to four major classes of antiarrhythmics. (See Table 5-1.)
1. **Sodium channel blockade (Classes IA, IB,** and **IC)**
2. **β-blockade (Class II)**
3. **Increased refractoriness due to potassium channel blockade (Class III)**
4. **Calcium channel blockade (Class IV)**

E. **CLASS IA** antiarrhythmics are **sodium channel blockers** (direct action) with anticholinergic activity (indirect action).
1. **Effects** of the two actions are listed in Table 5-2.
2. Changes of the myocardial action potential are illustrated in Figure 5-5.
   a. **Slowing of the diastolic depolarization** (Phase 4) leads to the reduced automaticity.
   b. **Slowing of the rate of rise** of the action potential (Phase 0) leads to the reduced excitability and reduced conduction velocity.

TABLE 5-1 SUMMARY OF ANTIARRHYTHMIC DRUGS

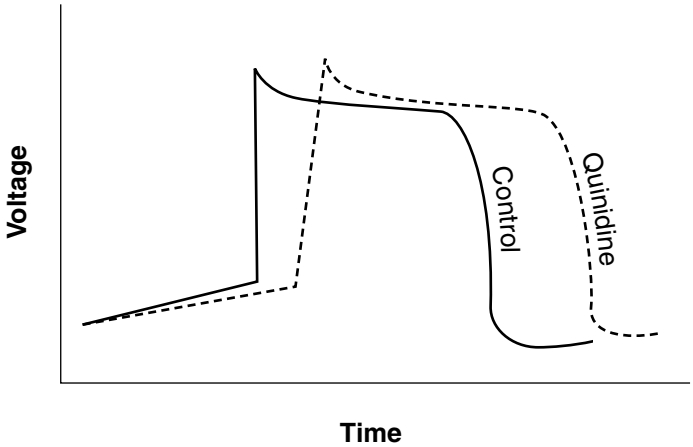
Class	Category	Mechanism	AP/ERP Length	Uses
IA	Na^+ channel blocker	Slows phase 0 depolarization	Longer	SV, ventricular tachycardia
IB	Na^+ channel blocker	Shortens phase 3 repolarization	Shorter	Ventricular tachycardia
IC	Na^+ channel blocker	Slows phase 0 depolarization	No change	Refractory ventricular arrhythmias
II	Beta blocker	Suppresses phase 4 depolarization	Longer	Atrial arrhythmias, SV tachycardia
III	K^+ channel blocker	Prolongs phase 3 repolarization	Longer	Atrial arrhythmias, ventricular tachycardia
IV	Ca^{2+} channel blocker	Shortens action potential	Longer	Atrial arrhythmias, SV tachycardia

AP = action potential. ERP = effective refractory period. SV = supraventricular

TABLE 5-2 CHANGES IN MYOCARDIAL CELL PROPERTIES DUE TO THE DIRECT (SODIUM CHANNEL BLOCK) AND INDIRECT (VAGAL BLOCK) ACTIONS OF GROUP IA ANTIARRHYTHMICS

Sodium Channel Block	Vagal Block (SA and AV nodes)
↓ automaticity	↑ automaticity
↓ excitability	↑ excitability
↑ effective refractory period	↓ effective refractory period
Sum total of effects of IA antiarrhythmics: SA and AV nodes—variable effects atrial and ventricular muscle—direct effects predominate	

AV = atrioventricular; SA = sinoatrial; ↑ = increased; ↓ = decreased



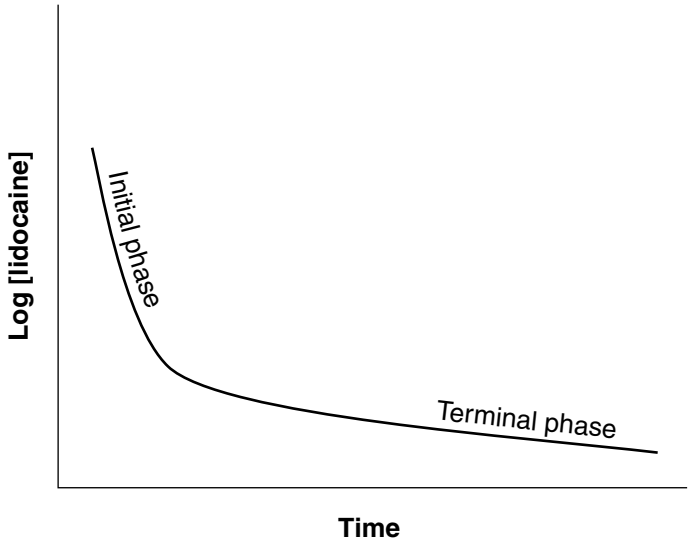
● **Figure 5-5** Changes in the myocardial action potential induced by Class IA antiarrhythmics (e.g., quinidine). There is a decrease in the slope of phases 4 and 0, as well as prolongation of the action potential and the effective refractory period.

c. **Prolongation** of the action potential leads to the increased effective refractory period.

3. **Indirect actions** from the **anticholinergic activity** only occur at the SA and AV nodes because these are the primary sites of parasympathetic innervation.
   a. The net effect of the IA antiarrhythmics on the SA and AV nodes is variable, depending upon whether the direct or indirect effects predominate.
   b. At atrial and ventricular muscle, the direct effects predominate, because there is little parasympathetic innervation.
4. Class IA antiarrhythmics are **often combined with cardiac glycosides.**
   a. The indirect effects (anticholinergic) of the antiarrhythmic oppose the indirect effects (vagomimetic) of the cardiac glycoside.
   b. The combination results in little indirect activity, and leads to sodium channel blockade with increased myocardial contractility.
5. Several Class IA antiarrhythmics are commonly used.
   a. **Quinidine** (*Quinidex, Cardioquin*) is only used orally, as parenteral administration has marked hypotensive effects.
      i. The side effects include **cinchonism,** which is characterized by ringing in the ears, blurred vision, nausea, and vomiting.
      ii. **Thrombocytopenia** can also be induced.
      iii. Quinidine reduces the renal elimination of digoxin, which can lead to an increase in the toxicity from digoxin.
   b. **Procainamide** (*Pronestyl*) can be used orally or intravenously.
      i. N-Acetylprocainamide is an active metabolite that behaves like a class III drug.
      ii. **A lupus-like syndrome** can be induced, especially in patients who have a **slow acetylator phenotype.**
   c. **Disopyramide** (*Norpace*) is an oral antiarrhythmic that is also the most potent antimuscarinic.
6. **Some side effects** are common to all Class IA antiarrhythmics.
   a. **Ventricular arrhythmias** induced by Class IA antiarrhythmics can lead to **syncope.**
   b. **AV block** induced by the Class IA antiarrhythmics can lead to an **increased PR interval.**
   c. There may also be increased QRS and QT intervals. The polymorphic ventricular arrhythmia, *torsades de pointes,* can be induced by the prolonged QT interval.
   d. **Decreased contractility** can aggravate heart failure, especially with disopyramide.
   e. Direct **vasodilation** can lower blood pressure.
7. **Uses** for Class IA antiarrhythmic drugs are:
   a. **Treatment and prophylactic control of symptomatic ventricular tachyarrhythmias**
   b. **Prophylactic control of supraventricular arrhythmias**

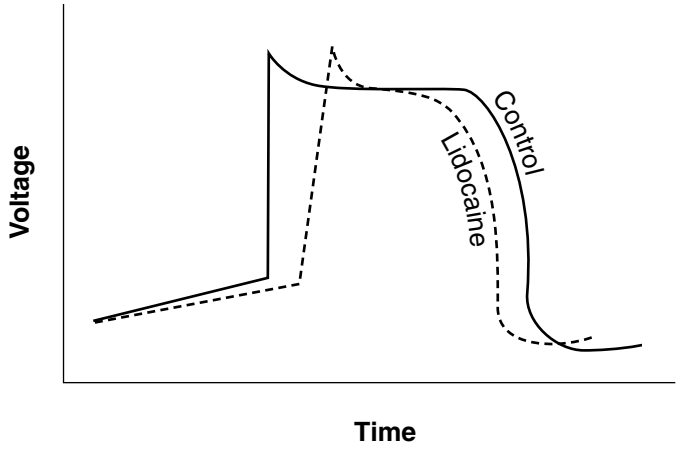
F. CLASS IB antiarrhythmic drugs are **sodium channel blockers** without anticholinergic activity.

1. **Lidocaine** (*Xylocaine*) is a very effective **parenteral** antiarrhythmic.
   a. It is rapidly metabolized in the liver **(high extraction ratio)** and has a **low bioavailability** (0.3); thus it is not used orally.
      i. **Heart failure** will decrease the liver blood flow and thereby slow the metabolism of lidocaine.
      ii. The **maintenance dose** of lidocaine should be **reduced** in patients with heart failure or liver disease.



● **Figure 5-6** Lidocaine concentration versus time relationship, which displays two phases (two compartments).

b. The **elimination of lidocaine** follows **two-compartment** kinetics (Figure 5-6); thus, repeated dosing will increase the duration of the therapeutic effect.
c. The **effects** of lidocaine **on the myocardial action potential** are illustrated in Figure 5-7.
   i. **Automaticity is decreased.**
   ii. **Excitability is decreased.**
   iii. **The effective refractory period is decreased.**
d. The actions of lidocaine on myocardial muscle are **frequency-dependent,** with the highest activity at the higher frequencies. Thus it acts preferentially on arrhythmic muscle.
e. There are **few side effects;** however, **at large dosages** it can
   i. Produce local anesthetic side effects, such as **tremors** and **convulsions**



● **Figure 5-7** Changes in the myocardial action potential induced by Class IB antiarrhythmics (e.g., lidocaine). Phase 3 repolarization is shortened, which decreases the duration of the action potential. In addition, lidocaine decreases the slope of phase 0, thereby decreasing the effective refractory period.

ii. **Reduce myocardial contractility**
iii. **Slow AV conduction**

f. The **indications** for lidocaine are limited to **ventricular** tachyarrhythmias, including:
i. **Ventricular tachycardia**
ii. **Premature ventricular complexes**
iii. **Ventricular fibrillation**
iv. **Digitalis-induced ventricular arrhythmias**

2. **Mexiletine** (*Mexitil*) has effects that are similar to lidocaine. However:
a. It is **effective when given orally,** as there is no first-pass metabolism.
b. Its half-life is much **longer.**

3. **Phenytoin** (*Dilantin*), an anticonvulsant, also has antiarrhythmic effects.

G. CLASS IC antiarrhythmic drugs (e.g., **flecainide** [*Tambocor*], **propafenone** [*Rythmol*]) induce marked reductions of the sodium permeability changes.

1. They cause **marked slowing of conduction in all cardiac tissue,** with minor effect on duration of action potential and effective refractory period.
2. Class IC drugs are used to **treat refractory ventricular arrhythmias,** but they can cause ventricular tachycardia as a side effect.

H. CLASS II antiarrhythmics are **β-blockers** (e.g., **propranolol** [*Inderal*], **metoprolol** [*Toprol*])

1. They act primarily by **reducing the effects of the sympathetic nervous system on the myocardium.**
a. **Phase 4 depolarization is reduced,** leading to a reduction of automaticity and conduction velocity in the SA node, the AV node, and the Purkinje fibers.
b. **Excitability is reduced.**
c. The effective refractory period of the AV node is increased.
2. High doses may induce sodium channel blockade.
3. **Indications** for β-blockers include:
a. **Sympathetic-induced tachyarrhythmias.**
b. **Paroxysmal supraventricular tachycardia (PSVT),** because β-blockers reduce reentry at the AV node.
c. **Atrial flutter and fibrillation,** because β-blockers slow AV conduction, thereby reducing the ventricular rate.
d. **Prophylaxis after an acute MI;** β-blockers reduce sudden death.

I. CLASS III antiarrhythmics **prolong the action potential and effective refractory period** by blocking potassium channels and prolonging phase 3 repolarization.

1. **Amiodarone** (*Cordarone*) has effects of all four major classes, but its predominant effect is to increase the refractory period.
a. It **acts at all sites** in the myocardium, which is unusual for an antiarrhythmic, and it effectively reduces almost any arrhythmia.
b. The **half-life is very long,** approximately 30 days.
c. **Toxicity is very high,** including:
i. **Pneumonitis and pulmonary fibrosis.** Pulmonary toxicity is fatal in 10% of patients affected.
ii. **Change of thyroid function.**
iii. **Blue skin discoloration** due to its iodine content.
iv. **Hepatotoxicity.**
2. **Bretylium** (*Bretylol*) decreases catecholamine release, prolongs the action potential, and increases the effective refractory period in the myocardium. It is rarely used.

3. **Sotalol** (*Betapace*) is a nonselective β-blocker with Class III activity.
4. **Ibutilide** (*Corvert*) given IV prolongs the action potential and can be used to **convert atrial flutter or fibrillation to normal sinus rhythm.**

J. **CLASS IV** antiarrhythmics are **calcium channel blockers** (e.g., **verapamil** [*Calan, Isoptin*]).
1. Calcium channels are particularly important for action potential generation in the SA and AV nodes.
2. Blockade of the L-type calcium channels **decreases heart rate, slows AV conduction,** and **increases the effective refractory period.**
3. Verapamil has a low bioavailability due to first-pass metabolism, and 80%–90% of verapamil in the serum is bound to plasma proteins.
4. **Indications** for the calcium channel blockers include supraventricular arrhythmias, such as:
   a. **PSVT**
   b. **Atrial flutter**
   c. **Atrial fibrillation**
5. **Side effects** of verapamil include:
   a. **Bradycardia**
   b. **AV block**
   c. Excessive ventricular rate in patients with Wolff–Parkinson–White syndrome who are being treated for atrial fibrillation
   d. **Heart failure,** due to reduced myocardial contractility
   e. Constipation
6. The effects of calcium channel blockers on the myocardium can be antagonized by catecholamines, digoxin, or calcium.

K. **MISCELLANEOUS** antiarrhythmics are also useful.
1. **Adenosine** (*Adenocard*) hyperpolarizes supraventricular muscle membranes and is used to **terminate PSVT.** The duration of action is very brief.
2. **Digoxin** (*Lanoxin*) has antiarrhythmic effects due to **depression of AV nodal conduction.**
   a. Increased myocardial contractility and the long duration of action of digoxin are unusual for antiarrhythmics.
   b. **Uses** include:
      i. **Atrial flutter and fibrillation**
      ii. **PSVT**
      iii. **Arrhythmias in patients with congestive heart failure**
3. **Phenylephrine** increases blood pressure, which reflexly reduces heart rate and reduces PSVT.
4. **Potassium and magnesium** can be useful to decrease digoxin toxicity.

Chapter 6

Pharmacology of Blood and Blood Vessels

I Anticoagulants

A. A THROMBUS is a **blood clot** that forms **inside the vessels.** A **detached thrombus** is called an **embolus.**

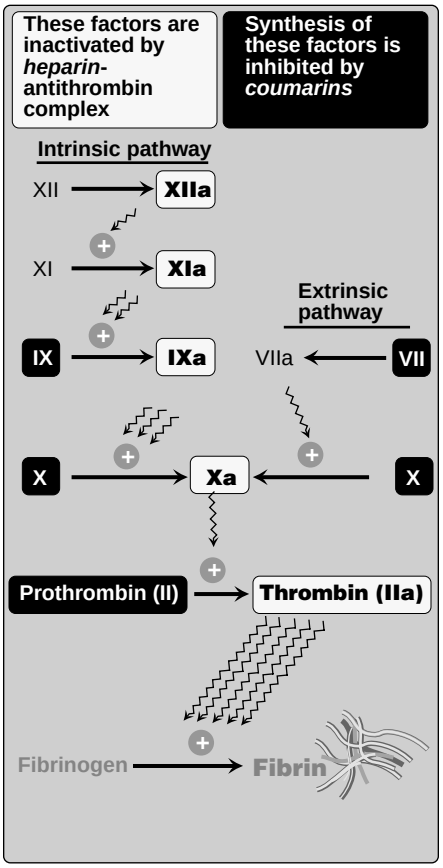
1. **Pathological clotting** is favored by three conditions known as **Virchow's triad: stasis of blood, vascular injury,** and a **procoagulative state.**
2. **Arterial clots** are often caused by **shearing and other vascular injury.** Because these clots tend to contain many **platelets,** they usually form **white thrombi.**
3. **Venous clots** are often caused by **blood stasis.** They tend to contain many **red blood cells** and form **red thrombi.**

B. THE COAGULATION CASCADE has **two initiating pathways (extrinsic and intrinsic),** as well as a **common pathway.** (See Figure 6-1.)

1. **The extrinsic pathway** is initiated by **vascular damage. Tissue factor (TF, thromboplastin)** and activated **factor VIIa** together convert **factor X to factor Xa,** thereby **activating the common pathway.**
2. **In the common pathway, factor Xa activates prothrombin (factor II)** to **thrombin (factor IIa),** which converts **fibrinogen (factor I)** to **fibrin (factor Ia)**.
3. **The intrinsic pathway** activates the common pathway, and it also activates the **kinin pathway** via **factor XII (Hageman factor).**
   a. Activation of the **enzyme kallikrein** by factor XIIa results in the synthesis of **bradykinin.**
   b. Bradykinin has multiple effects.
      i. **Vasodilation** of **arterial vascular smooth muscle;** however, most venous and non-vascular smooth muscle is contracted.
      ii. **Stimulation** of **sensory nerve endings** induces **pain.**
      iii. **Capillary permeability** is **increased.**
   c. Bradykinin is not used clinically, but its effects are clinically important.
      i. Because **angiotensin-converting enzyme (ACE)** inactivates bradykinin, inhibition of ACE increases the half-life of bradykinin.
      ii. This prolongation of bradykinin activity is responsible for a significant portion of the antihypertensive effects of ACE inhibitors.

C. HEPARIN (*Liquaemin*) is an **acidic mucopolysaccharide** mixture that is an **indirect thrombin inhibitor.**

1. High endogenous concentrations occur in the mast cells in the lungs.
2. It is a **very large, polar,** and **water-soluble molecule.**
   a. It must be **given intravenously** or **subcutaneously.**
   b. Distribution is limited to the **vascular space,** making it useful for anticoagulation during pregnancy.



● **Figure 6-1** Intrinsic, extrinsic, and common pathways of the coagulation cascade. From Howland RD. Lippincott's Illustrated Reviews: Pharmacology. 3rd ed. Baltimore: Lippincott Williams & Wilkins, 2005: 233, fig. 20.10.

c. **Inactivation** is due to **metabolism,** which follows **zero–order kinetics.** Increasing the dose increases the time to eliminate 50% of the drug.

3. Heparin has **two major effects** and several minor effects.
   a. One major effect is the **formation of an inactive thrombin complex** by **catalyzing** the reaction between **antithrombin** and **thrombin (factor IIa).**
   b. The other major effect is **complexing and inactivation of factor Xa.**
   c. Minor effects of heparin include the complexing of factors XIIa, XIa, and IXa of the intrinsic pathway.
   d. The onset of action is **immediate.**
   e. The goal of treatment is to increase the **activated partial thromboplastin time (aPTT)** by approximately **2 times** the normal value. The aPTT should be measured after 4–5 half lives (approximately 6 hours).

4. **Side effects** include:
   a. **Hemorrhage**
   b. **Heparin-induced thrombocytopenia (HIT),** which can be immunologically or nonimmunologically mediated
      i. **Type I HIT** occurs **early** after initiation of therapy and involves a **mild decrease in platelet count** that is **not immunologically mediated.**

ii. **Type II HIT typically** occurs **within 5–14 days** after initiation of treatment, although it can occur **earlier in a previously sensitized patient.**
(a) The **platelets are activated** by **IgG antibodies against heparin,** causing **thrombosis and a severe thrombocytopenia.**
(b) **Type II HIT can be fatal** if not recognized. Heparin treatment should be discontinued immediately.

c. **Allergic reactions** or **anaphylaxis**
d. **Osteoporosis** and **mineralocorticoid deficiency** after **long-term use**

5. A mild heparin overdose can be treated by discontinuing administration of heparin. **Protamine,** a basic compound that **complexes heparin,** is the **antidote** for heparin and can be administered to treat a more serious heparin overdose.

D. LOW-MOLECULAR-WEIGHT HEPARINS (LMWHs), e.g., **enoxaparin** (*Lovenox*), **dalteparin** (*Fragmin*)

1. **Act preferentially on factor Xa** but still have some effect on factor IIa. Monitor Xa concentration rather than aPTT.
2. Are **better absorbed after subcutaneous injection** than heparin.
3. Are **eliminated by the kidney,** by **first-order kinetics.** They should not be used in patients with renal failure.
4. Have a **more predictable dose-response relationship** than heparin.
5. Have **a lower incidence of thrombocytopenia** than heparin.
6. Have a **longer half-life** than heparin (4 hours versus 2 hours, respectively).

E. FONDAPARINUX (*Arixtra*) is the active pentasaccharide portion of heparin.

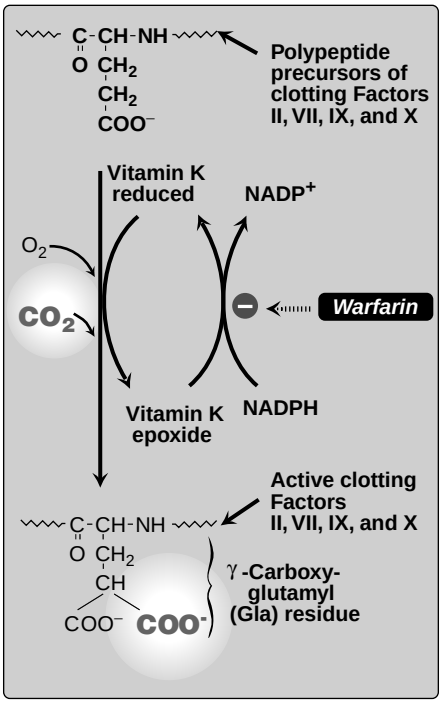
1. It **exclusively inactivates factor Xa** and cannot inactivate factor IIa.
2. The benefits of fondaparinux are that it has a **long half-life** (15 hours) and **does not appear to cause heparin-induced thrombocytopenia (HIT).**
3. Care must be taken when administering fondaparinux as **its activity is not reversible with protamine.**

F. DANAPAROID (*Orgaran*) is another inhibitor of factor Xa that has similar properties to the LMWHs.

1. It is a **mixture of heparan sulfates, dermatan,** and **chondroitin.**
2. Because danaparoid does not contain any heparin or heparin fragments, it can be used to treat patients who have developed HIT type II due to heparin treatment.

G. DIRECT THROMBIN INHIBITORS prevent coagulation by **inhibiting thrombin.**

1. **Lepirudin** (*Refludan*) is a **peptide** that **irreversibly inactivates thrombin.**
   a. It can be used in patients who have developed type II HIT.
   b. The most serious side effect of lepirudin is **bleeding.** The **aPPT** should be monitored as for heparin therapy.
   c. Patients treated with lepirudin may develop **drug–antibody complexes.** These complexes are **pharmacologically active** and are eliminated more slowly than the drug alone.
   d. Lepirudin is **eliminated by the kidney** and should be used with caution in patients who have renal failure.
2. **Bivalirudin** (*Angiomax*) can also be used to treat patients who have type II HIT. It has a **shorter half-life** than lepirudin.
3. **Argatroban** (*Novastan*) also has a short half-life. Unlike lepirudin and bivalirudin, which bind to both the active site and the substrate-recognition sites on thrombin, **argatroban binds only to the active site of thrombin.**



● **Figure 6-2** Inhibition of vitamin K epoxide reduction by warfarin. From Howland RD. Lippincott's Illustrated Reviews: Pharmacology. 3rd Ed. Baltimore: Lippincott Williams & Wilkins, 2005: 237, Fig. 20.19.

H. WARFARIN (*Coumadin, Panwarfin*) is an **oral anticoagulant.**

1. Blockade of the reduction of vitamin K to its active form **decreases the carboxylation and synthesis of vitamin K-dependent clotting factors** (II, VII, IX, and X) as well as protein C and protein S. (See Figure 6-2.)
   a. The **onset of action is delayed** (8–12 hours), because stores of the clotting factors must be depleted.
   b. The maximum anticoagulant effect of warfarin occurs after 1 week of administration.
   c. The therapeutic goal is an International Normalized Ratio (INR) of 2 to 3, which will approximately double the prothrombin time.
2. Because warfarin is **effective when given orally,** it is more useful than heparin for outpatients.
3. **Many drug interactions** can occur.
   a. Extensive plasma protein binding (99%) can result in competition with other drugs for the binding sites.
   b. Metabolism of warfarin in the liver can be enhanced or inhibited by many other drugs.
      i. **Azole antifungals** and **cimetidine increase the concentration** of warfarin due to inhibiting CYP 450 enzymes.
      ii. **Rifampin** and **barbiturates decrease the concentration** of warfarin by inducing CYP 450 enzymes.
4. **Side effects** include:
   a. **Hemorrhage,** which can be reversed by the **antidotes vitamin K or vitamin-K dependent clotting factors.**

i. **Mild hemorrhage** can be reversed by **stopping administration** of warfarin.
ii. **Severe hemorrhage** may require a **blood or plasma transfusion.**

b. **Skin necrosis,** due to thrombosis of the microvasculature in the skin.
c. **Teratogenicity,** because it readily crosses the placenta and affects bone formation in the developing fetus.

5. Acute anticoagulant therapy is often initiated with both heparin and warfarin.
a. Initially, **warfarin inactivates Protein C and Protein S** and has a **procoagulant effect.**
b. Thus, it is necessary to overlap warfarin administration with heparin in states of high thrombotic risk.
c. As the warfarin becomes effective, the heparin is withdrawn.

6. Warfarin and heparin slow the production of a clot, but they do not dissolve clots.

II Fibrinolytics

A. FIBRINOLYTICS DISSOLVE CLOTS.

B. TISSUE PLASMINOGEN ACTIVATOR (tPA, alteplase), urokinase, streptokinase and anistreplase enhance the formation of plasmin from plasminogen.

1. The plasmin breaks down fibrin, thereby dissolving clots.

2. Dissolution of clots by **intravenous administration of a fibrinolytic** can restore coronary blood flow after an **MI.**
a. This will reduce myocardial damage if given within a few hours of the MI.
b. Fibrinolytics can also induce hemorrhaging at other sites.
c. Antithrombotic or antiplatelet drugs are often coadministered with fibrinolytics in order to prevent formation of a new thrombus.

3. **Streptokinase** forms a **complex with plasminogen,** and this complex activates other plasminogen molecules.
a. **Both circulating plasminogen** and **plasminogen bound to clots are activated** by streptokinase.
b. Because streptokinase is a bacterial protein, it can cause an **allergic or anaphylactic reaction.**

4. **Alteplase** has a **short half-life** (about 5 minutes) and is **more selective for clots** compared to streptokinase because it **preferentially activates plasminogen bound to fibrin.**

5. Dissolution of clots in the brain by fibrinolytics can reduce central nervous system (CNS) injury after a **thrombotic stroke.** However, fibrinolytics must not be used after a hemorrhagic stroke or more than 3 hours after onset of ischemic stroke (due to elevated risk of intracranial hemorrhage).

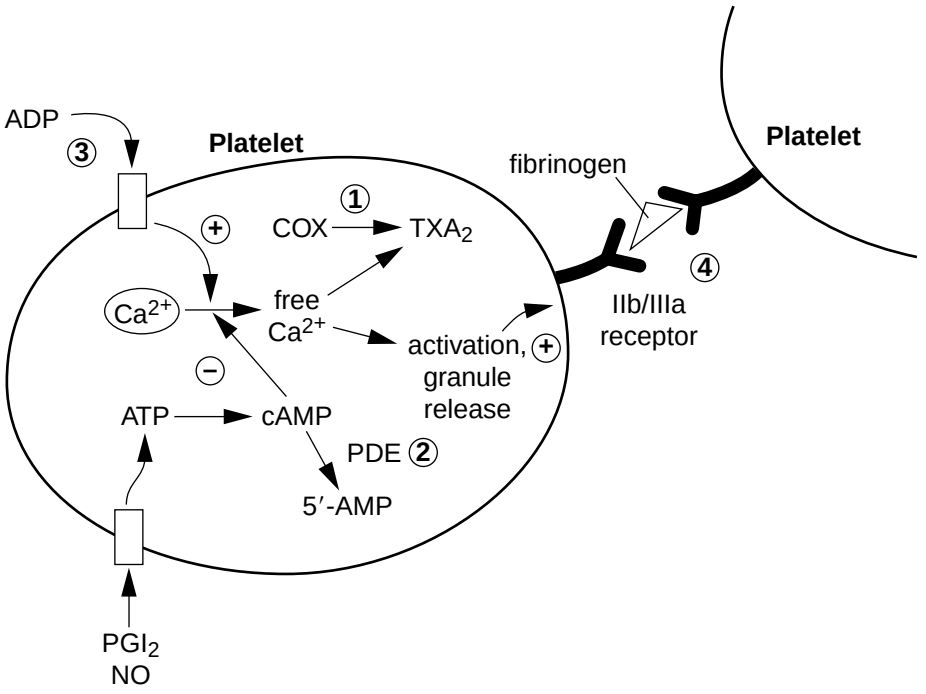
C. The **antidote** for the fibrinolytics is **aminocaproic acid,** a plasmin antagonist.

III Antiplatelet Drugs

A. INTACT ENDOTHELIUM synthesizes **vasodilators** such as **prostacyclin (PGI_2)** and **NO,** which bind to platelet receptors. (See Figure 6-3.)

1. Binding of these vasodilators leads to an **increased concentration of cyclic adenosine monophosphate (cAMP)** in the platelet, causing **sequestration of calcium.**

2. **Low levels of calcium** in the platelet **prevent platelet activation** and **aggregation.**



● **Figure 6-3** Mechanisms of action of antiplatelet drugs. 1 = aspirin (blocks COX and inhibits TXA_2 formation); 2 = dipyridamole (blocks PDE and inhibits cAMP breakdown; thus, calcium stays sequestered); 3 = ticlopidine and clopidogrel (block ADP receptor so calcium stays sequestered); 4 = abciximab, eptifibatide, tirofiban (block GP IIb/IIIa receptor and inhibit fibrinogen cross-linking). PDE = phosphodiesterase. COX = cyclooxygenase. TXA_2 = thromboxane A_2. PGI_2 = prostacyclin.

B. When platelets bind to **thrombin**, **thromboxanes,** or **collagen** under a **damaged endothelium, they adhere and become activated.** (See Figure 6-3.)

1. The platelets undergo a **change in shape** and **release compounds from granules,** including **adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), serotonin, thrombin, and platelet-activating factor (PAF).**
2. These compounds bind to other platelets, thereby activating them.
3. Platelets express **activated glycoprotein IIb/IIIa receptors,** which **bind to fibrinogen or circulating von Willebrand factor** and **link the platelets together.**
4. **Fibrinogen is cleaved to fibrin** by thrombin from the coagulation cascade, which **cross-links the platelets and stabilizes the clot.**

C. Antiplatelet drugs, given prophylactically, reduce the incidence of MI and stroke.

1. **Low doses of aspirin irreversibly inhibit cyclooxygenase,** which **decreases thromboxane synthesis.** This decreases platelet aggregation by preventing platelet activation.
2. **Dipyridamole** (*Persantine*) inhibits phosphodiesterase (PDE), thereby increasing the concentration of cyclic AMP in platelets. It is used in combination with aspirin or warfarin.
3. **Ticlopidine** (*Ticlid*) and **clopidogrel** (*Plavix*) **interfere with the binding of ADP to the ADP receptors on platelets,** which **inhibits activation of the GP IIb/IIIa receptors** on platelets and prevents platelet aggregation.
   a. These drugs are commonly used in patients who have acute coronary syndromes or who have received stents.

b. The **major adverse effect for both drugs is bleeding;** there is no antidote besides stopping administration of the drug. Other side effects include **gastrointestinal (GI) effects** and, rarely, **thrombocytopenic purpura.**
c. Both drugs can **inhibit cytochrome (CYP) 450 enzymes** and interfere with the metabolism of other drugs.
d. **Ticlopidine can also cause neutropenia.**

4. **GP IIb/IIIa receptor inhibitors block the binding of fibrinogen and von Willebrand factor to platelets, thereby preventing platelet aggregation.** The **major adverse effect** for all GP IIb/IIIa receptor inhibitors is **bleeding.**
a. **Abciximab** (*ReoPro*) **is a monoclonal antibody.**
b. **Eptifibatide** (*Integrilin*) **is a peptide inhibitor.**
c. **Tirofiban** (*Aggrastat*) **is a small molecule inhibitor.**

IV Antibleeding Drugs

A. PLASMINOGEN ACTIVATION INHIBITORS (e.g., aminocaproic acid) can be used to stop bleeding. The major adverse effect is excessive clotting.

B. PROTAMINE ANTAGONIZES THE ANTICOAGULANT EFFECT OF HEPARIN.
1. **Heparin** is highly **acidic,** whereas **protamine** is highly **basic.** The two molecules interact to form **a stable, inactive complex.**
2. **Adverse effects** include **allergic reaction** and **anaphylaxis.**

C. VITAMIN K can be used to treat a **warfarin overdose.**
1. It has a long (24 hours) onset of action; thus, plasma transfusion may also be used.
2. **Vitamin K supplementation** is needed for patients being treated with **cephalosporins** (e.g., cefamandole, cefoperazone, moxalactam).

D. APROTININ (*Trasylol*) is a **serine protease inhibitor** that blocks plasmin and streptokinase.
1. It has been used in surgery to **decrease perioperative blood loss.**
2. However, the FDA suspended marketing of this drug as of November 2007 due to the potential for thrombotic complications and renal insufficiency.

E. CONCENTRATED PLASMA FRACTIONS or **recombinant clotting factors** are used to treat bleeding diseases such as **hemophilia A (factor VIII deficiency)** and **hemophilia B (factor IX deficiency,** aka **Christmas disease).**

V Drugs for Anemia

A. IRON DEFICIENCY causes **microcytic anemia,** which can be corrected by **administration of ferrous sulfate.**

B. MEGALOBLASTIC ANEMIA is due to **decreased DNA synthesis** caused by vitamin deficiency:
1. **Folic acid (vitamin B_9) deficiency** can be caused by **pregnancy, poor absorption** in the GI tract**, alcoholism,** or **use of tetrahydrofolate inhibitors** (e.g., methotrexate, trimethoprim).
2. **Vitamin B_{12} (cyanocobalamin) deficiency** is often caused by a **lack of intrinsic factor in the GI tract,** and leads to **pernicious anemia.**
3. Megaloblastic anemia should be treated with **both vitamin B_{12} and folic acid** to prevent masking of a vitamin B_{12} deficiency that can occur with folic acid treatment alone.

C. ERYTHROPOIETIN [EPO (*Procrit*)] is a renal hormone that stimulates red blood cell production.

1. It is useful in patients with renal disease and HIV patients being treated with zidovudine (AZT), because these patients are often anemic due to low production of EPO.
2. Coadministration of iron and folate may also be necessary.

D. GRANULOCYTE COLONY STIMULATING FACTOR [filgrastim (*Neupogen*)] and **granulocyte-macrophage colony stimulating factor [sargramostim** (*Leukine*)] are used to stimulate **leukocyte production** after cancer chemotherapy.

E. INTERLEUKIN-11 [oprelvekin (*Neumega*)] stimulates **megakaryocyte growth** in patients with thrombocytopenia.

F. HYDROXYUREA is used to treat **sickle cell anemia.** It increases the proportion of fetal hemoglobin and is given as a prophylaxis to prevent sickling crises.

VI Antihyperlipidemics

A. The **goal of antihyperlipidemic treatment** is **reduction of low-density lipoprotein (LDL) cholesterol** and other **modifiable coronary heart disease (CHD) risk factors.** (See Tables 6-1 and 6-2.)

B. The first mode of therapy for hypercholesterolemia is **modifying the diet** to reduce fat and caloric intake, and **implementing an exercise program.**

C. LOVASTATIN (*Mevacor*), **SIMVASTATIN** (*Zocor*), **ROSUVASTATIN** (*Crestor*), **PRAVASTATIN** (*Pravachol*), **FLUVASTATIN** (*Lescol*), and **ATORVASTATIN** (*Lipitor*) **competitively inhibit hydroxymethylglutaryl CoA** (HMG CoA) **reductase.**

1. This enzyme is the **rate-limiting** step in the synthesis of cholesterol. Rosuvastatin and atorvastatin are the most potent inhibitors.
2. Reduced cholesterol synthesis leads to an increase in the number of hepatic **LDL receptors,** which enhance the uptake of LDL cholesterol from the serum.
   a. **Serum LDL cholesterol is reduced.**
   b. **High-density lipoprotein** (HDL) cholesterol is slightly increased.
   c. Triglycerides are slightly reduced.
   d. The risk of myocardial infarction (MI) is reduced but not eliminated. Diet, exercise, and/or an additional drug may be required in addition to the statin.

TABLE 6-1 RISK FACTORS FOR CORONARY HEART DISEASE

Modifiable	Nonmodifiable
Uncontrolled high LDL (>160 mg/dL) and/or low HDL (<40 mg/dL)	Family history of CHD
Uncontrolled hypertension (>140/90 mmHg)	Age
Uncontrolled diabetes	Sex (male)
Smoking	
Sedentary lifestyle	

TABLE 6-2 TARGET CHOLESTEROL LEVELS BASED ON CHD RISK

	Low CHD Risk	High CHD Risk	Secondary Prevention
Goal Total Cholesterol	<200 mg/dL	<200 mg/dL	<200 mg/dL
Goal LDL	<160 mg/dL	<130 mg/dL	<100 mg/dL
Goal HDL	>40 mg/dL (men) >50 mg/dL (women)	>40 mg/dL (men) >50 mg/dL (women)	>40 mg/dL (men) >50 mg/dL (women)

3. **Side effects** of statins include:
   a. **Hepatotoxicity.** Liver function should be evaluated periodically.
   b. **Myositis,** an inflammation of skeletal muscle; and **rhabdomyolysis,** a breakdown of muscle tissue. Plasma **creatine kinase levels** should be monitored.
   c. Warfarin levels will be increased in patients taking warfarin with statins.

D. CHOLESTYRAMINE (*Questran*), **COLESTIPOL** (*Colestid*), and **COLESEVELAM** (*Welchol*) are **quaternary ammonium ion-exchange resins** that are **not absorbed** from the intestine.
1. They **bind bile salts** and eliminate them in the feces.
   a. Bile salt synthesis from cholesterol is increased.
   b. Cholesterol content in the liver is reduced.
   c. The liver increases the number of LDL receptors, which lowers the serum LDL cholesterol.
   d. The decrease in cholesterol levels is less than that seen with statins.
2. **Side effects** include:
   a. Abdominal discomfort and constipation.
   b. Binding of fat-soluble vitamins (A, D, E, and K) and anionic drugs.
   c. An increase in very low density lipoproteins (VLDL) and triglycerides.
   d. Colesevelam has fewer side effects than the others.

E. NIACIN (nicotinic acid, vitamin B_3) at high dosages has antihyperlipidemic actions.
1. It is currently the most effective drug for raising HDL levels.
2. Many effects occur and the exact mechanism is unclear.
   a. It decreases lipolysis in adipose tissue which decreases the free fatty acids in the plasma.
   b. Triglyceride synthesis is markedly reduced, which decreases the hepatic secretion of VLDL.
   c. Decreased LDL production leads to reduced serum cholesterol.
3. A common **side effect** is **cutaneous flushing,** due to **prostaglandin** release. This effect can be reduced by inhibiting prostaglandin synthesis with **aspirin.**

F. GEMFIBROZIL (*Lopid*), **FENOFIBRATE** (*Tricor*), and **CLOFIBRATE** (*Atromid-S*) are more active in **lowering triglycerides.**
1. They bind to peroxisome proliferator-activated receptors (PPARs) and increase the transcription of genes that regulate lipid metabolism.
2. **Increases in lipoprotein lipase activity** lead to a reduction of VLDL, which predominantly transports triglycerides.
3. Elimination of cholesterol in the bile is also enhanced, which can lead to **gallstones** as a **side effect.**
4. They can cause **myositis,** especially when **coadministered with a statin.**

5. Fibrates compete for protein-binding sites in the blood with other drugs such as warfarin. This can raise free warfarin levels.

G. EZETIMIBE (*Zetia*) **inhibits the intestinal absorption of dietary and biliary cholesterol** and may cause impaired hepatic function.

H. COMBINATION DRUG THERAPY is used when lifestyle modifications and a single drug do not lower cholesterol to target levels. In general, combinations should include drugs that work by complementary mechanisms (e.g., statin + ezetimibe, statin + niacin, fibrate + bile sequestrant).

Chapter 7

Autacoids, Drugs for Inflammatory and Gastrointestinal Disorders, and Vitamins

I Definition of Autacoids

A. Autacoids are signaling molecules that function as local hormones or neuromodulators in the body (i.e., autocrine substances).

B. They are formed by multiple tissues, as opposed to endocrine hormones, which are formed by specialized endocrine glands.

II Histamine

A. Histamine is an autacoid that is present in many tissues, particularly mast cells and circulating basophils.

B. Histamine **acts on H_1 and H_2 receptors** at many sites in the body.
1. The important pharmacological effects of histamine are listed in Table 7-1.
2. **A triple response** is induced after intradermal injection.
   a. **Direct vasodilation** produces a localized **red spot** at the site of injection.
   b. **Activation of nerve endings** induces an axon reflex that produces vasodilation and a **flare.**
   c. **Increased capillary permeability** induces a **wheal** at the site of the red spot.

C. **THE CLINICAL USES** of histamine are of minor importance.
1. **Achlorhydria** after the administration of histamine is useful for diagnosing **pernicious anemia.** The treatment for pernicious anemia is **vitamin B_{12} (cyanocobalamin).**
2. Supersensitivity to histamine can be useful for the **diagnosis of asthma.**
3. Histamine can be used for autonomic function testing for **small fiber neuropathy.**

III Histamine Blockers

A. Allergic disorders and motion sickness can be treated with histamine blockers. The antiemetic activity seems to occur via a different mechanism than the antihistamine activity.

B. The effects of endogenous histamine release can be blocked by several classes of drugs.
1. **Cromolyn** (*Intal*) **reduces mast cell degranulation.**
   a. The release of all mast cell mediators, including histamine, is decreased.
   b. The primary clinical use of cromolyn is in the **prophylactic treatment of asthma and allergic disorders.** (See Section IV.)

TABLE 7-1 EFFECTS OF HISTAMINE

Receptors	Effects
H_1	**Respiratory** and **GI:** contracts bronchial and intestinal smooth muscle
H_1	**Neurological:** acts on sensory nerve endings to cause pain and itching
H_1 and H_2	**Vascular:** vasodilates arterioles/venules (leads to hypotension and shock); increases capillary permeability (leads to edema)
H_2	**Cardiac:** Increases heart rate and contractility
H_2	**GI:** Increases gastric secretions (HCl)

2. **H_1 antihistamines are competitive antagonists** at H_1 receptors. Drugs in this class include diphenhydramine (*Benadryl*), dimenhydrinate (*Dramamine*), chlorpheniramine (*Chlor-Trimeton, Teldrin*), promethazine (*Phenergan*), and meclizine (*Antivert*).
   a. Ongoing histamine effects are only weakly reduced; thus, the H_1-antihistamines work best if administered before exposure to an allergen.
   b. The activity against acute allergic reactions is better than the activity in chronic allergies.
   c. There are many **clinical uses** for H_1 antihistamines, including treatment of
      i. **Seasonal allergic rhinitis**
      ii. **Acute urticaria**
      iii. **Anxiety**
      iv. **Insomnia**
      v. **Nausea**
      vi. **Parkinson's disease**
   d. First-generation drugs have multiple **side effects** due to cross-reactivity with muscarinic cholinergic and α-adrenergic receptors including:
      i. **Sedation**
      ii. **Anticholinergic symptoms,** such as constipation, urinary retention, and dry mouth
   e. Second-generation H_1-antihistamines (e.g., loratadine [*Claritin*], fexofenadine [*Allegra*]), desloratidine [*Clarinex*], ceterizine [*Zyrtec*]) do not have these side effects.
      i. These antihistamines are more specific for H_1 receptors versus first-generation drugs.
      ii. Second-generation antihistamines do not readily enter the CNS.
   f. Antihistamines can potentiate CNS depressants. In addition, they should not be co-administered with MAOIs.
3. **The H_2 antihistamines** (e.g., cimetidine [*Tagamet*], ranitidine [*Zantac*], famotidine [*Pepcid*]) are used to treat **peptic ulcer disease.** (See section XI.)
   a. They have no effects on H_1 receptors.
   b. Binding of H_2 antagonists to their receptors on the parietal cells of the stomach decreases intracellular cyclic adenosine monophosphate (cAMP) and thereby reduces gastric acid secretion.

IV Antiasthmatic Drugs

A. ASTHMA appears to be caused by **inflammation of the airways** with **bronchoconstriction, bronchial wall edema, and increased respiratory secretions.**

B. HISTAMINE and the parasympathomimetics (e.g., **methacholine**) induce bronchoconstriction and can be used as **provocative** diagnostic tests for asthma, although these tests can be dangerous.

C. THE SYMPATHOMIMETICS relieve the acute symptoms of asthma by **β_2-mediated bronchodilation** and by reducing mediator release from mast cells.

1. **Ephedrine** is a weak sympathomimetic.
   a. It has a relatively long duration of action (hours).
   b. Tolerance to the clinical effect can develop.
   c. The stereoisomer **pseudoephedrine** (*Sudafed*) is used as a decongestant. Sales of pseudoephedrine are restricted due to its use in the production of methamphetamine.
   d. Ephedrine and pseudoephedrine are the active components of the herb **ma huang.** The FDA banned sales of ma huang in 2004, but the legal status of the ban is uncertain at this time.
2. **Epinephrine** (*Adrenalin*) induces β_2 effects, including dilation of bronchial airways as well as blood vessels in skeletal muscle.
   a. Epinephrine also has α-agonistic effects that **reduce airway congestion.**
   b. Cardiovascular side effects due to β_1-receptor activation, such as **increased blood pressure, heart rate, and myocardial contractility,** can be very pronounced.
   c. Epinephrine is the **treatment of choice for acute anaphylaxis.**
3. **Isoproterenol** (*Isuprel*) is a β-receptor agonist that has much weaker actions on α-receptors than epinephrine and induces more vasodilation.
   a. **Increases in heart rate and contractility** can be very large due to
      i. β_1 effects on the heart
      ii. Baroreceptor-mediated increases in sympathetic tone induced by the fall in blood pressure from the β_2-vasodilation
   b. Repeated administration can result in **anomalous bronchoconstriction.**
   c. Duration of action is **short** due to rapid metabolism.
4. **Terbutaline** (*Bricanyl, Brethine*), **albuterol** (*Proventil, Ventolin*) and **metaproterenol** (*Alupent*) are relatively **selective β_2 agonists** with only weak effects on β_1- and α-receptors. These drugs are administered by inhaler or nebulizer.
   a. **Reflex-induced tachycardia** will occur due to a fall in blood pressure.
   b. **A skeletal muscle tremor** is the most common side effect.
   c. The noncatecholamine structure leads to much **slower metabolism, longer duration of action, and greater oral efficacy.**
5. **Salmeterol** (*Serevent*) is a **long-acting β_2 agonist** that can be used for prophylaxis.

D. THE GLUCOCORTICOIDS are potent anti-inflammatory drugs that have the highest efficacy in the treatment of asthma.

1. They **reduce inflammation** in the airways by inhibiting phospholipase A_2 and interfering with arachidonic acid and leukotriene release. In addition, they enhance the β_2 effects of sympathetic activation on the airways.
   a. This decreases the number of immune cells involved in the inflammatory response to allergens.
   b. Glucocorticoids must be taken continuously to control inflammation.
   c. They can be inhaled or taken systemically.
2. Long-term administration of the systemic glucocorticoids leads to **many side effects, including adrenal suppression, ulcers, and osteoporosis.**

3. **Beclomethasone** (*Beclovent, Vanceril*), **triamcinolone** (*Azmacort, Nasocort*), **flunisolide** (*AeroBid*), and **fluticasone** (*Flovent*) are very effective **inhaled** glucocorticoids.
   a. Any drug that reaches the circulation is rapidly metabolized due to the first-pass effect in the liver.
   b. Blood concentrations remain low and there are **fewer side effects** than with systemic glucocorticoids.

E. CROMOLYN (*Intal*) stabilizes mast cells, probably by reducing the calcium influx during mast cell degranulation.
1. **Mediator release is reduced.**
2. The onset of action is very slow; thus, it can only be used **for prophylaxis.**
3. **Inhalation** of the dry powder or aerosol is the usual route of administration because cromolyn is not absorbed after oral administration.

F. THEOPHYLLINE (*Slo-Bid, Theo-Dur*) **blocks adenosine receptors.** It also inhibits phosphodiesterases, which increases the concentration of cAMP; however, this does not occur at therapeutic concentrations.
1. The rate of metabolism of theophylline in the liver is quite variable among patients (e.g., smokers metabolize it faster than nonsmokers).
2. **Side effects** can be pronounced.
   a. **CNS stimulation** can progress to convulsions.
   b. **Tachycardia and arrhythmias** can occur.
   c. Rapid intravenous (IV) injections are dangerous due to marked cardiovascular effects.
3. The blood theophylline concentrations should be monitored, because theophylline has a low therapeutic index.
4. Theophylline was previously the mainstay treatment for asthma; however, it has now been largely replaced by corticosteroids and β_2-agonists.

G. IPRATROPIUM (*Atrovent*) and **TIOTROPIUM** (*Spiriva*) are **inhaled quaternary anticholinergics.**
1. **Muscarinic blockade** results in bronchodilation and reduced respiratory secretions.
2. There are **no systemic anticholinergic effects** because these charged salts are not absorbed after being inhaled.

H. ZAFIRLUKAST (*Accolate*) and **MONTELUKAST** (*Singulair*) are **leukotriene receptor antagonists** that can be used for asthma prophylaxis**.**

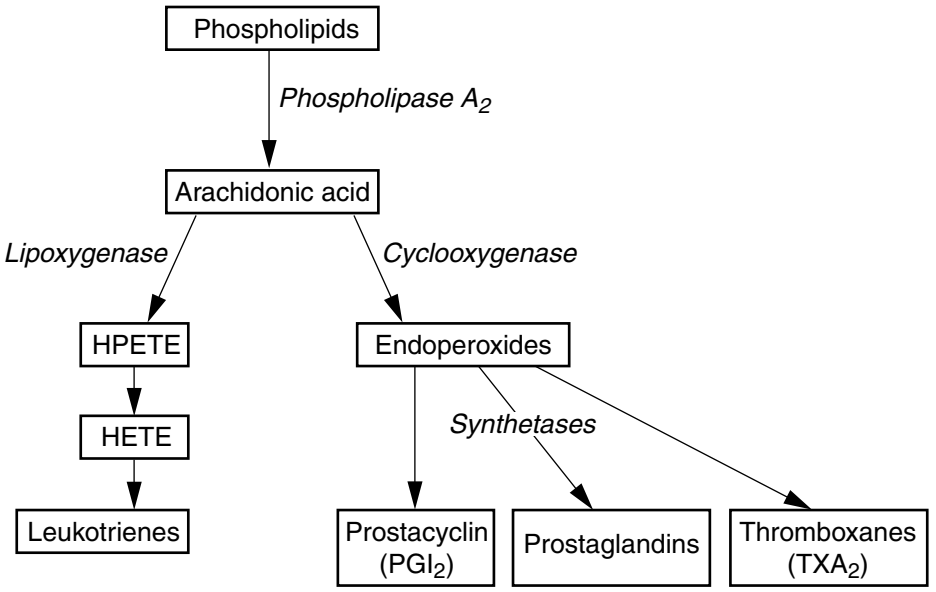
I. ZILEUTON (*Zyflo*), a **lipoxygenase inhibitor,** is also effective for the treatment of asthma. It prevents the formation of leukotrienes from arachidonic acid.

J. OMALIZUMAB (*Xolair*) is a monoclonal antibody against IgE. It blocks IgE from binding to its receptor on mast cells and basophils.

V Eicosanoids

A. This large group of autacoids is **widely distributed** in the body.

B. They are locally synthesized from arachidonic acid (Figure 7-1) and released as needed **(de novo synthesis).**

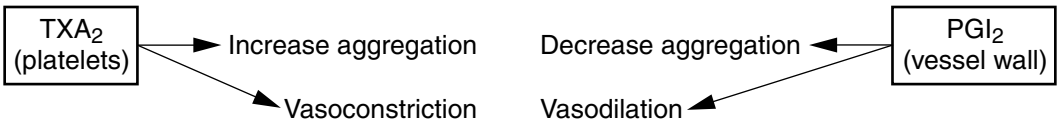


● **Figure 7-1** Synthesis of the eicosanoids. HPETE = hydroperoxyeicosatetraenoic acid; HETE = hydroxyeicosatetraenoic acid

C. The synthesis of prostacyclin (PGI_2), prostaglandins, and thromboxane (TXA_2) is reduced by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the cyclooxygenase enzymes. The NSAIDs have no effect on lipoxygenase, which synthesizes leukotrienes.

D. The eicosanoids have very **short durations** of action (approximately 1 minute) and induce many effects.

1. **Uterine Contractions.** Prostaglandin E_2 (PGE_2) or the synthetic prostaglandin dinoprostone (*Prostin E2*), and $PGF_{2\alpha}$, or carboprost (*Prostin 15M*), **increase uterine activity.**
   a. They can be used to **induce labor and abortions.**
   b. By blocking prostaglandin synthesis, ibuprofen reduces the symptoms of dysmenorrhea. Aspirin is less useful for this purpose.
2. **Body Temperature.** PGE_2, PGF_2, and PGI_2 induce fever.
3. **Airway Effects.** PGE and PGI cause **bronchodilation,** whereas PGF, PGD, and TXA lead to **bronchoconstriction.**
4. **GI Effects.** PGE and PGI_2 **decrease gastric acid secretions. Misoprostol** (*Cytotec*) is a PGE_1 derivative that is used to **reduce gastric ulcerations from the NSAIDs.**
5. **Pain Sensitization.** PGE and PGI_2 **sensitize afferent nerve endings to pain** by decreasing the threshold of nociceptors**.**
6. **Cardiovascular.** Eicosanoids also have circulatory effects.
   a. TXA_2 from platelets and PGI_2 from vessel walls are important local hormones in the **control of microcirculation** (Figure 7-2).
   b. Prostaglandin E_1 (PGE_1) or alprostadil (*Prostin VR*) can be used to relax vascular smooth muscle, inhibit platelet aggregation, and **maintain a patent ductus arteriosus.** (Indomethacin [*Indocin*] induces closure of a ductus arteriosus by blocking prostaglandin synthesis.)
   c. PGI_2 or epoprostenol (*Flolan*) vasodilates and can be administered from an IV infusion pump to **treat primary pulmonary hypertension. Treprostinil** (*Remodulin*) is a longer-lived prostacyclin analog also used to treat pulmonary hypertension.



● **Figure 7-2** Local hormonal control of the microcirculation by thromboxane (TXA_2) in the platelets and prostacyclin (PGI_2) in the vessel wall. PGE_1 also leads to vasodilation and decreased platelet aggregation.

d. Alprostadil injected into the penis causes vasodilation and induces a **penile erection.**

7. **Immunologic.** PGE_2 and PGI_2 limit T-cell proliferation, whereas leukotrienes and TXA_2 stimulate T-cell proliferation.

VI Drugs for Migraine Headaches

A. An initial intracranial vasoconstriction is followed by prolonged extracranial vasodilation during which the migraine headache occurs. Associated symptoms include **aura, nausea, vomiting,** and **photophobia;** however, auras do not always accompany migraines.

B. ACUTE TREATMENT can be administered using

1. **Mild analgesics** (NSAIDs) for weak migraines
2. **Ergot alkaloids**
   a. **Ergotamine,** often combined with caffeine (*Cafergot*) to induce **direct vasoconstriction,** is only used acutely because of the toxicity associated with chronic administration (e.g., prolonged vasoconstriction can result in gangrene).
   b. **Dihydroergotamine** (*Migranal*) can also be used.
3. **Triptans,** which cause vasoconstriction by activating serotonin receptors on small peripheral nerves that innervate cranial blood vessels
   a. **Sumatriptan** (*Imitrex*) is the prototype of this class.
   b. Although safer than ergot alkaloids, there is a risk of inducing a coronary vasospasm in patients with coronary artery disease.

C. PROPHYLAXIS is indicated in patients with several migraines per month and can be obtained with

1. **β-blockers** (e.g., propranolol) or **calcium channel blockers** (e.g., verapamil)
2. **Tricyclic antidepressants** (e.g., amitriptyline)
3. **Anticonvulsants** (e.g., divalproex)

VII Drugs for Rheumatoid Arthritis

A. Rheumatoid arthritis (RA) is an inflammatory disorder involving many organs in the body, including the joints.

B. Pain and inflammation due to RA can be treated with NSAIDs (Chapter 4-XII).

1. **Aspirin** at high dosages has anti-inflammatory activity that reduces the symptoms of rheumatoid arthritis.
   a. High dosages also saturate the metabolic enzymes and prolong the duration of the action of aspirin.

   b. The most common side effects are **gastric irritation and gastrointestinal (GI) bleeding.**
2. **Other nonsteroidal anti-inflammatory drugs (NSAIDs),** such as indomethacin (*Indocin*), tolmetin (*Tolectin*), ibuprofen (*Motrin*), sulindac (*Clinoril*) and naproxen (*Naprosyn*), also **act by inhibiting cyclooxygenase.**
   a. **The side effects are less pronounced** than with aspirin, but all produce some **GI bleeding.**
   b. **Renal toxicity** may occur, as reduction of prostaglandins in the kidney reduces renal blood flow and renal function. The resulting salt and water retention can reduce the effectiveness of most antihypertensives.
   c. **Hepatitis** can also be induced.
   d. **Diclofenac** (*Voltaren*) is more potent than indomethacin or naproxen and has the added advantage of accumulating in synovial fluid.
3. **Selective inhibitors of the COX-2 enzyme** (e.g., **celecoxib** [*Celebrex*], **valdecoxib** [*Bextra*], **and rofecoxib** [*Vioxx*]) appear to have
   a. Good antiinflammatory activity.
   b. **Low gastric irritation**
   c. No effect on platelet aggregation
   d. Valdecoxib and rofecoxib were removed from the market due to an **increased risk of heart attack and stroke.**

C. Nonselective NSAIDs and COX-2 inhibitors will decrease the pain and inflammation from arthritis, and decreased inflammation can slow joint damage. The disease continues to progress, however, unless disease-modifying antirheumatic drugs (DMARDs) are used.

1. **DMARDs** have **slow onsets** of action, taking months to induce an effect.
   a. They have **no analgesic activity;** thus they should initially be combined with NSAIDs.
   b. They **reduce the progression of joint erosion,** probably by reducing the activity of immune system cells and blocking other immune responses that are responsible for RA.
2. **Cytotoxic drugs** act by suppressing the immune system.
   a. **Methotrexate** (*Rheumatrex*) **blocks purine synthesis.** It is effective against RA at low dosages so little toxicity occurs. Coadministration of **folic acid** or **folinic acid** (*Leucovorin*) can further decrease adverse side effects.
   b. **Leflunomide** (*Arava*) **inhibits pyrimidine synthesis** in activated (rapidly replicating) T cells.
   c. Both drugs are **teratogenic** and should not be given to pregnant women.
3. Other drugs can be tried if needed to control the disease.
   a. **Gold compounds** can be administered intramuscularly (e.g., **aurothioglucose** [*Solganal*]) or orally (e.g., **auranofin** [*Ridaura*]).
   b. **Penicillamine** (*Cuprimine*), a chelator, can be given orally.
   c. **Hydroxychloroquine** (*Plaquenil*), an antimalarial, is given orally; but it can induce **retinopathy.**
4. **Tumor necrosis factor (TNF)-α-inhibitors** are effective but **increase risk of infection.**
   a. **Etanercept** (*Enbrel*), a **recombinant TNF-α receptor fusion protein that sequesters TNF-α,** has been approved for the treatment of rheumatoid arthritis.
   b. **Infliximab** (*Remicade*) and **adalimumab** (*Humira*) are **monoclonal antibodies** that also bind and **sequester TNF-α.**
5. **Anakinra** (*Kineret*) is a recombinant protein that **blocks the interleukin-1 receptor.**

D. THE GLUCOCORTICOIDS are the most potent anti-inflammatory drugs.
1. They have a fast onset of action.
2. **Many side effects** occur with chronic glucocorticoid administration, **including adrenal suppression, ulcers, and osteoporosis.**
3. **Alternate day therapy** may reduce the severity of these side effects.
4. Injection into a joint induces long-term effects on the joint with little systemic toxicity. However, repeated injections can lead to joint erosion.

E. Other rheumatoid and inflammatory arthritic conditions are treated with the same groups of drugs, although the specific regimens may vary. The exception is gout.

VIII Drugs for Gout

A. A DISORDER OF URIC ACID METABOLISM leads to the **hyperuricemia and acute gouty arthritis** that are characteristic of gout. Crystals are deposited in the joints and kidneys where they are phagocytosed by macrophages, leading to inflammation.

B. Many drugs can **reduce the gouty arthritic inflammation** without changing uric acid metabolism or elimination.
1. **Colchicine** depolymerizes tubulin in granulocytes, preventing them from migrating into joints and phagocytosing crystals.
   a. It may also decrease the release of leukotrienes.
   b. **An antimitotic** effect on the gastric mucosa frequently leads to **bloody diarrhea, nausea, vomiting,** and **abdominal pain.**
2. **NSAIDs** (e.g., indomethacin [*Indocin*]) are very effective.
3. **Glucocorticoids** or adrenocorticotropic hormone (ACTH) will reduce the acute attack but should not be used chronically due to their marked toxicity. Glucocorticoids can be given intra-articularly if the arthritic pain is localized to one or a few joints.

C. ASPIRIN IS CONTRAINDICATED in patients with gout because it can reduce the renal clearance of uric acid and thereby increase hyperuricemia.

D. HYPERURICEMIA can be reduced by two classes of drugs.
1. Most patients with gout **underexcrete uric acid. Uricosuric drugs,** such as **probenecid** (*Benemid*) and **sulfinpyrazone** (*Anturane*), **compete with uric acid transport** (especially reabsorption) in the proximal tubule of the kidney.
   a. Elimination of uric acid in urine is increased.
   b. **Renal calculi** from uric acid crystals may form; thus, the patient should ingest lots of **fluids with bicarbonate.**
   c. The mobilization of uric acid from the body stores **may induce an acute arthritic attack;** thus, the patient should also be given colchicine or indomethacin.
   d. It is **inappropriate** to use uricosuric drugs
      i. During an **acute arthritic attack**
      ii. In patients with **renal failure**
      iii. When the **body burden of uric acid is very high,** such as in patients
         (a) **With many tophi**
         (b) **With hematological disorders**
         (c) **During cancer chemotherapy**

2. **Inhibitors of uric acid synthesis** will reduce the production of uric acid, and are useful in patients who produce excessive amounts of uric acid.
   a. **Allopurinol** (*Zyloprim*) **inhibits xanthine oxidase.** It is also metabolized by xanthine oxidase to an active product, alloxanthine.
      i. The uric acid concentration in the urine is reduced.
      ii. **Xanthine and hypoxanthine** concentrations in the urine are increased.
         (a) Xanthine and hypoxanthine are **more water soluble** than uric acid.
         (b) There are **multiple substances** in the urine; thus more total product can be excreted without causing crystalluria.
   b. Levels of 5-phosphoribosylpyrophosphate (PRPP), a precursor of purine synthesis, are also reduced by allopurinol.
   c. An acute attack can be induced; thus, colchicine or indomethacin should be used in combination with the synthesis inhibitor and should not be given during an acute attack.
   d. Allopurinol inhibits inactivation of azathioprine and 6-MP, which are metabolized in part by xanthine oxidase.

IX Drugs for Acne

A. BENZOYL PEROXIDE is a keratolytic that reduces acne. It is applied topically and is available in combination with erythromycin (*Benzamycin*) or clindamycin (*Benzaclin*)

B. Topical antibiotics such as clindamycin, sulfacetamide, metronidazole, and erythromycin can be used. Long-term treatment with orally administered **erythromycin or tetracyclines** is also effective.

C. ISOTRETINOIN (*Accutane*), a vitamin A derivative, is administered orally for treatment of severe cases of cystic acne.
1. It inhibits the sebaceous glands.
2. **Side effects** can be very marked.
   a. It is **teratogenic.** Women of child-bearing age should use contraception while taking isotretinoin.
   b. **Hypervitaminosis A** can lead to irritated skin.

D. RETINOIC ACID (*Tretinoin*) is applied topically; it is thought to work by increasing epidermal cell turnover. Improvement should be seen in 2–3 months.

E. AZALEIC ACID (*Azelex, Finacea*) is applied topically to treat acne vulgaris and acne rosacea.

X Vitamins

A. VITAMINS ARE ESSENTIAL NUTRIENTS FOR METABOLIC REACTIONS. Most vitamins must be obtained in the diet.

B. WATER-SOLUBLE VITAMINS ARE READILY ELIMINATED by the kidney and are usually nontoxic. **Fat-soluble vitamins can accumulate** and be more toxic; caution should be used if high doses are administered.

C. The deficiency and overdose syndromes for the vitamins are listed in Table 7-2.

TABLE 7-2 DEFICIENCY AND TOXIC STATES FOR VITAMINS

	Deficiency	Common Causes of Deficiency	Toxicity
Water-Soluble Vitamins			
Thiamine (B_1)	Beriberi Wernicke-Korsakoff syndrome	Polished rice diet Alcoholism	None
Riboflavin (B_2)	Infrequent	N/A	None
Niacin (nicotinic acid, B_3)	Pellagra (3Ds: dermatitis, diarrhea, dementia)	Low protein diet	Lower serum triglycerides and cholesterol Flushing and GI distress
Pantothenic acid (B_5)	Infrequent	N/A	None
Pyridoxine (B_6)	Peripheral neuropathy Microcytic anemia	Infrequent–ISONIAZID	Peripheral neuropathy Lower anticonvulsant and L-dopa effects
Cyanocobalamin (B_{12})	Pernicious anemia (megaloblastic, macrocytic) Neurological symptoms	Gastrectomy (no intrinsic factor), Autoimmune destruction of gastric parietal cells	None
Folic acid (B_9)	Megaloblastic, macrocytic anemia Neural tube birth defects	Alcoholism, Anticonvulsants, Pregnancy	None
Ascorbic acid (C)	Scurvy	Dietary	None
Biotin	Infrequent	Raw egg whites	None
Fat-Soluble Vitamins			
Vitamin A	Decreased dark adaptation Night blindness Xerophthalmia	Dietary	Dry, scaly skin
Vitamin D	Rickets (kids) Osteomalacia (adults)	Lack of sunlight Dietary	Hypercalcemia
Vitamin E	Infrequent hemolytic anemia	Premature infants	Least toxic fat-soluble vitamin
Vitamin K	Decreased blood coagulation	Warfarin, Otherwise rare in adults	Jaundice in newborn Decreased effect of oral anticoagulants

D. The primary medical **uses** of vitamins are
1. Treatment of **vitamin deficiencies**
2. **Prophylaxis** to avoid deficiencies in
   a. Growing children
   b. Pregnant women
   c. Nursing mothers
   d. People on unusual diets

XI Drugs for Gastrointestinal Disorders

A. There are **three strategies** for **treating ulcers: treat the infection, decrease stomach acid,** and **protect the stomach mucosa.**

1. **Triple therapy** including two **antibiotics** and a **proton pump inhibitor** (e.g., amoxicillin, clarithromycin, omeprazole) will kill the ***Helicobacter pylori*** that causes most ulcers.
   a. A permanent **cure** can be produced in many patients.
   b. Antibiotic therapy is **inappropriate for salicylate-induced and nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers.**
   c. Metronidazole can be used in patients who are allergic to penicillins.
2. **Neutralization or decreased production of stomach acid** helps allow ulcers to heal by preventing further damage to the stomach mucosa.
   a. **H_2-Antihistamines,** such as cimetidine (*Tagamet*), ranitidine (*Zantac*), and famotidine (*Pepcid*) are competitive antagonists at H_2-receptors in the intestinal tract. They are used less commonly now vs. proton pump inhibitors.
      i. **Acid and pepsin secretion** are **reduced.** Proton release due to gastrin or histamine binding is completely inhibited, whereas proton release due to acetylcholine binding is partially inhibited.
      ii. The release of intrinsic factor is unchanged.
      iii. There are **no effects at H_1-receptors.**
      iv. **Cimetidine** has several side effects:
         (a) **Impotence** and **swelling of the breasts** due to antiandrogen activity
         (b) **Increased prolactin release,** which can cause galactorrhea
         (c) **Inhibition** of **cytochrome P450 enzymes,** which can **slow the metabolism of many drugs** (e.g., warfarin, propranolol) and enhance their effects
      v. **Ranitidine** and **famotidine** have **fewer side effects** and **longer durations** of action.
      vi. H_2 blockers compete with other basic drugs (e.g., pramipexole, procainamide) for secretion by the renal organic cation transporter.
   b. **Omeprazole** (*Prilosec*), **lansoprazole** (*Prevacid*), and **esomeprazole** (*Nexium*) are **proton pump inhibitors.**
      i. They **irreversibly inhibit** the **H^+/K^+ ATPase,** which blocks the final step in acid secretion**.**
      ii. These drugs are very effective, especially for gastroesophageal reflux (heartburn) and are generally well tolerated. Thus, they are often the first-line class of drugs used to treat ulcers.
   c. **Antacids directly neutralize stomach acid;** however their duration of action is limited by stomach-emptying time.
      i. **Sodium bicarbonate** is a **systemic** antacid.
         (a) It is readily absorbed into the body.
         (b) **Side effects** are common, including **metabolic alkalosis, hypernatremia, fluid retention,** and **acid rebound,** due to high gastric pH.
      ii. **Nonsystemic** antacids are poorly absorbed into the body.
         (a) **Magnesium hydroxide** induces the side effect of **diarrhea,** whereas **aluminum hydroxide** induces **constipation.** Thus, magnesium hydroxide and aluminum hydroxide are combined to create an antacid preparation with little effect on GI motility.
         (b) **Calcium carbonate** (*Tums*) has more **side effects,** including **hypercalcemia** (e.g., milk alkali syndrome), **acid rebound,** and **constipation.**
3. **Physical protection of the gastric mucosa** can be an effective strategy**.**
   a. **Sucralfate** (*Carafate*) adheres to the ulcerated mucosal wall of the stomach and provides a **barrier** to acid and pepsin. It should not be coadministered with H_2 antagonists or antacids because acid is required for the sucralfate to work.

b. **Misoprostol** (*Cytotec*), a prostaglandin E_1 analog, enhances the mucosal barrier by stimulating mucus and bicarbonate secretion. It is used for **NSAID-induced** ulcers.

4. **Metoclopramide** (*Octamide, Reglan*) is an **antidopaminergic** drug that **increases lower esophageal sphincter tone.**
   a. Gastroesophageal reflux is decreased.
   b. It also has antiemetic actions due to blocking D_2 receptors in the medulla.

B. ANTIDIARRHEAL DRUGS are useful to reduce the loss of fluid and electrolytes that occurs with diarrhea. These drugs **should not be used for treating diarrhea that is caused by a toxin, an infection, or chronic ulcerative colitis.**

1. **Opiates** act by increasing the tone and reducing the motility of the GI tract.
   a. **Diphenoxylate,** which is insoluble and poorly absorbed, is combined **with atropine** (*Lomotil*).
   b. **Loperamide** (*Imodium*) has no systemic side effects.
2. **Bismuth salicylate** (*Pepto-Bismol*) decreases fluid secretion in the bowel.
3. **Attapulgite,** a hydrophilic substance, absorbs water and reduces the looseness of the feces. **Kaolin/pectin** (*Kaopectate*) is another adsorbent agent.

C. LAXATIVE CATHARTICS add bulk and water to the feces, thereby stimulating peristalsis and relieving constipation. They should **never be used for undiagnosed abdominal pain or when there is possible intestinal obstruction.**

1. **Bulk laxatives** (e.g., psyllium and methylcellulose) are **fiber,** which increases the volume of the GI contents and thereby enhances peristalsis.
2. **Osmotic (bulk) cathartics** are also called saline laxatives.
   a. **Magnesium sulfate** (*milk of magnesia*) and **polyethylene glycol** (*MiraLAX, GoLytely*) cause osmotic retention of large amounts of water in the gut.
   b. The increased bulk **markedly enhances peristalsis.**
3. **Castor oil and bisacodyl** (*Dulcolax*) are contact laxatives.
   a. The active metabolite of castor oil is ricinoleic acid.
   b. **Irritation of nerve endings** increases peristaltic contractions.
   c. Prolonged use can lead to irritable bowel syndrome.
4. **Docusate** (*Colace, Doxinate*) and **mineral oil** are **fecal softeners** that make the passage of stools easier.

D. ANTIEMETICS ANTAGONIZE D_2 and $5HT_3$ RECEPTORS in the **chemoreceptor trigger zone** of the brain to **prevent vomiting.** These chemoreceptors sense chemical stimuli, whereas the actual act of vomiting is controlled by the medulla.

1. **Anticholinergic drugs** (scopolamine) and **H_1-antagonists** (**meclizine** [*Antivert*], **dimenhydrinate** [*Dramamine*]) **prevent motion sickness** but do not prevent stimulation of the chemoreceptor trigger zone.
2. Several drugs are used to control **chemotherapy-induced nausea and vomiting:**
   a. **D_2 dopamine receptor antagonists** include **prochlorperazine** (*Compazine*), **metoclopramide** (*Reglan*), and **droperidol** (*Inapsine*). Use of droperidol is associated with prolonged QT and torsades de pointes.
   b. **Odansetron** (*Zofran*) is a **$5HT_3$ serotonin receptor antagonist.**
   c. **Cannabinoids** like **dronabinol** (*Marinol*) work by an unknown mechanism and are not commonly used.
   d. **Aprepitant** (*Emend*) **blocks neurokinin receptors in the chemoreceptor trigger zone.**

Chapter 8

Endocrine Pharmacology

I Pituitary Hormones

A. The principle hormones produced by the anterior pituitary include **FSH, LH, ACTH, TSH, prolactin,** and **GH.** Most of these hormones are released in response to **hypothalamic-releasing hormones.**

1. The release of **growth hormone (somatotropin)** from the pituitary gland is regulated in an inhibitory fashion by the hypothalamic hormone somatostatin and is stimulated by growth hormone–releasing hormone (GHRH).

a. Challenge tests are available to

i. Increase the release of growth hormone, using

(a) Insulin, which induces hypoglycemia

(b) Bromocriptine

(c) L-Dopa

ii. Decrease the release of growth hormone, using

(a) Glucose

(b) Glucocorticoids, which induce hyperglycemia

(c) Somatostatin

b. **A growth hormone deficiency before puberty** will result in pituitary **dwarfism.**

i. **Somatrem** (*Protropin*) and **somatropin** (*Humatrope, Norditropin*) are human growth hormone produced by recombinant DNA technology.

(a) Replacement therapy will increase growth.

(b) However, replacement therapy cannot induce linear growth after epiphyseal closure has occurred in the long bones.

ii. **Androgens and estrogens** also increase growth; however, they are less effective than growth hormone and can induce epiphyseal closure, which limits further growth.

c. **Excessive growth hormone** leads to **gigantism** before puberty and **acromegaly** after puberty.

i. **Surgical removal** of part of the pituitary gland is the treatment of choice.

ii. **Bromocriptine** (*Parlodel*), a dopamine receptor agonist, inhibits growth hormone release in patients with excessive growth hormone. This is the opposite of the effect seen in normal subjects.

iii. **Octreotide** (*Sandostatin*), a somatostatin analog, will also inhibit growth hormone release.

iv. **Lanterotide** *(Somatuline–Depot)* is a long-acting somatostatin analog.

v. **Pegvisomant** *(Somavert)* is a **growth hormone receptor blocker.**

2. **Gonadotropin-releasing hormone** (GnRH) should increase serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

3. **Corticotropin-releasing hormone** (CRH) should increase the serum levels of adrenal corticotropic hormone (ACTH).
   a. ACTH release is highest in the morning and increases in response to stress.
   b. ACTH binds to receptors in the adrenal cortex and increases production of adrenocortical steroids, mainly glucocorticoids (see Section II).
4. **Thyrotropin-releasing hormone** (TRH) should increase the serum levels of thyroid-stimulating hormone (TSH).
5. **Prolactin-releasing hormone** (PRH) may increase or decrease serum levels of prolactin, whereas **dopamine** from the hypothalamus inhibits prolactin release.
   a. Prolactin stimulates lactation.
   b. **Hyperprolactinemia** is treated with a **dopamine agonist** such as **bromocriptine** (*Parlodel*) or **cabergoline** (*Dostinex*).
6. **End-organ hormones,** rather than deficient pituitary hormones, are used for replacement therapy of a pituitary deficiency.
7. **Glucocorticoids should be replaced before the thyroid hormone** to avoid precipitating adrenal crisis.

B. Hormones produced by the hypothalamus and stored in the posterior pituitary include **antidiuretic hormone (ADH, vasopressin)** and **oxytocin.**

1. **Vasopressin** is an important regulator of urine osmolarity, as it increases the permeability of the collecting ducts in the kidney to water. An inadequate vasopressin effect leads to **diabetes insipidus.**
   a. **Diagnosis** of the cause of the diabetes insipidus is based on the administration of vasopressin.
      i. If there is a **pituitary deficiency** of vasopressin, administered vasopressin will increase urine osmolarity (**central diabetes insipidus**).
      ii. If the diabetes is **nephrogenic, administered vasopressin will have no effect** on urine osmolarity (**nephrogenic diabetes insipidus**).
   b. **Treatment** depends on the cause.
      i. If diabetes insipidus is due to a **pituitary deficiency,** replacement therapy is instituted.
         (a) **Vasopressin** (*Pitressin*) can be given intramuscularly, but it can increase blood pressure due to vasoconstriction.
         (b) **Lypressin** (*Diapid*), **administered intranasally,** lasts 4 hours.
         (c) **Desmopressin** (*DDAVP, Stimate*), administered intranasally, lasts **12 hours** and **does not increase blood pressure.** It is also available in tablet form.
      ii. If the diabetes is **nephrogenic, thiazides** (unexpectedly) are effective treatment.
2. **Oxytocin** (*Pitocin, Syntocinon*) can be used to **increase uterine contractility.**
   a. **Estrogens increase and progestins decrease** the effects of oxytocin on the uterus.
   b. As term approaches, the number of oxytocin receptors in the uterine muscle increases, thereby increasing sensitivity to oxytocin.
   c. **The primary use for oxytocin is to induce labor** at term.
      i. Low doses will increase rhythmic contractions.
      ii. High doses should be avoided because they can induce a sustained uterine contraction, leading to complications.
   d. **Ergonovine** (*Ergotrate*) also has oxytocic activity; however, it induces a **sustained uterine contraction.** It is useful during the third stage of labor to
      i. **Induce expulsion of the placenta**
      ii. **Reduce postpartum hemorrhaging** by compressing the uterine blood vessels

e. **Premature labor** can be reduced by administering a **β_2-adrenoceptor agonist,** such as ritodrine (Yutopar).

II Adrenocortical Steroids

A. The adrenal cortex has three layers: the **zona glomerulosa, the zona fasciculata, and the zona reticularis** (from outside to inside: GFR, which make hormones for salt/sugar/sex)

1. The zona glomerulosa is stimulated by the renin–angiotensin system to produce the **mineralocorticoid aldosterone.**

2. The zona fasciculata and the zona reticularis are stimulated by ACTH to produce **glucocorticoids** and **sex hormones,** respectively.

3. **Steroids** diffuse across the cell membranes and **bind to steroid receptors** in the **cytoplasm.** The steroid-receptor complex **migrates to the nucleus** and acts on DNA to **increase mRNA and protein synthesis.**

B. Three types of effects can be induced by glucocorticoids/mineralocorticoids:

1. **Glucocorticoid effects** result from

a. **Enhanced gluconeogenesis** that leads to increased glucose production (diabetogenic) and increased glycogen synthesis and storage in the liver

b. **Enhanced lipolytic effects** that redistribute fat

2. **Anti-inflammatory effects** occur, although the mechanism is not well established. It is related at least in part to decreasing the number of peripheral lymphocytes and macrophages, as well as interfering with prostaglandin synthesis.

3. **Mineralocorticoid effects** result from increased sodium ion exchange for potassium and hydrogen ions in the kidney.

a. Hypokalemic alkalosis can be induced.

b. The increased sodium load can lead to edema and hypertension, which are treated with potassium-sparing diuretics (e.g., spironolactone, eplerenone, amiloride).

4. The mineralocorticoid effects have been separated from the glucocorticoid and anti-inflammatory effects (Table 8-1); however, it has not been possible to separate the glucocorticoid actions from the anti-inflammatory actions.

a. Dexamethasone is the most selective for glucocorticoid activity.

b. Fludrocortisone is the most selective for mineralocorticoid activity.

C. **CORTISOL,** also called hydrocortisone, is the primary adrenal glucocorticosteroid.

1. **Transcortin (corticosteroid-binding globulin, [CBG])** binds 75% of cortisol in circulation.

TABLE 8-1 RELATIVE MINERALOCORTICOID TO GLUCOCORTICOID ACTIVITIES OF THE ADRENOCORTICAL STEROIDS, AS COMPARED TO CORTISOL (HYDROCORTISONE)

Adrenocortical Steroid	Ratio of Mineralocorticoid Activity to Glucocorticoid Activity
Cortisol ([hydrocortisone] [*Cortef, Cortril*])	1
Cortisone (*Cortone*)	1
Prednisone (*Deltasone*)	0.1
Dexamethasone (*Decadron, Hexadrol*)	0.01
Fludrocortisone (*Florinef*)	10

a. The bound hormone is inactive.
b. **Estrogens and thyroxine increase CBG** but do not change the free cortisol concentration.
c. **Androgens decrease CBG.**

2. Cortisol is metabolized by mixed function oxidases (MFOs) in the liver.

D. There are **many side effects** that can occur with the adrenocorticoids, including:
1. **Hypokalemic alkalosis**
2. **Hyperglycemia,** which can aggravate diabetes mellitus
3. **Increased susceptibility to infections**
4. **Proximal myopathy**
5. **Osteoporosis**
6. **Symptoms of Cushing's syndrome**
7. **Depression**
8. **ACTH suppression,** which induces adrenal atrophy from which recovery takes several months. Thus, withdrawal from long-term glucocorticoid treatment should be slow and tapered.

E. Several drugs can **inhibit adrenal** cortical function.
1. **Aminoglutethimide** (*Cytadren*) inhibits desmolase and reduces the production of all adrenal steroids.
2. **Metyrapone** (*Metopirone*) reduces cortisol synthesis by inhibiting 11β-hydroxylase. This leads to increased sodium/water retention and hirsutism.
3. **Ketoconazole** (*Nizoral*), an antifungal drug, reduces cortisol and sex hormone synthesis and release. It also inhibits gonadal release of sex hormones.
4. **Spironolactone** (*Aldactone*) and **eplerenone** (*Inspra*) inhibit aldosterone receptors, thereby decreasing sodium/water reabsorption. Spironolactone can cause gynecomastia; eplerenone has fewer anti-androgenic effects than spironolactone does.
5. The antiprogestin **mifepristone** is a glucocorticoid antagonist at high doses.

F. There are many **clinical uses** for the adrenal steroids.
1. **Adrenal insufficiency** (Addison's disease) is treated with a glucocorticoid.
   a. Two thirds of the dose is administered in the morning and the other one third in the afternoon to mimic physiologic cycles.
   b. A mineralocorticoid is added if the insufficiency is primary (adrenal) but is usually not necessary for a secondary insufficiency (pituitary).
   c. For acute adrenal insufficiency, an intravenous glucocorticoid and saline are administered.
2. **Congenital adrenal hyperplasia** is due to an adrenal enzyme deficiency (e.g., 21-hydroxylase), which leads to increased ACTH release and increased androgen production. It is treated with a glucocorticoid, and a mineralocorticoid is added if needed.
3. Dexamethasone is very useful in **diagnosing** Cushing's syndrome.
   a. **Primary** adrenal hormone secretion is **not suppressed.**
   b. **Secondary, pituitary-dependent** hormone secretion **is suppressed**
   c. ACTH-secreting bronchial carcinoids can also be suppressed by dexamethasone.
4. **The anti-inflammatory effects** of the adrenal steroids are very useful in treating **allergic reactions, inflammatory diseases, tissue rejection, and leukemias.**
   a. They are safe during short-term therapy.
   b. **Many side effects occur with long-term therapy.**

i. It is possible to reduce the pituitary suppression somewhat by using **alternate-day therapy.** This involves doubling the dose one day and using only NSAIDs on the next day.
ii. Adrenocortical steroids should be used for chronic therapy only as a last resort.

5. Glucocorticoids can be used to **accelerate lung maturation in preterm infants.**

III Female Sex Hormones

A. Sex hormone-binding globulin and albumin bind estradiol and testosterone.
1. The hormones dissociate from these carriers and bind to receptors.
2. There are two estrogen receptors.
a. **The α receptor activates gene transcription**
b. **The β receptor represses gene transcription.**
3. The receptor–steroid complexes translocate to the nucleus and form homodimers with estrogen response elements on DNA.

B. EFFECTS OF ESTROGENS include:
1. Control of reproductive organs
2. Control of secondary sex characteristics
3. Anabolic effects that promote growth, which are fewer than with androgens

C. THE ESTROGEN PREPARATIONS are
1. Natural
a. **Estradiol** (*Estrace*), which is the most potent natural estrogen. It is usually conjugated (*Premarin*) for longer duration of action.
b. **Estrone** and **estriol,** which are formed by the liver and the adrenals.
2. Synthetic, which are more potent and longer acting than natural estrogens
a. **Ethinyl estradiol** (*Estinyl*) has less first-pass metabolism, allowing for administration of lower doses.
b. **Mestranol** is metabolized to ethinyl estradiol.
c. **Diethylstilbestrol** (*Stilphostrol*), which is **nonsteroidal** and can induce **vaginal adenomas in female offspring after puberty.** It may also affect male offspring
3. Transdermal patches, topical estrogen preparations, and depo injections can be used to decrease the first-pass metabolism seen with orally administered estrogens.

D. SIDE EFFECTS of the estrogens include:
1. Minor consequences, such as
a. **Nausea and vomiting**
b. **Edema**
c. **Breast tenderness**
d. **Headaches**
2. Major consequences, such as
a. **Thrombophlebitis, deep vein thrombosis,** and **pulmonary embolism,** especially in smokers over age 35. The increased risk is similar to the risk during pregnancy.
b. **Breast cancer** and **endometrial cancer.**
c. Fluid retention and mild hypertension.

E. EFFECTS OF THE PROGESTINS include:

1. Induction of **secretory changes in the endometrium of the uterus** that are necessary for pregnancy during the luteal phase of the menstrual cycle.
2. **Maintenance of the uterine lining if pregnancy occurs.**
3. If no pregnancy occurs, induction of **menstruation** when the progestin levels fall.

F. PROGESTIN PREPARATIONS include:

1. Progesterone, which is not useful due to a very short half-life
2. **Synthetic progestins,** which have a **longer half-life** than progesterone due to **decreased first-pass metabolism**
   a. **Medroxyprogesterone** (*Provera*)
   b. **Norethindrone** (*Norlutin*), which has some androgenic activity and can cause acne, hirsutism, and raised low-density lipoprotein (LDL) levels
   c. **Levonorgestrel** (*Norplant*)
   d. **Desogestrel,** a newer preparation

G. There are many **uses** for the female sex steroids.

1. **Contraceptives** can act by many different mechanisms.
   a. The **combined oral estrogen–progestin pill reduces FSH** and **LH release** by negative feedback of estrogen on the pituitary, which inhibits ovulation.
      i. Active birth control pills (BCPs) are taken for 21 or 24 days, followed by 7 or 4 days of dummy pills, respectively, for a total cycle of 28 days. Dummy pills are taken to induce menstruation.
      ii. The new preparations have lower estrogen concentrations to reduce the side effects. However, BCPs should not be used by smokers over age 35, women with a history of deep-vein thrombosis, or women with estrogen-dependent neoplasms.
      iii. Phasic preparations have more progestin during the second and third weeks of the menstrual cycle, whereas monophasic pills have constant progestin levels throughout.
      iv. BCPs decrease the risk of ovarian and endometrial cancer.
      v. Drugs that activate MFOs (e.g., rifampin) can reduce the effectiveness of the estrogen–progestin contraceptives.
   b. **The continuous oral progestins (minipills)** reduce the likelihood of implantation of the fertilized ovum. A common side effect is irregular menstruation. Minipills are less effective than the combined estrogen-progestin pill.
   c. **Depot medroxyprogesterone** (*Depo-Provera*) or **levonorgestrel** (*Norplant*) are progestins that are useful when compliance is a concern. They can be injected or implanted in the arm to release hormones slowly over several months or years.
   d. **Acute, high-dose estrogen therapy** is used postcoitally to reduce the likelihood of implantation (morning-after pill).
   e. **Mifepristone (RU 486) is an antiprogesterone** that blocks preparation of the uterus for pregnancy. It is usually combined with prostaglandins (e.g., misoprostol) when used to induce abortions.
   f. **Nonoxynol-9** acts as a spermicide.
2. **Hypogonadism** is treated by replacement therapy with physiological doses of sex steroids. This includes:
   a. **Menopausal symptoms** induced by the loss of female sex hormones
      i. **Estrogens will decrease the symptoms of menopause** (e.g., hot flashes, night sweats, and vaginal atrophy) as well as **decrease the risk of osteoporosis.**

ii. In women who have not undergone a hysterectomy, **progestins** are added to reduce the high incidence of **endometrial cancer** caused by using estrogens alone.

b. **Amenorrhea**
   i. Estrogen–progestin preparations will **induce menstruation.**
   ii. **Growth and sexual development** will be induced when the sex hormones are administered at the age of puberty.

c. **Dysfunctional uterine bleeding**

3. **Inhibition of ovarian function** can be induced by pharmacological doses of sex steroids.
   a. **Dysmenorrhea** is reduced due to inhibition of ovulation. Indomethacin is also effective because it inhibits prostaglandin release, which may be involved in inducing dysmenorrhea.
   b. **Hirsutism** due to ovarian androgens is reduced.
4. **Some cancers** are treatable with sex hormones or sex hormone antagonists. (See Chapter 11 for details.)
   a. **Selective estrogen receptor modulators (SERMs) have selective agonist or antagonist effects,** depending on the tissue.
   b. **Tamoxifen** (*Nolvadex*) is used to treat **advanced breast cancer in postmenopausal women.** It can cause **menopausal symptoms** and **endometrial hyperplasia.**
   c. **Toremifene** (*Fareston*) is a SERM that does not affect the endometrium.
5. **Raloxifene** (*Evista*) **increases bone density by decreasing bone resorption** in postmenopausal women. It decreases the risk of breast cancer and does not seem to affect the endometrium.
6. An inappropriate indication for estrogens is a threatened miscarriage; estrogens are **contraindicated during pregnancy.**

IV Fertility Drugs

A. CLOMIPHENE (*Clomid*) is a **partial estrogen agonist that reduces feedback inhibition** of estrogen on the pituitary gland and hypothalamus.
1. Increased release of GnRH, FSH, and LH **enhances ovulation.**
2. A functional pituitary gland and functional ovaries are required.
3. The incidence of multiple pregnancies is increased.

B. HUMAN MENOPAUSAL GONADOTROPINS (hMG) (*Pergonal*) and **human chorionic gonadotropins** (hCG) (*Follutein, Pregnyl*) have **FSH and LH activities;** thus, a functional pituitary gland is not required. **Follitropin β** (*Follistim*) is a recombinant FSH with similar properties.

C. GnRH preparations act on the pituitary gland.
1. Pulsatile administration of **gonadorelin** (*Factrel*) induces the release of FSH and LH.
2. Sustained administration of **leuprolide** (*Lupron*) decreases the release of FSH and LH, which is useful in the **treatment of infertility from endometriosis.**

D. DANAZOL (*Danocrine*) is a testosterone derivative that reduces gonadotropin release.
1. Endometrial atrophy is produced, which reduces **endometriosis.**
2. Upon discontinuing the danazol, fertility is increased.

E. BROMOCRIPTINE (*Parlodel*) is a **dopamine receptor agonist** that reduces prolactin release from the pituitary gland. It increases fertility in patients with **hyperprolactinemia.**

V Male Sex Hormones

A. These sex hormones have **androgenic and anabolic** activities.

B. **MANY PREPARATIONS** are available.
1. **Testosterone** is usually administered, **intramuscularly,** as an ester (*Delatestryl*) to prolong the duration of action. Testosterone is also available in topical preparations.
2. **Methyltestosterone** (*Metandren, Testred*) and **fluoxymesterone** (*Halotestin*) are effective when given **orally** and have longer durations of action than testosterone.
3. **Nandrolone** (*Durabolin*) is an **anabolic** steroid, although it still has some androgenic effects.

C. **THE SIDE EFFECTS** include:
1. **Masculinization** (acne, deeper voice, hirsutism)
2. **Edema** due to fluid retention
3. **Increased LDL/HDL ratio**
4. **Polycythemia**

D. **USES** for male sex hormones, gonadotropins, and antiandrogens include:
1. **Treatment of hypogonadism**
   a. Potency and fertility (if given with gonadotropins) are increased.
   b. Growth is increased in children, although epiphyseal closure induced by the steroids can limit final height.
2. **hCG** is used to treat **cryptorchidism.**
3. Adjuvant **treatment of prostate cancer** (the GnRH agonist leuprolide [*Lupron*]) and **treatment of benign prostatic hyperplasia (**finasteride [*Proscar*]).
4. **Anabolic actions**
   a. To hasten recovery after an injury
   b. To treat anemias

E. An inappropriate use of steroids is to increase athletic performance. Anabolic steroids can cause:
1. Reduced growth after an initial growth spurt, by inducing premature epiphyseal closure in young athletes
2. Reduced fertility due to feedback inhibition by the steroids on gonadotropin release
3. Virilization in females
4. Hepatotoxicity and hepatic tumors
5. Edema and hypertension

F. **SPIRONOLACTONE** (*Aldactone*) and **FLUTAMIDE** (*Eulexin*) have **antiandrogen activity** and can be used to treat hirsutism, prostate cancer, and precocious puberty.

VI Thyroid Hormones

A. **HYPOTHYROIDISM,** whether primary, secondary, or tertiary, is the major indication for the thyroid hormone preparations. Symptoms include **bradycardia, feeling cold,** and **mental and physical slowing** due to decreased metabolism.
1. T_4 is converted to T_3 and binds to its receptor inside cells. The hormone-receptor complex then binds to DNA to affect transcription of the appropriate genes.

2. T_4 will reduce the symptoms of hypothyroidism and reduce TSH release. Treatment is initiated slowly in high risk patients to avoid cardiovascular symptoms.
3. **T_4** is usually preferred because it has a simpler dosing regimen than T_3. T_3 is the most active form of TH; it is used to treat hypothyroid coma because it has a rapid onset of action.
4. **Side effects** from thyroid hormone replacement stem from a dose that is too high, and are due to an **increase in metabolic rate.** They include:
   a. **Heat intolerance, flushing,** and **excessive sweating**
   b. **Weight loss**
   c. **Increased appetite**
   d. **Tachycardia, palpitations,** and rarely, angina
   e. **Diarrhea**
   f. **Forgetfulness, inability to focus**
   g. **Irregular or light menstrual periods**
5. In the hypothyroid newborn, aggressive treatment within 1 month of birth is necessary to avoid cretinism. After 3–4 months of untreated hypothyroidism in the newborn, brain dysfunction will occur.
6. Patients sometimes abuse TH in an effort to lose weight. This is dangerous due to the risks associated with uncontrolled hyperthyroidism.

B. THYROID PREPARATIONS include:

1. **Levothyroxine (T_4)** (*Levothroid, Synthroid*), which is identical to natural T_4.
   a. **Highly bound** to thyroxine binding globulin **(TBG)**
   b. Half-life is **7 days**
2. **Liothyronine (L-triiodothyronine, T_3)** (*Cytomel*), which is identical to natural T_3
   a. It is less well bound than T_4 to TBG; thus, it is **more potent.**
   b. The half-life is **1 day,** which is much shorter than the half-life of T_4.
3. **Desiccated thyroid,** which is powdered animal thyroid glands containing both T_4 and T_3.
4. **Thyroglobulin** (*Proloid*), which is extracted from animal thyroids.
5. Liotrix and Thyrolar, which are combinations of T_4 and T_3.
6. **TSH** (*Thytropar, Thyrogen*) and **TRH** (protirelin [*Thypinone*]), which are used for diagnostic purposes.

C. SYMPTOMS OF HYPERTHYROIDISM include tachycardia, cardiac arrhythmias, nervousness, tremor, and heat intolerance due to a fast metabolism. Treatments include:

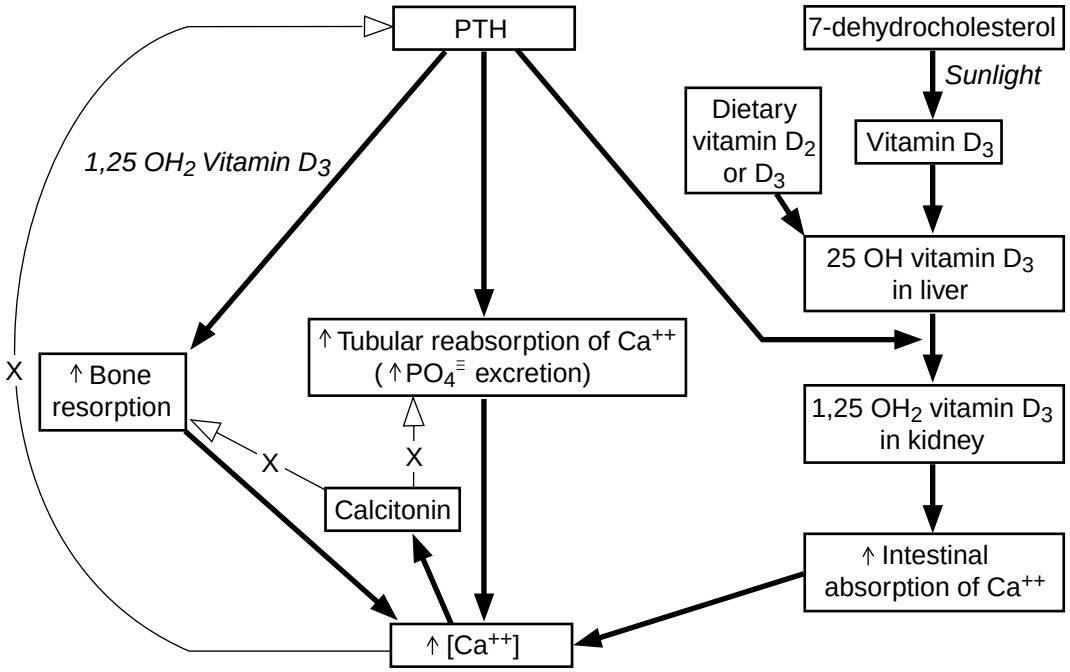
1. Administration of **thioamides,** such as **propylthiouracil** and **methimazole** (*Tapazole*), which reduce the synthesis and release of thyroid hormones.
   a. **Reduced I_2 binding to tyrosine and reduced coupling of iodotyrosines** leads to a depletion of thyroid hormones.
      i. Release of T_4 and T_3 is reduced.
      ii. Increased TSH release from reduced feedback inhibition can induce **goiter;** T_4 is occasionally added to the regimen to reduce TSH release.
      iii. The onset is **slow** (6–11 weeks for Graves' disease patients) because stores of thyroglobulin have to be depleted.
   b. Graves' disease is not usually curable with these antithyroid drugs.
   c. Propylthiouracil and methimazole cross the placenta and will affect the fetus.
   d. Propylthiouracil also inhibits the peripheral conversion of T_4 to T_3.
2. **A partial thyroidectomy** can result in a permanent cure.
   a. Possible adverse consequences of surgery are **hypoparathyroidism** and **hypothyroidism.** Hypothyroidism is the goal in patients with Graves' disease.

b. Propylthiouracil or iodide can be used pre-operatively to reduce the size and vascularity of the thyroid gland.

3. **Radioactive iodine (^{131}I),** given orally, is concentrated in the thyroid, where β-radiation can destroy thyroid cells. **^{131}I** treatment
   a. Has a **slow onset;** thus, treatment with antithyroid drugs may be necessary until **^{131}I** becomes effective.
   b. Can result in **hypothyroidism** (this is desirable in Graves' disease).
   c. **Must be avoided during pregnancy.**
   d. Could theoretically induce genetic abnormalities. Female patients are advised to avoid pregnancy for 6–12 months after radioactive iodine administration.
   e. **Thyroid cancer** can be treated with **^{131}I** if the cancer cells concentrate iodide.
4. **Iodide in large amounts** rapidly reduces thyroid hormone release, although the effect is transient. It also reduces the vascularity of the thyroid gland.
5. **The sympathetic blockers** (e.g., propranolol [*Inderal*]) do not affect the thyroid, but do rapidly **reduce the myocardial stimulation** that occurs with elevated thyroid hormone levels.
6. **Thyroid storm** (acute hyperthyroid crisis) is treated with **propranolol, other β-blockers, calcium channel blockers, antipyretics, iodide, antithyroid drugs, corticosteroids,** and **supportive measures** (oxygen, ventilation, correction of electrolyte abnormalities, glucose).

VII Calcium and Phosphate Metabolism

A. Three main hormones are involved in the regulation of serum calcium concentration (Figure 8-1).



● **Figure 8-1** Regulation of calcium metabolism by parathyroid hormone, vitamin D and calcitonin. Ca^{++} = calcium; OH = hydroxy; OH_2 = dihydroxy; $PO_4^{\equiv}$ = phosphate; PTH = parathyroid hormone

1. **Parathyroid hormone** release, induced by hypocalcemia, increases serum calcium by increasing
   a. **Formation of active 1,25-dihydroxyvitamin D_3** in the kidney, which increases the **absorption of calcium in the gut**
   b. **Bone resorption** and **release of calcium**
   c. **Kidney reabsorption of calcium** (and increasing phosphate excretion)
2. **Vitamin D_3** (cholecalciferol) from the diet or from exposure to sunlight is hydroxylated to **25-hydroxyvitamin D_3** (calcidiol, calcifediol [*Calderol*]) in the liver.
   a. This intermediate is further hydroxylated in the kidney to **1,25-dihydroxyvitamin D_3, calcitriol** (*Rocaltrol*).
   b. Dihydroxyvitamin D_3 **increases the intestinal absorption of calcium** and **phosphate.**
3. **Calcitonin** release, in response to hypercalcemia, decreases bone resorption and increases excretion of calcium and phosphate by inhibiting reabsorption in the kidneys.
4. Other factors can also affect calcium and phosphate homeostasis.
   a. **Fibroblast growth factor 23 (FGF 23)** inhibits vitamin D production in opposition to PTH, which stimulates vitamin D. Vitamin D in turn inhibits PTH secretion.
   b. **Glucocorticoids** antagonize vitamin D-mediated calcium absorption, stimulate renal excretion of calcium, and inhibit bone formation.
   c. **Estrogens** are thought to reduce the bone-resorbing action of PTH and increase blood vitamin D levels.

B. HYPOPARATHYROIDISM results in hypocalcemia, hyperphosphatemia, and increased membrane excitability (hypocalcemic tetany).

1. **Treatment** involves the administration of a 1-hydroxylated **vitamin D preparation and calcium.** Parathyroid hormone is not very useful as it must be given by injection.
2. **Pseudohypoparathyroidism** can be treated with calcium plus high doses of vitamin D, which appears to directly increase bone resorption.

C. OSTEOMALACIA (hypovitaminosis D) is also treated with **vitamin D.**

1. If gastrointestinal (GI) absorption is poor, vitamin D can be administered parenterally.
2. If liver function is reduced, 25-hydroxylated forms such as calcifediol or calcitriol should be administered.
3. If kidney function is reduced, α_1-hydroxylated forms such as calcitriol or **dihydrotachysterol** (*Hytakerol*) should be administered.
   a. Dihydrotachysterol has a **rapid onset of action** (2 hours).
   b. It is metabolized in the **liver** to the active form.

D. HYPERPARATHYROIDISM usually results in **hypercalcemia.**

1. **Surgery** is the preferred mode of treatment.
2. **Corticosteroids** can be used to **reduce the absorption of calcium** by the intestine.
3. **Acute treatment** of hypercalcemia involves the administration of
   a. **Fluids.**
   b. **Calcitonin** (subcutaneous injections every 12 hours for 72 hours).
   c. **IV bisphosphonates** such as pamidronate *(Iridia)* or zoledronate *(Zometa)*.
   d. **Loop diuretics,** which increase calcium excretion by the kidneys. All fluid losses should be replaced to avoid dehydration, which worsens hypercalcemia.

e. **Phosphate,** if hypophosphatemia is present. Caution must be used because the $[Ca^{2+}][PO_4^{3-}]$ product is normally constant; too much phosphate can cause hypocalcemia.

4. **Cinacalcet** (*Sensipar*) **activates the calcium-sensing receptor** (CaSR), thus blocking PTH secretion. It is used in patients with secondary hyperparathyroidism and renal failure.

E. HYPERVITAMINOSIS D results in hypercalcemia and is acutely treated much like hyperparathyroidism.

F. OSTEOPOROSIS is a skeletal disorder in which calcium hormone function is normal. It is characterized by low bone density and increased susceptibility to fracture.

1. **Treatment of postmenopausal osteoporosis involves the administration of**
   a. **Vitamin D.**
   b. **Calcium.**
   c. **Estrogen** has been used, but it has fallen out of favor due to concerns about increased risk of heart disease, breast cancer, and uterine cancer.
2. **Bisphosphonates stabilize bone** by inhibiting mevalonic acid production. This results in a decrease in bone turnover, inhibition of the osteoclast proton pump, decrease in osteoclast differentiation, and an increase in osteoclast apoptosis. Bone formation continues unabated.
   a. **Alendronate** (*Fosamax*) and **risedronate** (*Actonel*) are taken once a week orally on an empty stomach.
   b. **Zoledronate** (*Reclast*) is the most potent bisphosphonate, and must be administered parenterally once a year.
   c. **Ibandronate** (*Boniva*) is another oral bisphosphonate that has a more convenient dose schedule (once a month) versus alendronate.
3. **Teriparatide** (*Forteo*) is a **recombinant portion of PTH. It has anabolic properties** and is currently the only osteoporosis treatment that **increases bone formation** rather than simply inhibiting bone resorption. It is given as a daily subcutaneous injection.
4. **Selective estrogen receptor modulators (SERMs),** such as raloxifene (*Evista*)
   a. Stimulate bone and lower serum lipids by binding to estrogen receptors
   b. Have no effect on the endometrium or breasts
   c. Do not prevent hot flashes and still increase the risk of blood clots
5. **Thiazide diuretics** increase calcium reabsorption in the distal tubules.
6. **Other treatment modalities** can be used.
   a. **Calcitonin** can be administered intranasally or subcutaneously.
   b. Other therapies include **weight-bearing exercise** and **smoking cessation.**

G. PAGET'S DISEASE involves a rapid turnover of calcium in bone. **Treatment** utilizes

1. **Calcitonin** (*Calcimar*), parenterally. Salmon calcitonin is the most active form.
2. **Bisphosphonates** such as **etidronate** (*Didronel*) or alendronate, which reduce bone turnover. They are **effective when given orally** and have better efficacy than calcitonin. Zoledronate is currently the most effective treatment.

VIII Drugs for Diabetes Mellitus

A. Diabetes is due to an inadequate effect of insulin that can lead to **hyperglycemia, ketonemia,** and **ketoacidosis.**

1. **Type 1 (insulin-dependent) diabetes mellitus** results from the loss of endogenous insulin and is thought to be an autoimmune disorder.
2. **Type 2 (non–insulin-dependent) diabetes mellitus** is probably due to insulin resistance, which is often associated with obesity. The disease begins with hyperinsulinemia and results in hyperglycemia due to inability of the β cells to compensate for the increasing insulin resistance.
3. Several rare forms of diabetes, called **maturity-onset diabetes of the young (MODY),** occur due to specific gene mutations.
4. **Gestational diabetes** is due to increased insulin resistance during pregnancy.

B. TREATMENT of diabetes involves **balancing of caloric intake, exercise, and hypoglycemic medications.**

1. The diet is a major factor in diabetic control, and the caloric intake should be constant and regular.
2. Patients with **type 1** diabetes mellitus must use **insulin.**
3. Patients with **type 2** diabetes mellitus can use either **insulin** or **oral hypoglycemic drugs.** Insulin is preferred for gestational diabetes patients and type 2 diabetes mellitus patients with
   a. Reduced renal function
   b. Reduced hepatic function
   c. Persistent hyperglycemia
4. The efficacy of treatment should be followed by **self-monitoring of blood glucose** by the patient and physician monitoring of glycosylated hemoglobin.
5. Effective treatment should **eliminate the acute symptoms** of diabetes, including the hyperglycemia, polyphagia, polydipsia, polyuria, hypoglycemia, and ketoacidosis.
6. Based on clinical studies, **rigid control** of blood glucose **reduces the chronic complications** of diabetes, including:
   a. **Neuropathy**
   b. **Retinopathy**
   c. **Nephropathy**
   d. Possibly **cardiovascular disease**

C. INSULIN is a **polypeptide** that is ineffective when given orally and is usually administered subcutaneously by injection or infusion pump. It can also be administered intravenously.

1. Insulin
   a. Increases glucose transport into muscle and adipose tissue
   b. Increases glycogen synthesis, decreases glycogenolysis and decreases gluconeogenesis in liver tissue
   c. Decreases lipolysis in adipose tissue and stimulates lipogenesis
2. Several sources are available.
   a. **Animal insulin** (bovine or porcine) is no longer used because of its potential immunogenicity.
   b. **Human insulin** (*Humulin, Novolin*) is produced by recombinant DNA technology.
3. A variety of **insulin analogs** are available with different durations of action. The less soluble insulin preparations have slower onsets and are longer acting.
   a. **Rapid-onset/ultrashort acting**
      i. **Regular insulin (crystalline zinc insulin).**
      ii. **Lispro** (*Humalog*), **aspart** (*Novolog*), and **glulisine** (*Apidra*) insulins are even faster onset and shorter duration than crystalline zinc insulin.

b. **Intermediate acting**
   i. Insulin can be conjugated with proteins or crystallized in various forms which slows the onset and increases the duration of action.
   ii. **NPH** lasts up to 24 hours.
c. **Prolonged acting**
   i. **Detemir** (*Levemir*) is bound to albumin, which prolongs its action.
   ii. **Insulin glargine** precipitates at the injection site to form crystals that slowly dissolve.

4. The side effects of insulin can be very severe.
a. **Hypoglycemia** can occur from excessive doses, inadequate food intake after insulin injection, exercise, or alcohol.
   i. Initial symptoms are due to **sympathetic activation** (e.g., tachycardia). Propranolol will block this sympathetic activation, making it more difficult for diabetics to sense that they are hypoglycemic.
   ii. Severe hypoglycemia can produce **CNS effects,** which can progress to convulsions, loss of conciousness, permanent CNS injury, and death.
   iii. The hypoglycemia can be **reversed by**
      (a) Ingestion of candy, orange juice, or other **sugar** source
      (b) **Glucagon, intramuscularly or subcutaneously**
      (c) **Glucose, intravenously**
b. Formation of **insulin antibodies** can lead to **cutaneous allergic reactions or resistance** to insulin. The risk of antibody formation for the insulin preparations is: bovine > porcine > purified porcine > human.
c. Increases in body weight frequently occur.

D. ORAL ANTIDIABETIC DRUGS are effective in type 2 diabetics who cannot be managed by diet and exercise alone.

1. Insulin secretagogues trigger insulin release from the pancreas; thus, a functional pancreas is required.
a. **The sulfonylureas increase insulin release by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels in the β cells;** they also slightly decrease peripheral resistance to insulin.
   i. **Tolbutamide** (*Orinase*) is short acting (6–12 hours) and is metabolized in the liver by oxidation.
   ii. **Chlorpropamide** (*Diabinese*) is long acting and is partially excreted in the unchanged form by the kidney.
   iii. **Glyburide** (*DiaBeta, Micronase*), and **glipizide** (*Glucotrol*) are second-generation sulfonylureas.
   iv. **Glimeperide** (*Amaryl*) is a third-generation sulfonylurea; its action is somewhat dependent on ambient glucose.
b. **Meglitinide analogs** such as **repaglinide** (*Prandin*) and **nateglinide** (*Starlix*) have the same mechanism of action as sulfonylureas, but a shorter onset of action and shorter duration. The side effects are milder compared to the sulfonylureas.
c. **The side effects** of the insulin secretagogues include hypoglycemia and weight gain.

2. Insulin sensitizers decrease insulin resistance but do not increase insulin secretion.
a. **Metformin** (*Glucophage*) is a biguanide that **enhances the hepatic response** to insulin and **decreases gluconeogenesis in the liver.**
   i. A rare, but serious, complication is lactic acidosis.
   ii. Metformin can also be used to treat polycystic ovary disease.

b. Thiazolidinediones (glitazones) activate peroxisome proliferator–activated receptor-gamma receptors, thereby reducing insulin resistance primarily in muscle and fat tissue.
   i. Currently available glitazones include **rosiglitazone** (*Avandia*) and **pioglitazone** (*Actos*).
   ii. Liver function should be monitored in patients on these drugs due to the potential for hepatotoxicity. Weight gain can also occur.

3. **Acarbose** (*Precose*) and **miglitol** (*Glyset*) are **α-glucosidase inhibitors,** which slow the breakdown of carbohydrates in the gut. Both have gastrointestinal side effects (flatulence, diarrhea).
4. **Dipeptidyl peptidase (DPP)-IV inhibitors** increase the action of **incretins,** which are hormones (glucagonlike peptide-1 [GLP-1] and glucose dependent insulinotropic peptide [GIP]) that cause the body to secrete more insulin and less glucagon in response to meals. Incretins also are thought to suppress appetite and increase gastric emptying time.
   a. Type 2 diabetics are GLP-1 deficient, but they will respond more normally to glucose when given GLP-1. However, GLP-1 is too short lived to use as a drug. **Exenatide** (*Byetta*) is an analog of **GLP-1.**
   b. **Sitagliptin** (*Januvia*) is a **dipeptidyl peptidase-IV (DPP-IV) inhibitor.** Inhibition of DPP-IV prevents breakdown of incretins, thereby increasing their concentration.

E. DIABETIC KETOACIDOSIS OR HYPEROSMOLAR (NONKETOTIC) COMA should be managed with
1. **Fluid and electrolytes, especially potassium**
2. Crystalline zinc insulin, intravenously
3. Correction of acidosis
4. Carbohydrates

IX Drugs for Hypoglycemia

A. GLUCAGON, which is physiologically released from α cells in the pancreas, **increases glycogenolysis and gluconeogenesis.**
1. These actions **increase the blood glucose** concentration in diabetics who are hypoglycemic.
2. The effectiveness will be lost when the **glycogen stores are depleted.**
3. It is a polypeptide that must be given **parenterally.**

B. GLUCOSE can be administered orally or parenterally to treat hypoglycemia in diabetics.

C. DIAZOXIDE (*Proglycem*) is an antihypertensive, when given intravenously.
1. After **oral** administration, diazoxide **reduces insulin release** from the pancreas by stabilizing the ATP-dependent potassium channel in the open position. Thus, it is ineffective for the treatment of insulin-induced hypoglycemia.
2. It is useful to treat the hypoglycemia resulting from an **insulinoma.**

D. SOMATOSTATIN decreases insulin secretion by binding to a G-protein coupled receptor, thereby decreasing intracellular calcium and hyperpolarizing the β cell. Because somatostatin has a short half life, **octreotide** can be used instead.

E. Many hormones can increase the serum glucose concentration, including:
1. Glucocorticoids (cortisol)
2. Growth hormone
3. Epinephrine
4. Estrogens and progestins
5. Thyroid hormone

X Drugs for Obesity

A. Appetite suppressants
1. **Phentermine** (*Adipex-P, Fastin*) is an amphetamine-like stimulant that can be used as an anorectic for a short period of time (up to 3 months).
2. SSRIs and SNRIs such as **sibutramine** (*Meridia*) can be used. Sibutramine should not be used with an antidepressant, and monthly blood pressure and heart rate monitoring is necessary.

B. **ORLISTAT** (*Alli, Xenical*) is a **lipase inhibitor** that **prevents fat breakdown** and **absorption.** Side effects include **GI symptoms** (flatulence, oily stools) and **inhibition of fat-soluble vitamin absorption.**

Chapter 9

Drugs for Bacterial Infections

I Principles of Bacterial Chemotherapy

A. Bacterial chemotherapy involves the administration of drugs that **kill or slow the growth of bacteria without affecting host cells.** This phenomenon is called **selective toxicity.**

B. BACTERICIDAL DRUGS KILL BACTERIA, often by inhibiting cell wall synthesis or DNA gyrases. One exception to this rule is the aminoglycosides, which are bactericidal inhibitors of translation.

1. Bactericidal drugs include:
   a. β-Lactams (cell wall synthesis inhibitors)
      i. Penicillins
      ii. Cephalosporins
      iii. Aztreonam
      iv. Imipenem
   b. Vancomycin (cell wall synthesis inhibitor)
   c. Quinolones (DNA gyrase inhibitors)
   d. Aminoglycosides (translation inhibitors)

2. Bactericidal drugs are necessary for
   a. Patients with severe infections
   b. Patients with severe or debilitating diseases
   c. Patients who are immunocompromised

C. BACTERIOSTATIC DRUGS only **inhibit replication of bacteria,** often by reducing protein synthesis or interfering with folic acid metabolism.

1. The immune system eradicates the infection.

2. Bacteriostatic drugs include:
   a. Tetracyclines (translation inhibitors)
   b. Erythromycin (translation inhibitors)
   c. Chloramphenicol (translation inhibitors)
   d. Clindamycin (translation inhibitors)
   e. Sulfonamides (folic acid synthesis inhibitors)
   f. Trimethoprim (folic acid synthesis inhibitor)

D. SINGLE DRUGS ARE PREFERRED to treat infectious diseases, unless a drug combination is the accepted mode of therapy (usually to reduce the development of resistance or to reduce the amount of potentially toxic agents that would be needed if given singly). Inappropriate drug combinations can

1. Increase the incidence of side effects

2. Result in antagonism between drugs

3. Increase the risk of superinfections

E. BACTERIAL RESISTANCE TO DRUGS can be

1. **Natural.** No target site in the bacteria—for example, all mycoplasma are naturally resistant to cell wall inhibitors like the penicillins because mycoplasma do not have cell walls.
2. **Acquired**
   a. Resistance acquired by **mutation** is unusual, although it is common with tuberculosis (TB) because there is a large population of bacteria. (See Section XIII "Drugs for Mycobacterial Infections.")
   b. Resistance acquired from **R-factors** on plasmids is a common, **very rapid** method of acquiring resistance that often involves resistance to many antibiotics.
3. **Methods of resistance**
   a. **Altered targets** (e.g., the bacterium develops modified penicillin binding proteins that won't bind to beta-lactams)
   b. **Decreased accumulation** can occur in one of two ways:
      i. **Decreased permeability** (e.g., porins in the outer membrane of Gram-negative bacteria are closed or lost, preventing β-lactams from entering the cell)
      ii. **Increased efflux** (e.g., multidrug efflux pumps actively pump β-lactams out of the cell)
   c. **Enzymatic inactivation** (e.g., the bacterium produces β-lactamase enzymes, which can cleave the β-lactam ring and inactivate the drug)

F. Changes in the natural bacterial flora in the gastrointestinal (GI) tract that are induced by antibiotics frequently lead to symptoms of GI irritation, such as nausea, vomiting, and diarrhea.

G. SUPERINFECTIONS due to an **overgrowth of insensitive environmental microbes,** such as *Pseudomonas*, *Clostridium*, and *Candida*, are most prevalent:

1. With broad-spectrum antibiotics
2. With long-term therapy
3. In patients with severe illnesses

H. DOSING ANTIBIOTICS. For sensitive organisms, antibiotics have a minimum inhibitory concentration (MIC) at which they are able to kill the bacteria or inhibit their growth.

1. **Concentration-dependent.** Antibiotic action is more effective as the concentration is raised higher above the MIC.
   a. Examples include quinolones, aminoglycosides
   b. Should be administered by an infusion once a day to obtain high peak levels that exceed the MIC
2. **Concentration-independent.** Raising the antibiotic concentration higher above the MIC does not increase the antibiotic's activity.
   a. Examples include β-lactams, glycopeptides, macrolides, and clindamycin
   b. Should be administered continuously or frequently throughout the day to maximize the time that antibiotic concentrations are at or above the MIC

I. The properties of the antibacterial drugs are summarized in Table 9-1.

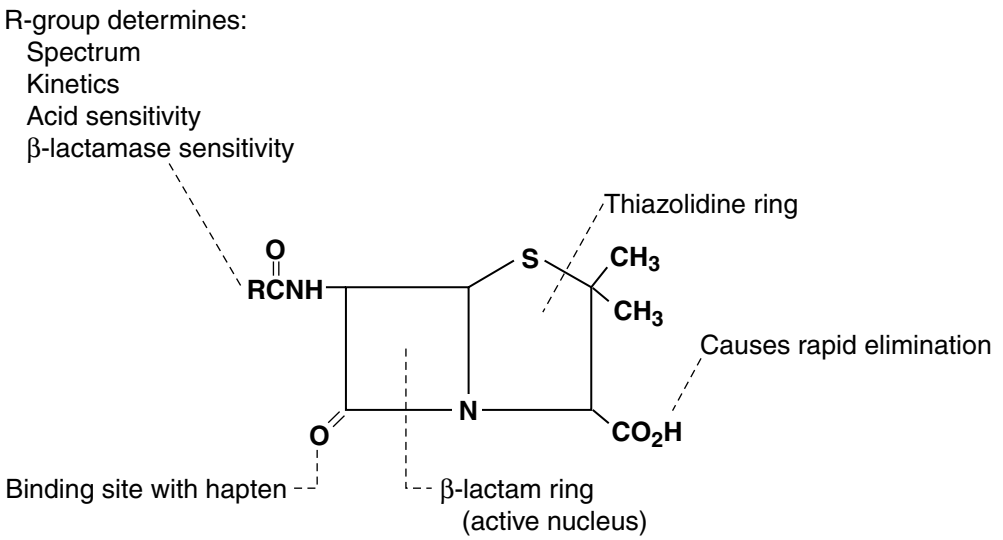
II Cell Wall Inhibitors: Penicillins

A. THE ACTIVE NUCLEUS of the penicillin molecule is a 4-membered ring, called the **β–lactam ring** (Figure 9-1).

TABLE 9-1 OVERVIEW OF ANTIBACTERIAL DRUGS*

Class	Site of Action[1]	Activity[2]	Administration[3]	Clearance[4]	Distribution to CSF[5]	Toxicity[6]	Spectrum[7]	Acquired Resistance[8]
Penicillin G	W	C	O,P	K	s	H,G	+,N	E,A,R
Penicillins, extended	W	C	O,P	K	s	H,G,N	+,~	E,A,R
Cephalosporins, 1st	W	C	o,P	K	s	H	+,~,N	E,A,R
Cephalosporins, 3rd	W	C	o,P	K	G	H,S	+,–,N	E,A,R
Aztreonam	W	C	P	K	s	G	–	E
Imipenem/Cilastatin	W	C	P	K	i	G,H,C	+,–,N	R
Aminoglycosides	30S	C	P	K	i	O,K	–	E,R
Tetracyclines	30S	S	O,p	K,L	s	B,P,S	+,–,N	R
Erythromycin	50S	S	O,p	L	i	G,L	+,N	A,R
Chloramphenicol	50S	S	O,P	L	G	A	+,–,N	E
Clindamycin	50S	S	O,P	L	i	G,S	+,N	A,R
Vancomycin	W	C	P	K	s	N,O,K	+	A
Quinolones	G	C	O,P	K,L	G	G,E	+,–	A,R
Sulfonamides	FA	S	O	L,K	G	A,H,U	+,–,N	A,R
Trimethoprim	FA	S	O	K	G	A	+,–,N	A
Metronidazole	D	C	O,P	L	G	D	N	

*There are many exceptions to the general properties listed in this table.
[1]Site of Action: W = cell wall; 30S = ribosome; 50S = ribosome; G = gyrase; FA = folic acid metabolism; D = DNA.
[2]Activity: C = bactericidal; S = bacteriostatic.
[3]Administration: O = oral; o = occasionally oral; P = parenteral; p = occasionally parenteral.
[4]Clearance: K = kidney; L = liver
[5]Distribution to CSF: G = good; s = some; i = inadequate
[6]Toxicity: A = anemias; B = binds calcium; C = convulsions; D = disulfiram-like; E = erosion of cartilage; G = gastrointestinal; H = hypersensitivity; K = kidney toxicity; L = liver toxicity; N = nonallergic rash; O = ototoxic; P = photosensitivity; S = superinfection; U = crystalluria.
[7]Spectrum: +, Gram(+); –, Gram(–); ~, some Gram(–); N = anaerobes.
[8]Acquired resistance: A = active site change; E = enzymatic break-down; R = reduced accumulation.



● **Figure 9-1** General structure of the penicillins.

B. PENICILLIN BINDS TO PENICILLIN BINDING PROTEINS and induces many effects that inhibit cell wall synthesis (e.g., **inhibition of transpeptidases**).

1. **Cross-linking of the bacterial cell wall is reduced.**
2. The cell wall is weakened and the bacteria rupture due to the high internal osmotic pressure; thus, the penicillins are **bactericidal.**
3. **Autolytic enzymes are activated.**

C. THE PHARMACOKINETIC PROPERTIES of penicillin G affect how it is used.

1. It is relatively **unstable in acid;** thus, the bioavailability is low. It can be administered orally; however, serum penicillin concentrations are variable after this route of administration.
2. There is **poor penetration into the cerebrospinal fluid (CSF),** unless inflammation is present.
3. **Active renal tubular secretion** results in a short half-life. Probenecid, which blocks active secretion, will reduce the renal clearance of penicillin G.
4. Depot preparations (penicillin G procaine or penicillin G benzathine intramuscularly) have long durations of action due to slow absorption from the site of injection.

D. Although the penicillins are very safe antibiotics, they have some important **adverse effects.**

1. **Hypersensitivity** reactions can develop.
   a. **Immediate hypersensitivity** reactions, characterized by **anaphylaxis,** occur within 20 minutes.
      i. Penicillin interacts with proteins to form **minor determinants** that act as haptens for inducing the immediate hypersensitivity reaction.
      ii. The reaction is mediated by **IgE antibodies.**
      iii. **Anaphylactic reactions** should be treated with **epinephrine.**
   b. **Accelerated** (occurring within 1 day) and **delayed** (occurring within 1 week) reactions are less severe, often leading to skin rashes.
      i. Penicilloic acid, which is a product of the breakdown of penicillins, interacts with proteins to form **major determinants,** which act as haptens for inducing the reactions.
      ii. These reactions are mediated by **IgG or IgM antibodies.**

c. Patients may display hypersensitivity to the first dose. This hypersensitivity is probably due to the environmental levels (e.g., in food) of penicillins.
d. **Cross-sensitivity between the penicillins** is very high.
e. **Skin tests** are available to check for hypersensitivity.
i. **Penicillin G** is useful but somewhat unreliable.
ii. **Penicilloyl-polylysine** is a major determinant.
iii. Minor determinants are not widely available.

2. **Superinfections** can develop, especially with the broad-spectrum penicillins such as ampicillin.
3. **Sodium loading** from the penicillins is most common with carbenicillin and ticarcillin, which are disodium salts.
4. **Convulsions,** caused by γ-aminobutyric acid (GABA) receptor blockade, can be induced at high dosages of penicillins.
5. **Nonallergic skin rashes** can occur with ampicillin, especially in patients with infectious mononucleosis.
6. **Nephritis** can occur, especially with patients given methicillin.

E. THE SPECTRUM of penicillin G includes:
1. **Gram-positive bacteria**
2. **Gram-negative cocci,** but not most other Gram-negative bacteria
3. Some anaerobes

F. Penicillin G is especially effective for treating infectious diseases due to
1. *Neisseria meningitidis*
2. Streptococci, including pneumococci (although there is now significant resistance), β-hemolytic streptococci, and some viridans streptococci
3. *Clostridium perfringens*
4. *Fusobacterium*
5. *Treponema pallidum* (syphilis)

G. Acquired **resistance** to penicillin G is usually due to **penicillinases** or **β-lactamases,** which split the active part of the molecule, the β lactam ring.

H. AMIDASES are used to alter the side chain of penicillin G (Table 9-2), resulting in groups of:
1. **Natural penicillins.** Penicillin V is more effective after oral administration than penicillin G.
2. **Penicillinase-resistant penicillins.** These penicillins are useful for the treatment of infections involving penicillinase-producing bacteria, such as *Staphylococcus aureus* or *S. epidermidis*.
3. **Extended-spectrum penicillins.** These penicillins have more Gram-negative activity than penicillin G.
a. Ampicillin or amoxicillin are useful for infectious diseases due to:
i. *Enterococcus faecalis*
ii. *Proteus mirabilis*
iii. *Listeria monocytogenes*
b. The antipseudomonal penicillins have higher activity versus *Pseudomonas aeruginosa*.
c. All extended-spectrum penicillins are penicillinase sensitive.
i. Either **clavulanic acid, tazobactam,** or **sulbactam,** which are **β-lactamase inhibitors,** can be combined with the extended-spectrum penicillins.
ii. Resistant organisms will be more sensitive to this combination.

TABLE 9-2 PROPERTIES OF THE PENICILLINS

	Effectiveness When Taken Orally	Resistance to Penicillinases	Spectrum
Natural Penicillins			
Penicillin G	Variable	None	Narrow
Penicillin V (*Pen-Vee, V-Cillin*)	Good	None	Narrow
Penicillinase-Resistant Penicillins			
Methicillin (*Staphcillin*) (side effect: nephritis)	Poor	Yes	Narrow
Cloxacillin (*Tegopen, Cloxapen*)	Good	Yes	Narrow
Nafcillin (*Unipen*)	Variable	Yes	Narrow
Dicloxacillin (*Dynapen*)	Good	Yes	Narrow
Extended-Spectrum Penicillins			
Ampicillin (*Omnipen*) (side effect: nonallergic rash)	Good	None	Extended
Amoxicillin *(Amoxil, Larotid)*	Better	None	Extended
Extended-Spectrum Antipseudomonal Penicillins (can be combined with) β-lactamase inhibitors)			
Carbenicillin (*Geocillin*)	Poor	None	Extended
Ticarcillin (*Ticar*)	Poor	None	Extended
Piperacillin (*Pipracil*)	Poor	None	Extended

iii. These β-lactamase inhibitors contain a β-lactam ring, but they are not bactericidal themselves. Instead, they bind to and inactivate β-lactamase enzymes so that the coadministered β-lactam antibiotic will remain active (i.e., not be cleaved).

III Cell Wall Inhibitors: Cephalosporins

A. The structures and pharmacological properties of the cephalosporins (Figure 9-2) are similar to the penicillins. Cephalosporins have a β-lactam ring attached to a dihydrothiazine ring.

1. Inhibition of transpeptidases leads to the inhibition of cell wall synthesis, resulting in a **bactericidal** effect.

2. Most cephalosporins are eliminated by active tubular secretion in the kidneys.

3. Penetration into the CSF is poor for most cephalosporins unless inflammation is present.

4. The side effects are also similar to those from the penicillins, including:

a. **Hypersensitivity**

i. There is **some cross-hypersensitivity with the penicillins.**

ii. In patients with a history of a mild accelerated or delayed reaction to penicillin, cephalosporins may be considered.

iii. In patients with a history of an immediate reaction to penicillin, cephalosporins should be avoided.

b. **Superinfections,** especially with the broader spectrum cephalosporins

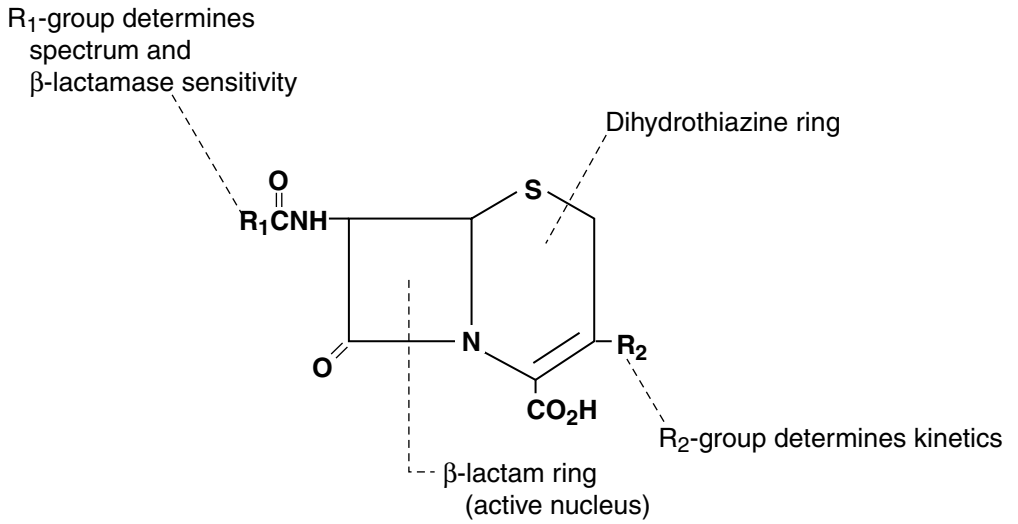
c. **Nephrotoxicity**

B. The cephalosporins also have important **differences from the penicillins.**

1. The antibacterial **spectrum is broader.**

2. They are **more resistant to β-lactamases.**

3. Most are ineffective when taken orally due to breakdown by acid in the stomach.



● **Figure 9-2** General structure of the cephalosporins.

C. Four generations of cephalosporins are available. In general, the cephalosporins progress from being narrower spectrum and more active against Gram-positive organisms in the first-generation class to becoming broader spectrum and more active against Gram-negative organisms in the later-generation classes.

1. **First-generation** cephalosporins include cefazolin (*Ancef, Kefzol*) and oral cephalexin (*Keflex*), which is the prototype of this class.
   a. These have **narrow spectrums for cephalosporins,** but the spectrums are similar to ampicillin.
   b. They have some resistance to β-lactamases.
   c. They are the **most active** cephalosporins **for Gram-positive bacterial infections.**
2. **Second-generation** cephalosporins include cefoxitin (*Mefoxin*), oral cefuroxime (*Zinacef*), which is the prototype of this class, and oral cefaclor (*Ceclor*).
   a. They have broader spectrums and are more resistant to β-lactamases.
   b. An important use of first- and second-generation cephalosporins is **prophylaxis during surgery** if an infection is likely to occur.
3. **Third-generation** cephalosporins as a group have
   a. The **broadest spectrums**
   b. The **highest activities against Gram-negative bacteria**
   c. The **lowest activities against Gram-positive bacteria**
   d. The **highest resistance to β-lactamases**
   e. The **highest lipid solubilities**
   f. The **best penetration into the CSF**
   g. The most clinical usefulness, including treatment of infectious diseases due to:
      i. *Neisseria gonorrhoeae*
      ii. *Escherichia coli*
      iii. *Haemophilus ducreyi*
      iv. *H. influenzae,* if severe
      v. *Klebsiella pneumoniae*
      vi. *Proteus* (indole positive species)
      vii. *Salmonella*
   h. There are also some unique properties of **individual third-generation cephalosporins.**
      i. **Ceftriaxone** (*Rocephin*) has the **longest half-life** (8 hours) of any cephalosporin.
      ii. **Cefixime** (*Suprax*) is an **oral** preparation.

iii. **Ceftazidime** (*Fortaz*) is a good **antipseudomonal** cephalosporin.
iv. **Cefoperazone** (*Cefobid*) is eliminated **(70%) in the bile** and is thus very useful in patients with renal failure.

4. Cefepime (*Maxipime*) is a fourth-generation cephalosporin.

IV Cell Wall Inhibitors: Other β-Lactams

A. AZTREONAM (*Azactam*) is a **monobactam.**

1. It decreases cell wall formation and thus is **bactericidal.**
2. **Only aerobic Gram-negative bacteria,** especially *Pseudomonas,* are affected. There is no activity against Gram-positive bacteria or anaerobes.
3. It is resistant to most β-lactamases.
4. Kinetics are similar to the penicillins, although it must be **administered parenterally.**
5. There is **no cross-allergenicity with penicillins.**

B. CARBAPENEMS

1. **Imipenem with cilastatin** (*Primaxin*) inhibits cell wall transpeptidation.
   a. This results in **bactericidal** activity against most bacteria; thus, imipenem has a **very broad spectrum.**
   b. It is resistant to most β-lactamases.
   c. It **distributes to most tissues** in the body except CSF, unless the meninges are inflamed.
   d. Imipenem is **nephrotoxic.**
      i. Metabolism of imipenem in the kidneys by **dehydropeptidases** leads to an inactive product that is nephrotoxic.
      ii. **Cilastatin inhibits the dehydropeptidases** and eliminates nephrotoxicity; thus, it is always administered in combination with imipenem.
   e. It is especially useful for treating infectious diseases due to:
      i. Many of the resistant *Enterobacteriaceae* such as *Serratia, Klebsiella,* and *Escherichia coli*
      ii. *Pseudomonas aeruginosa*
      iii. *Acinetobacter.*
      iv. *Campylobacter fetus*
2. **Meropenem** (*Merrem*) is another carbapenem that does not get metabolized by the kidneys and thus does not require coadministration with cilastatin.
3. **Ertapenem** (*Invanz*) has no activity against *P. aeruginosa*, but it is active against many other Gram-negative organisms. It can be used in outpatients.

V Cell Wall Inhibitors: Non β-Lactams

A. VANCOMYCIN

1. **Binding of vancomycin** (*Vancocin*) **to D-Ala D-Ala dipeptides in the cell wall inhibits cell wall synthesis** by preventing cross-linking of peptidoglycan precursors. This drug is therefore **bactericidal.**
2. Because it is poorly absorbed by the oral route, vancomycin is given **intravenously** except when being used to treat enteric infections.
3. It is cleared by renal **glomerular filtration** without being metabolized**.**
4. The high activity of vancomycin against **Gram-positive microorganisms** makes it useful as the last alternative to treat **methicillin-resistant** *Staphylococcus aureus* or *epidermidis* and penicillin-resistant *S. pneumoniae*, as well as in people who are allergic to β-lactams.

5. Vancomycin is **synergistic with aminoglycosides.**
6. **Side effects** include:
   a. **Dose-dependent ototoxicity,** especially when it is coadministered with aminoglycosides
   b. **Nephrotoxicity**
   c. **Erythema** ("red man syndrome") due to histamine release, especially after rapid infusion

B. Another glycopeptide that blocks cell wall synthesis is **teicoplanin** (*Targocid*), which has a similar spectrum of activity to vancomycin.

C. BACITRACIN (*Baciguent*) inhibits cell wall synthesis by **decreasing precursor transport** to the cell wall.
1. It is a polypeptide mixture active against both Gram-positive and Gram-negative organisms.
2. Bacitracin must be applied topically due to its nephrotoxicity.

VI Protein Synthesis (30S Ribosome) Inhibitors: Aminoglycosides and Spectinomycin

A. The **aminoglycosides** include **gentamicin** (*Garamycin*), **tobramycin** (*Nebcin*), **amikacin** (*Amikin*), **neomycin** (*Mycifradin*), **kanamycin** (*Kantrex*), **netilmicin** (*Netromycin*), and **streptomycin.**
1. **Inhibition of protein synthesis** occurs as a result of **irreversible** aminoglycoside binding to the **30S ribosomal subunit.**
   a. Formation of the translation initiation complex is inhibited.
   b. Misreading of the mRNA template occurs.
2. Although aminoglycosides act as protein synthesis inhibitors, they are **bactericidal.** This may be due to the irreversible binding at the site of action.
3. The **selective toxicity** may relate to the fact that **humans do not have 30S ribosomal subunits.**
   a. Mammals have 80S ribosomes composed of 60S and 40S subunits.
   b. Bacteria have 70S ribosomes composed of 50S and 30S subunits.
4. Aminoglycosides are **only active against Gram-negative aerobes** because the drugs must be accumulated in the bacteria by oxygen-dependent active transport. The activity is maintained even after the plasma drug concentration falls. This is called a **post-antibiotic effect.**
5. **The pharmacokinetics** is typical for large, polar molecules.
   a. **Parenteral administration** is necessary.
   b. Distribution is limited to the extracellular fluid.
   c. They **do not reach the CSF.**
   d. **Elimination** occurs via **glomerular filtration;** thus, the creatinine clearance is used to determine the maintenance dose.
6. **Resistance** is mediated by **R-factors** transmitted by conjugation and can occur via several mechanisms.
   a. **An altered 30S ribosome** with **decreased affinity** for the drug.
   b. Membrane uptake of the aminoglycosides can be reduced due to loss of active uptake system or porins.
   c. Bacterial **enzymes** can inactivate the aminoglycosides, e.g., by **acetylation.**
   d. Amikacin induces a much lower incidence of microbial resistance than the other aminoglycosides, and netilmicin is less susceptible to bacterial enzymes.

7. The aminoglycosides are **very toxic** in a **dose-dependent fashion;** thus, it is important to **monitor the serum concentrations** of these drugs.
   a. **Ototoxicity** can lead to
      i. **Loss of equilibrium**
      ii. **Loss of hearing**
   b. **Nephrotoxicity** can occur.
   c. **Neuromuscular blockade** can reduce respiratory function, especially after surgery.
8. The aminoglycosides are very useful for several indications:
   a. *Enterococcus faecalis*, in combination with a β-lactam or vancomycin
   b. *Pseudomonas aeruginosa* in combination with other agents
   c. *Mycobacterium tuberculosis* (streptomycin)
   d. Preoperative suppression of normal intestinal flora (neomycin)
9. An aminoglycoside coadministered with a β-lactam or vancomycin is a synergistic combination that provides broad (empiric) antibiotic treatment.

B. SPECTINOMYCIN (*Trobicin*) also **inhibits protein synthesis** by binding the **30S** ribosomal subunit.
1. It is only **bacteriostatic.**
2. The only important indication is as an alternate treatment for **gonorrhea.**

VII Protein Synthesis (30S Ribosome) Inhibitors: Tetracyclines

A. This class of antibiotics includes **tetracycline** (*Achromycin, Panmycin*), **doxycycline** (*Vibramycin*), and **tigecycline** (*Tygacil*), which are **bacteriostatic inhibitors of protein synthesis.**
1. Reversible binding to the **30S ribosomal subunit** inhibits the mRNA acceptor (A) site.
2. Binding of tRNA to the mRNA–ribosomal complex is blocked.

B. SELECTIVE TOXICITY occurs because the tetracyclines are **actively accumulated by bacteria** but not actively accumulated by host cells. However, tetracyclines are toxic to mitochondrial ribosomes in high concentrations.

C. RESISTANCE is mediated by **R-factors** that **reduce the active drug accumulation via active efflux (TetA).**

D. THE PHARMACOKINETICS varies depending on the specific drug.
1. All tetracyclines can be administered orally.
   a. Tetracycline, in particular, **chelates metal ions and is inactivated by calcium (milk), magnesium, aluminum (antacids), and iron;** it should be taken when the stomach is empty.
   b. Doxycycline is a less avid chelator and can be taken with a meal.
2. Some tetracyclines are cleared by metabolism in the liver and some are cleared by glomerular filtration in the kidneys.
3. **Doxycycline,** uniquely, is cleared as a **chelate in the feces.** Elimination is not dependent on either liver or kidney function, which allows doxycycline to be administered to patients in renal failure.

E. THE SPECTRUM IS VERY BROAD.
1. Tetracyclines are especially useful for infectious diseases involving *Chlamydia, Rickettsia*, *Mycoplasma pneumoniae*, and *Borrelia burgdorferi*.
2. Tigecycline has a very broad spectrum but has no activity against *P. aeruginosa.*

F. These antibiotics have few **side effects.**

1. **Do not administer tetracyclines to children or pregnant women** because of chelation of calcium.
   a. Can **discolor developing teeth**
   b. Can **reduce growth** in developing bone
   c. Can **cross the placenta** and harm the fetus
2. **Photosensitivity** can occur.
3. Hepatotoxicity and nephrotoxicity have been reported.
4. Because tetracyclines have broad spectrums, **superinfections** from *Clostridium* and *Candida* can develop secondary to their use.

VIII Protein Synthesis (50S Ribosome) Inhibitors: Macrolides

A. ERYTHROMYCIN is a **bacteriostatic** inhibitor of protein synthesis, although it can be bacteriocidal at high concentrations. Reversible binding to the **50S** ribosomal subunit of Gram-positive microorganisms inhibits translocation of the peptidyl molecule from the A-site to the P-site on the mRNA.

1. It is effective when taken orally and is **eliminated in the bile** in its unaltered form.
2. **Reduction of mixed function oxidase (MFO) activity** enhances the effects of many drugs metabolized by MFOs (e.g., theophylline).
3. The spectrum includes **Gram-positive and intracellular bacteria.**
   a. Erythromycin (*Ilosone, Erythrocin*) is especially useful for infectious diseases involving
      i. *Chlamydia*
      ii. *Mycoplasma pneumoniae*
      iii. *Legionella pneumophila*
   b. It is also a useful alternative to the penicillins for Gram-positive infections in people allergic to penicillins.
4. **Cholestatic hepatitis** and GI side effects can occur.
5. **Resistance** to erythromycin can be due to **decreased accumulation, decreased affinity of the 50S ribosomal subunit** for the drug due to **methylation of its 23S** component, or the action of **antimacrolide esterases.**

B. New macrolides are very useful.

1. **Clarithromycin** (*Biaxin*) is **more stable in acid** than erythromycin.
2. **Azithromycin** (*Zithromax*) has a **long half-life** (3 days).
3. **Telithromycin** (*Ketek*) is a ketolide that is sometimes active against organisms resistant to other macrolides. Like erythromycin, telithromycin inhibits the cytochrome P450 system.

IX Other Protein Synthesis (50S Ribosome) Inhibitors

A. CHLORAMPHENICOL

1. **Bacteriostatic inhibition of protein synthesis** results from reversible binding of chloramphenicol (*Chloromycetin*) to peptidyl transferase. As a result, protein elongation is reduced.
2. It is effective when **given orally, penetrates membranes very well,** and **readily reaches the CSF.**
3. **Metabolism** by glucuronyl transferase **(glucuronide conjugation)** occurs in the liver.

4. **Toxicity** is a major limitation with chloramphenicol.
   a. **Gray baby syndrome** can be induced when chloramphenicol is administered to newborns. **Slow metabolism,** which is due to a lack of glucuronyl transferase, results in toxic blood concentrations of chloramphenicol when standard doses are administered.
   b. **Anemias** can be induced.
      i. **Dose-dependent bone marrow depressio**n results from inhibition of mitochondrial 70S ribosomes.
      ii. An infrequent, **irreversible aplastic anemia** that is **not dose related** and is **frequently fatal** has limited the usefulness of chloramphenicol to seriously ill patients who cannot be treated with safer drugs.
5. The **spectrum** of activity is **very broad, including anaerobes,** but it is only used as an alternative drug to treat infections, such as *Salmonella typhi* and *Haemophilus influenzae*. It is bactericidal for *H. influenzae*.
6. **Resistance** occurs due to **R-factors** that code for the enzyme, **chloramphenicol acetyltransferase,** which acetylates and inactivates the drug.

B. CLINDAMYCIN

1. **Bacteriostatic inhibition of protein synthesis** results from binding of clindamycin (*Cleocin*) to the **50S** ribosomal subunit.
2. Clindamycin is effective when given **orally** and is useful to treat **anaerobic infections.**
3. The incidence of **pseudomembranous colitis** (a superinfection from *Clostridium difficile*) is high, and this limits the usefulness of clindamycin. This superinfection should be **treated with metronidazole** or vancomycin, given orally.

C. STREPTOGRANINS

1. **Quinupristin/dalfopristin** (*Synecid*) is a drug combination that **inhibits protein synthesis** by acting at the **50S** ribosomal subunit.
2. It has bactericidal activity and a postantibiotic effect, and it can be **used to treat vancomycin-resistant infections.**
3. **Resistance** is often due to **enzymes** that methylate the 23S ribosome or acetylate the drug, but can also be due to **efflux pumps.**
4. Both drugs inhibit the cytochrome P450 system and can cause toxicity due to decreased metabolism of other drugs.

D. LINEZOLID (*Zyvox*) is a synthetic oxazolidinone that is **bacteriostatic** in most cases.

1. It binds the 50S ribosomal subunit near the interface with the 30S subunit, **preventing formation of the 70S ribosome complex.**
2. **Linezolid** is active against **Gram-positive** organisms, including **vancomycin-resistant organisms.**
3. **Side effects** include **GI upset, thrombocytopenia, and possible monoamine oxidase inhibition.**
4. **Resistance** is due to **modification of the 50S ribosome.** There is **no cross-resistance** with **other protein synthesis inhibitors.**

X DNA Gyrase Inhibitors: Quinolones

A. NORFLOXACIN (*Noroxin*) AND CIPROFLOXACIN (*Cipro*) inhibit bacterial **DNA gyrases (topoisomerases II and IV),** which results in a **bactericidal** effect. They are structurally similar to **nalidixic acid** (*NegGram*), a urinary tract antiseptic and first-generation fluoroquinolone.

1. **First-generation quinolones (nalidixic acid)** are active against **Gram-negative** organisms and used to treat **urinary tract infections.** They are not commonly used.
2. **Second-generation quinolones (ciprofloxacin, levofloxacin** [*Levaquin*], **norfloxacin)** are active against **Gram-negative** organisms, **Gram-positive cocci,** and some others.
3. **Third-generation quinolones** like **sparfloxacin** and **gatifloxacin** have an even broader spectrum.
4. **Fourth-generation quinolone trovofloxacin** has activity against **anaerobes and Gram-negative** and **Gram-positive** organisms. These newer fluoroquinolones are not used as first-line drugs, and many have been removed from the U.S. market due to their toxicity.

B. **RESISTANCE** develops due to a mutational **change in the gyrases, or by decreased accumulation** due to **loss of porins** or **increased efflux.**

C. **THE SPECTRUM** is **very broad,** although most quinolones have **no effect on anaerobes.** Ciprofloxacin is very useful for treatment of
1. Infections due to *Shigella* and other enteric pathogens
2. Urinary tract infections and pseudomonal infections in cystic fibrosis patients due to *Pseudomonas aeruginosa*
3. **Prophylaxis and treatment of anthrax** due to *Bacillus anthracis*

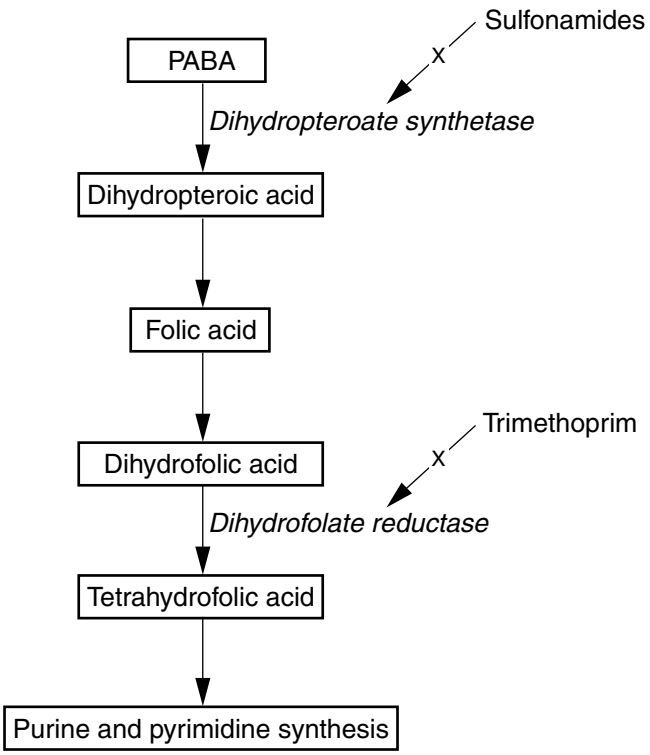
D. Both oral and intravenous administration is effective, and the drugs distribute widely in the body. As with tetracyclines, fluoroquinolones should not be taken with milk, antacids, or iron supplements.

E. **ELIMINATION** is primarily due to **renal secretion** of the active drug.

F. **EROSION OF CARTILAGE** by the quinolones can lead to **tendinitis** and **tendon rupture.** They can also cause **GI upset, CNS problems,** and **phototoxicity. Trovofloxacin** can cause **liver toxicity.**

XI Tetrahydrofolic Acid Synthesis Inhibitors

A. The **sulfonamides** (e.g., sulfisoxazole [*Gantrisin*], sulfamethoxazole) are **analogs of para-aminobenzoic acid (PABA)** that compete with PABA in the synthesis of folic acid (Figure 9-3).
1. **The decrease in tetrahydrofolic acid** inhibits DNA synthesis, primarily by decreasing thymidylate synthesis.
2. **Selective toxicity** occurs because
   a. **Bacteria have no active transport for folate and must synthesize it.** This synthesis is blocked by the sulfonamides.
   b. **Humans cannot synthesize folate.** They must obtain it from the diet and it is actively transported into the host cells. Inhibition of folate synthesis has no host effects.
3. These drugs are usually **bacteriostatic,** although with the selective absence of thymine, they can be bactericidal.
4. **The spectrum is very broad,** and they are **distributed to all body fluids** including CSF.
5. The major limitation of the sulfonamides is **R-factor–mediated resistance,** which is very common. Resistance may be due to **altered dihydropteroate synthetase, decreased cellular permeability,** or **increased production of PABA.**



● **Figure 9-3** Synthesis of folic acid. The sites of sulfonamide and trimethoprim actions are indicated. *PABA* = para-aminobenzoic acid

6. **Side effects** can usually be avoided.
   a. **Displacement of bilirubin** from plasma albumin–binding sites can induce **kernicterus** in the newborn.
   b. Sulfonamides are eliminated by the kidneys. Due to their poor solubility, some of the older sulfonamides can **crystallize in the urine,** as can their acetylated metabolites**.**
   c. **Hypersensitivity reactions** (e.g., Stevens–Johnson syndrome) do occur, particularly with long-acting sulfonamides, which are now rarely used.
   d. **Hemolytic anemia** can be induced in G6PD-deficient patients.
7. The important **indications** for use of the sulfonamides are
   a. **Urinary tract infections** that are acute and uncomplicated
   b. **Recurrent otitis media**

B. TRIMETHOPRIM (*Proloprim, Trimpex*) is a **competitive inhibitor of dihydrofolate reductase.** This enzyme synthesizes tetrahydrofolate, the active form of folic acid.

1. This inhibitory action leads to effects on folic acid synthesis that are similar to the sulfonamides, although the onset is more rapid.
2. **Selective toxicity** occurs because the **bacterial reductase is 20,000 times as sensitive** as the human reductase.
3. **Resistance** is often due to **alteration of the dihydrofolate reductase enzyme.**

C. TRIMETHOPRIM AND THE SULFONAMIDES are usually combined. **Cotrimoxazole** (*Bactrim, Septra, Septrin*), a combination of **sulfamethoxazole** and **trimethoprim,** is often used because these two drugs have similar half-lives.

1. A **synergistic** effect occurs with the combination because two different steps in folic acid synthesis are inhibited.
2. This is a very useful combination for treating:
   a. **Recurring urinary tract infections**
   b. **Chronic prostatitis**
   c. **Nocardiosis**
   d. *Pneumocystis carinii (now called P. jirovecii)* infections in HIV-positive patients
   e. **Upper respiratory tract infections from** *Haemophilus influenzae*
3. The combination can induce a **folate deficiency in the host,** leading to an **anemia** that is treatable with folinic acid. Folinic acid cannot enter bacterial cells.
4. Resistance is decreased with use of sulfonamide–trimethoprim combinations because the organisms would have to develop resistance to both drugs.

XII Miscellaneous Antimicrobials

A. URINARY TRACT ANTISEPTICS ARE RAPIDLY ELIMINATED IN THE ACTIVE FORM BY THE KIDNEYS; thus, drug concentrations in the urine are very high. This makes them useful for treating urinary tract infections.

1. **Nitrofurantoin** (*Macrodantin*) damages DNA and has a **broad antimicrobial spectrum.** It is bacteriostatic.
2. **Methenamine** (*Mandelamine*) is broken down by the **low pH** of urine to **formaldehyde,** which is bactericidal, especially against **Gram-negative bacteria.** No resistance develops against formaldehyde. Methenamine should not be used with sulfonamides.

B. POLYMIXIN B AND COLISTIN (*Coly-Mycin*) **increase membrane permeability,** leading to the loss of essential intracellular substances.

C. DAPTOMYCIN (*Cubicin*) is a glycopeptide that binds to the bacterial membrane, depolarizes it, and thus causes inhibition of DNA, RNA, and protein synthesis.

XIII Drugs for Mycobacterial Infections

A. TUBERCULOSIS DRUG COMBINATIONS, often initially with four drugs, are always used in the long-term treatment (9–12 months) of TB to **avoid development of antibiotic resistance.** Due to rapid development of resistance, single-drug therapy is only useful for prophylaxis.

1. **Isoniazid** (*Nydrazid*) decreases the **synthesis of mycolic acid,** which is a long-chain fatty acid cell wall component in the *Mycobacterium*. **Isoniazid** is a synthetic derivative of **pyroxidine (vitamin B_6).**
   a. It is **bactericidal** in rapidly dividing cells; however, resistance develops rapidly by mutation due to the large population of bacteria in an active infection. Mutation leads to **enzyme modification or overexpression.**
   b. **Oral** administration of isoniazid is effective, and the drug **is distributed to all body fluids** and sites of infection, including tubercles in the lungs.
   c. Isoniazid is **acetylated** in the liver. The rate of acetylation varies in a **bimodal distribution** due to **genetic polymorphisms.**
      i. **Fast acetylators will have lower blood concentrations.** This is the dominant trait.
      ii. **Slow acetylators are more likely to develop toxicity.**

d. **Side effects** from isoniazid are rare, are usually dose dependent, and include:
   i. **Hepatitis,** which increases in incidence with **age** and **use of alcohol.**
   ii. **Peripheral neuritis** due to increased pyridoxine excretion. This can be avoided by giving **pyridoxine.**

2. **Rifampin** (*Rifadin*, *Rimactane*) inhibits the β-subunit of DNA-dependent RNA **polymerase,** which selectively reduces RNA synthesis in the bacteria.
   a. Rifampin is also **bactericidal** for *Mycobacterium* and has **good penetration** into tissues and tuberculous lesions.
   b. It is also used **prophylactically** for patients exposed to:
      i. *Neisseria meningitidis*
      ii. *Haemophilus influenzae,* type b
   c. **Metabolism** occurs in the liver; **rifampin activates MFOs.**
      i. **Rifampin self-induces its own metabolism.**
      ii. It also enhances the metabolism of several other drugs. **Rifabutin** can be substituted for rifampin to avoid this problem.
   d. **Side effects** include:
      i. **Hepatotoxicity**
      ii. **Orange coloring of tears, sweat, and urine**
      iii. **A flulike syndrome**
   e. **Rifampin** is also not used as a single agent due to emergence of resistance. Resistance can be caused by alteration of the β-subunit of RNA polymerase, or decreased permeability to the drug.
3. **Pyrazinamide is bactericidal** by an unknown mechanism. It is effective when given orally, including good CSF penetration. Pyrazinamide is a **prodrug** that must be **hydrolyzed** to the active form. **Loss of hydrolase** leads to **resistance.**
4. **Ethambutol** (*Myambutol*) inhibits mycolic acid synthesis but is only **bacteriostatic.** It can also **impair red–green vision** and exacerbate gout**.**
5. **The aminoglycoside streptomycin** is **bactericidal,** but it:
   a. Must be administered **parenterally**
   b. Only kills extracellular organisms and does not penetrate into cells
   c. **Does not distribute** as widely in the body as the other drugs
6. **Fluoroquinolones and macrolides** also have antimycobacterial activity.

B. TREATMENT OF LEPROSY (*Mycobacterium leprae*) involves long-term administration of drug combinations of:

1. **Sulfones** [e.g., **dapsone** (*Alvosulfon*)], which are PABA analogs that reduce folic acid synthesis. They are analogous to sulfonamides.
2. Rifampin.
3. Thalidomide (*Thalomid*) for skin complications.
4. **Clofazimine** (*Lamprene*), a bacteriocidal drug that binds to DNA and prevents it from serving as template for replication. It may also cause formation of toxic oxygen radicals.

Chapter **10**

Drugs for Infections from Eukaryotic Organisms and Viruses

I Antifungal Drugs

A. ERGOSTEROL-BINDING DRUGS

1. **Amphotericin B** (*Fungizone*) **binds ergosterol** in fungal cells and **increases membrane permeability** by forming membrane pores.
   a. Selective toxicity occurs because there is less binding to cholesterol in host cell membranes.
   b. Amphotericin B is **fungicidal** at high dosages and fungistatic otherwise. It has no antibacterial activity.
   c. **Slow parenteral** administration is necessary.
   d. Amphotericin B has a low therapeutic index, and the **side effects** are **very severe,** including:
      i. **Acute febrile response**
      ii. **Dose-dependent delayed nephrotoxicity**
   e. It was previously the drug of choice for most systemic fungal infections. More recently, however, echinocandins and azoles such as voriconazole have become preferred due to the greater toxicity of amphotericin B.
   f. Amphotericin B lipid complex (*Abelcet Injection*) has similar effects but less toxicity. In general, adding more lipids to the formulation decreases nephrotoxicity but increases the price in comparison to plain amphotericin B.
   g. **Amphotericin B** can be **synergistic with flucytosine** (see below) because it makes the fungal cell membrane more permeable to flucytosine.
2. **Nystatin** (*Nilstat, Mycostatin*) acts like amphotericin B in that it binds ergosterol; however, it is only used **topically** to treat infections such as oral candidiasis due to its toxicity**.**

B. ERGOSTEROL SYNTHESIS INHIBITORS

1. **The azoles** interfere with **ergosterol synthesis by inhibiting the fungal cytochrome P450 system,** thereby increasing fungal membrane permeability.
   a. They are only **fungistatic.**
   b. They are valuable alternatives to amphotericin because of their effectiveness when administered orally and mild side effects.
      i. Azoles should not be coadministered with amphotericin B. By reducing ergosterol synthesis, the **azoles interfere with the mode of action of amphotericin B.**
      ii. They are **teratogenic** and should not be given to pregnant women.
   c. **Ketoconazole** (*Nizoral*) was the first azole to be used, and it is **less selective** compared to newer azoles. Thus, it is almost never used anymore.
      i. It can only be administered orally.

ii. It is **poorly absorbed if gastric pH is high** (e.g., with antacids); thus, it should be taken with an acidic drink.
iii. It has some **hepatotoxicity** and causes **gynecomastia.**
iv. **It inhibits host MFOs,** which will slow the metabolism of many drugs. Cortisol and testosterone synthesis will also be reduced because **ketoconazole inhibits gonadal and adrenal steroidal synthesis.**
v. **Resistance** can be due to **altered fungal enzymes** or to removal of the drug via **efflux pumps.**

d. **Fluconazole** (*Diflucan*) and **itraconazole** (*Sporanox*) have the same mechanisms of action and properties that are similar to ketoconazole, except that
i. Intestinal absorption of these drugs is **not affected as much by changes of gastric pH.**
ii. They can be given orally or **intravenously.**
iii. They both **lack** the **endocrinological side effects** seen with ketoconazole.
iv. **Fluconazole penetrates** much **better into the CSF.**

e. **Voriconazole** (*Vfend*) and **posaconazole** (*Noxafil*) are newer broad-spectrum triazoles that penetrate the CNS. Voriconazole can cause transient visual disturbances.
f. Other azoles like **miconazole** (*Monistat*) and **terconazole** (*Terazol*) are mainly used **topically** due to their toxicity.

2. Terbinafine (*Lamisil*) **blocks fungal cell membrane synthesis** by **inhibiting the conversion of squalene to squalene epoxide.** Squalene epoxide is a precursor of ergosterol as well as cholesterol, but the fungal enzyme is selectively inhibited.
a. Terbinafine accumulates in nails and is the **drug of choice** to treat **onychomycosis** (fungal infection of nail bed) and **dermatophytoses.**
b. Terbinafine is **fungicidal.**
c. **Side effects** are mild and include **gastrointestinal (GI) upset, headache,** and **rash.**

C. ECHINOCANDINS: CELL WALL SYNTHESIS INHIBITORS

1. Echinocandins interfere with fungal cell wall synthesis by blocking formation of the β(1,3)-D-glucan linkage.
2. Caspofungin (*Cancidas*) is the first approved **echinocandin;** it treats *Aspergillus* and *Candida* infections.
3. Two more recently approved echinocandins include **micafungin** (*Mycamine*) and **anidulafungin** (*Eraxis*).

D. ANTIMETABOLITES

1. Flucytosine (*Ancobon*) is metabolized by deaminases in the fungal cells to the active substance, **fluorouracil.**
a. Fluorouracil inhibits fungal DNA and RNA synthesis. It is **fungistatic.**
i. **Flucytosine** is coadministered with **amphotericin B** against *Cryptococcus* and *Candida* infections.
ii. Coadministering flucytosine with amphotericin B allows a lower dose of amphotericin B to be used, which decreases the toxic effects of amphotericin B.
iii. Flucytosine cannot be used alone due to development of resistance.
b. An advantage of flucytosine is its **wide distribution,** even to the CNS.
c. Like many antimetabolites, the major disadvantage of flucytosine is that it **depresses the bone marrow** and may cause neutropenia.

2. **Griseofulvin** (*Gris-PEG*, *Grisactin*) **binds to keratin** and is taken orally for fungal infections of the skin, hair, and nails.
   a. **Griseofulvin causes disruption of mitotic spindles,** which decreases mitosis. It is fungistatic. Absorption is improved with a high-fat meal; duration of action is very long (months) after oral administration.
   b. Because griseofulvin is metabolized in the liver and activates MFOs, patients taking this drug should not drink alcohol.
   c. It has largely been replaced by **terbinafine.**

II Antiprotozoal Drugs

A. MALARIA is a common protozoal disease in tropical climates that is usually caused by infection with one of four *Plasmodium* organisms. These include *P. falciparum* (the most serious type of *Plasmodium* infection), *P. ovale* and *P. vivax* (which chronically infect the liver as well as the red blood cells), and *P. malariae*. The organisms feed on hemoglobin in the red blood cells of humans.

1. **Blood schizonticidal drugs** clear plasmodia from the erythrocytes.
   a. **Chloroquine** (*Aralen*) is selectively **concentrated** (100×) by red blood cells that are infected with the parasites.
      i. After digesting the protein portion of hemoglobin, malarial parasites polymerize the toxic heme prosthetic groups to a nontoxic byproduct called **hemozoin.** Chloroquine **prevents the parasite from polymerizing the heme prosthetic groups.** Toxic levels of heme build up in the parasites' food vacuoles, killing them.
      ii. It acts on all erythrocytic *Plasmodium* infections, **except:**
         (a) **chloroquine-resistant *P. falciparum*,** now very prevalent
         (b) **chloroquine-resistant *P. vivax***
      iii. **Resistance** occurs due to **active efflux of the drug from the parasite's food vacuoles**.
      iv. **Once-a-week oral administration** is effective because chloroquine is highly concentrated in the liver and has a long half-life.
   b. **Pyrimethamine** (*Daraprim*) **inhibits dihydrofolate reductase,** leading to reduced folic acid synthesis, especially in parasites.
      i. It is often combined with a sulfonamide (e.g., sulfadoxine [*Fansidar*]).
      ii. **Teratogenicity** has been reported in animals.
   c. **Quinine** has a **very rapid onset** and short duration, making it useful for treating a **severe acute attack.**
      i. **Quinidine** is the stereoisomer of quinine. Although quinidine can be used to treat malaria, it is more commonly used to treat arrhythmias. Both drugs prevent the parasite from polymerizing heme.
      ii. **Side effects** include **cinchonism** (nausea, vomiting, tinnitus, vertigo) and **arrhythmias.**
   d. **Mefloquine** (*Lariam*) is a quinine derivative that has a **long half-life** and can be administered orally. It is thought to work by **damaging the parasite's cell membrane.**
   e. Tetracyclines also have antimalarial activity.
   f. **Artemisinin** is a Chinese herb that can be **used to treat severe, drug-resistant *P. falciparum* infection.** It produces **free radicals in the parasite's food vacuole** and damages plasmodial proteins.
2. **Primaquine** is the only drug that can eliminate the tissue forms of the parasites.
   a. It is active on the **exoerythrocytic forms** and the gametes of *P. vivax* and *P. ovale*. However, primaquine cannot kill the erythrocytic merozoites.

b. Primaquine is thought to work by forming toxic oxidation byproducts.
c. **Hemolytic anemia** can occur in patients with a glucose-6-P-dehydrogenase deficiency because they do not have sufficient glutathione in their cells to prevent the toxic effects of oxidizing agents like primaquine.
d. All types of plasmodia may become resistant to primaquine.

3. **Prophylaxis** is usually provided for travelers to countries where malaria is endemic. **Mefloquine** (1 dose/week) is given from 1 week before the trip to 4 weeks after.

B. AMEBIASIS involves both gastrointestinal lumen and tissue sites (GI wall, liver).

1. **Metronidazole** (*Flagyl*) has **both luminal and systemic activity.** It acts on *Entamoeba histolytica* trophozoites in the intestinal and hepatic sites but does not eliminate the intestinal cysts.
   a. It is metabolized by microorganisms to the active drug, which **forms free radicals** and **targets DNA and proteins.**
   b. It kills **protozoa** such as *Giardia, Entamoeba,* and *Trichomonas,* as well as **anaerobes** such as *Gardnerella, Bacteroides,* and *Clostridium.*
   c. A **disulfiram-like** reaction can occur if alcohol is ingested.
2. **Luminal amebicides**
   a. **Iodoquinol** (*Yodoxin*) is an **intestinal amebicide** that is not absorbed; thus there are few systemic effects or side effects, although local GI symptoms can occur. Iodoquinol kills both luminal cysts and trophozoites.
   b. **Diloxanide furoate** (*Furamide*) is used to treat asymptomatic shedders of cysts.
   c. **Paromomycin** (*Humatin*) is an aminoglycoside antibiotic used to treat luminal amoebas and tapeworms.
3. **Systemic amebicides** are used against liver or intestinal wall infections.
   a. Chloroquine is used in combination with other drugs to treat amoebic liver abscesses due to trophozoites.
   b. **Emetine** and **dehydroemetine** block protein synthesis of amoebae, but their toxicity limits their use.

C. TRYPANOSOMIASIS includes African sleeping sickness (caused by *Trypanosoma brucei*) and Chagas' disease (caused by *T. cruzi*).

1. Trypanosomes grow in the blood and CNS.
2. **Pentamidine** (*Pentam*) is thought to bind to DNA. It is active against the hematologic stage of the trypanosomal life cycle.
3. Other antitrypanosomal drugs not used in the United States include the arsenic derivative **melarsoprol** (*Arsobal*), **suramin** (*309 F*), and **nifurtimox** (*Lampit*).

D. Other protozoal infections respond to drug therapy.

1. *Toxoplasma gondii* infections are treated with pyrimethamine and a sulfonamide.
2. *Pneumocystis carinii* infections are treated with trimethoprim and sulfamethoxazole. Pentamidine is also active against this organism. Note that *P. carinii* is now called *P. jirovecii* and may be more appropriately classified as an atypical fungus than a protozoan.
3. **Leishmaniasis** is treated with **stibogluconate** (*Pentostam*), an antimony derivative.

III Anthelmintics

A. Anthelmintics are used to treat parasitic worm infections due to nematodes (roundworms), cestodes (tapeworms), or trematodes (flukes).

B. The specific treatment of a nematode infection will depend on the type of nematode involved.

1. **Intestinal nematodes** (*Enterobius* pinworms, *Ascaris* roundworms, *Trichuris* whipworms, *Necator* hookworms, and *Ancylostoma* hookworms) are the easiest to treat because the drugs do not have to be absorbed into the body of the host.
   a. **Pyrantel** (*Antiminth*) **activates nicotinic cholinoceptors,** inducing **muscle paralysis** in the helminth.
   b. **Mebendazole** (*Vermox*) **and albendazole** (*Zentel*) **inhibit glucose uptake and interfere with microtubule assembly.**
   c. After use of one of these drugs, the weakened parasites are then eliminated in the feces.
2. **Tissue nematodes** can be divided into 2 types.
   a. **Filarial nematodes** include *Wuchereria* (elephantiasis), *Brugia* (elephantiasis), *Onchocerca* (river blindness), *Loa* (loiasis), and *Dipetalonema* (heartworm).
      i. **Diethylcarbamazine** (*Hetrazan*) may increase helminth susceptibility to the host **immune system.**
         (a) It is **most active against the microfilaria** and least active against the adult filaria.
         (b) **An allergic reaction** can result from parasitic breakdown products. The severity is related to parasite load.
      ii. **Ivermectin** (*Mectizan*) **opens γ-aminobutyric acid–sensitive chloride channels** and induces muscle paralysis in the worms due to hyperpolarization.
   b. **Nonfilarial tissue nematodes** include *Angiostrongylus* (which causes meningitis from eating raw snails) and *Trichinella* (which causes trichinosis from eating raw pork).
      i. **Thiabendazole** (*Mintezol*) **inhibits fumarate reductase,** which is unique to helminths. It is also thought to possibly inhibit microtubule activation.
      ii. **Mebendazole** (*Vermox*) and **albendazole** (*Zentel*) are also effective.

C. CESTODE (tapeworm) infections (*Taenia saginata, T. solium, Diphyllobothrium latum* and *Hymenolepis nana*) can be treated with **praziquantel** (*Biltricide*) or the preferred treatment **niclosamide** (*Nicloside*).

1. Praziquantel induces **muscle stimulation and paralysis** in the helminths by increasing cell membrane permeability to calcium.
   a. **Vacuolization of the cuticle** also occurs.
   b. The tissue forms of *T. solium* (cysticercosis) are also effectively treated with either praziquantel or albendazole.
2. Niclosamide is the drug of choice for most cestode infections.
   a. **It inhibits conversion of ADP to ATP.**
   b. A **laxative** must be administered prior to treatment to prevent liberation of the ova and cysticercosis.

D. TREMATODE (fluke) infections, such as schistosomiasis, can be treated with **praziquantel** (*Biltricide*).

IV Antiviral Drugs

A. RESPIRATORY VIRUS INFECTIONS

1. **Amantadine** (*Symmetrel*) **and rimantadine** (*Flumadine*) act on RNA viruses by **inhibiting the uncoating** of viral nucleic acids, which reduces viral replication.
   a. Amantadine and rimantadine block the M2 ion channel in the viral membrane, which is required for fusion of the viral membrane with the host cell membrane.

b. Resistance occurs due to mutation of the viral M2 protein.
c. These drugs are used primarily for the **prophylaxis** of **type A influenza viral infections.** (Amantadine is also used as an anti-Parkinson drug.)
d. They can be administered as a supplement to the flu vaccine.
e. **Treatment** with either of these drugs is effective if initiated **within 48 hours** after the initial appearance of symptoms.

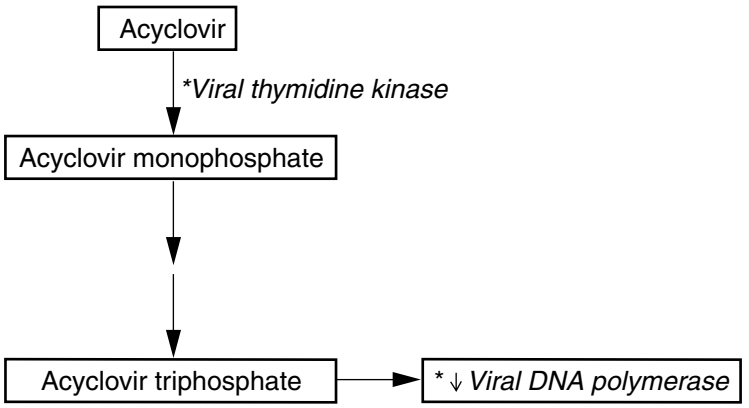
2. **Neuraminidase inhibitors** include **oseltamivir** (*Tamiflu*) and **zanamivir** (*Relenza*).
   a. They are sialic acid analogs that **inhibit the viral neuraminidase enzyme and prevent spread of virus** to other cells.
   b. Neuraminidase is inserted into the host cell membrane to allow the release of new virions. In the presence of neuraminidase inhibitors, virions accumulate at the infected cell's internal surface and cannot be released.
   c. These drugs are most effective if given prophylactically or within the first 48 hours after infection. They are effective for **both type A and type B influenza viral infections.**
3. **Ribavirin** (*Virazole*) is a guanosine analog that is effective against a broad spectrum of viruses. It is used to treat **respiratory syncytial virus (RSV) and chronic hepatitis C** (in combination with **interferon α**).
   a. Ribavirin inhibits guanine nucleotide formation, prevents mRNA capping, and blocks RNA-dependent RNA polymerase.
   b. Rhinoviruses and enteroviruses contain preformed mRNA and are therefore resistant to ribavirin.

B. HEPATIC VIRUS INFECTIONS

1. There are currently five hepatitis viruses (A-E), with B and C being the most common causes of chronic liver complications. Hepatitis A infection is acute.
   a. Hepatitis B is treated with **interferon α** (*Roferon*) or **lamivudine** (*Epivir*).
   b. Chronic hepatitis C is treated with a combination of **interferon α** and **ribavirin.**
2. **Interferon α** (*Roferon*) is a naturally occurring, inducible glycoprotein that interferes with the ability of viruses to infect new cells.
   a. It is thought to induce host cell enzymes that inhibit viral translation.
   b. Interferon α causes flu-like symptoms and interferes with hepatic drug metabolism.
3. **Nucleoside and nucleotide analogs** interfere with viral replication.
   a. **Lamivudine** (*Epivir*) is a cytosine analog that selectively inhibits the DNA polymerase of hepatitis B. It also inhibits human immunodeficiency (HIV) reverse transcriptase.
   b. **Adefovir dipivoxil** (*Hepsera*) is a nucleotide analog that is incorporated into hepatitis B viral DNA and causes chain termination.
   c. **Entecavir** (*Baraclude*) is a guanosine analog used against hepatitis B.

C. Drugs against **herpes virus infections** are only active during the acute and not the latent phases of the virus's life cycle.

1. **Acyclovir** (*Zovirax*) is a guanine analog that is a relatively safe antiviral drug.
   a. It has **two sites** of selective toxicity (Figure 10-1).
      i. **Viral kinases preferentially phosphorylate acyclovir to acyclovir monophosphate.**
      ii. **Acyclovir triphosphate is active against viral DNA polymerases.**
   b. Clinical **indications** include:
      i. **Genital and labial herpes simplex virus (HSV) types 1 or 2. There is no effect on the latent forms.**
      ii. **Herpes encephalitis and keratitis.**
      iii. **Varicella-zoster virus.**



● **Figure 10-1** Mechanisms of selective toxicity (*) for acyclovir.

c. **Valacyclovir** (*Valtrex*) is an orally bioavailable prodrug of acyclovir.
d. Resistance can occur due to alteration or loss of viral thymidine kinase.

2. **Ganciclovir** (*Cytovene*) is an analog of acyclovir that is used for **cytomegalovirus (CMV) and Epstein–Barr virus** infections.
   a. CMV does not have a thymidine kinase; thus, it is intrinsically resistant to acyclovir.
   b. **Valganciclovir** (*Valcyte*), a prodrug version of ganciclovir, is orally bioavailable.
3. **Cidofovir** (*Vistide*) is a cytosine analog that is used to treat CMV infections in HIV-positive patients. Such infections are now less common with the widespread use of highly active antiretroviral therapy (HAART). The antisense oligonucleotide **fomivirsen** (*Vitravene*) is used for the same purpose.
4. **Penciclovir** (*Denavir*) **and famciclovir** (*Famvir*) are acyclic guanosine analogs used against HSV-1, HSV-2, and varicella.
5. **Vidarabine (***Vira-A***)** is an adenosine analog used for herpetic and vaccinial eye infections in immunocompromised patients. It is less HSV-specific compared to acyclovir.
6. **Foscarnet** (*Foscavir*) is used to treat **mucocutaneous HSV and CMV.**
   a. It is a phosphonoformate that inhibits viral DNA and RNA polymerase at the pyrophosphate binding site and terminates chain elongation.
   b. Foscarnet has broad antiviral activity against CMV, acyclovir-resistant HSV, and herpes zoster.
   c. Resistance develops due to mutation of the viral polymerases.

D. DRUGS AGAINST HIV

1. Principles of treating HIV infection

a. **HIV is a retrovirus.** Its RNA genome is converted in the host cell to DNA using the viral enzyme **reverse transcriptase (RT).**
b. Because HIV-RT does not have a proofreading function, frequent mutation of the virus leads to rapid development of resistance to anti-HIV drugs.
c. In order to delay the development of resistance, HIV treatment is typically given in three-drug combinations, a strategy called **HAART.**
   i. Typically, a HAART drug "cocktail" consists of two **nucleoside reverse transcriptase inhibitors (NRTIs)** and one **protease inhibitor,** or else two NTRIs and one **nonnucleoside reverse transcriptase inhibitor (NNRTI).**
   ii. HAART therapy is highly effective at managing HIV infection. Failure is often due to poor patient compliance with the demanding drug regimens.
   iii. These regimens can dramatically reduce the symptoms of AIDS; however, no regimen can eliminate HIV.

2. The first HIV drugs were **nucleoside and nucleotide analogs** with a preference for viral reverse transcriptase (RT) over host DNA polymerases. These **nucleoside reverse transcriptase inhibitors (NRTIs)** lack the 3′-hydroxyl group.
   a. Their incorporation into viral DNA terminates viral DNA synthesis.
      i. NRTIs have significant adverse effects, which could be due to inhibition of mitochondrial DNA polymerases.
      ii. NRTIs with overlapping toxicities should not be coadministered.
   b. **Zidovudine** (*Retrovir*), formerly called azidothymidine (AZT), is a thymidine analog that is converted to the triphosphate form. It is the prototype NRTI.
      i. Zidovudine is used:
         (a) In the treatment of **HIV-positive and AIDS patients**
         (b) In pregnant women with HIV to reduce the transmission of HIV to the newborn
         (c) To reduce the incidence of HIV in health-care workers exposed to the virus via needlestick
      ii. **Bone marrow depression** may occur. Toxicity is potentiated if AZT is coadministered with other drugs that are also glucuronylated (e.g., ribavirin, stavudine, acetaminophen).
      iii. **Stavudine** (*Zerit*) is another thymidine analog that can cause peripheral neuropathy. It should not be given with AZT.
   c. **Zalcitabine** (*Hivid*) and **lamivudine** (*Epivir*) are deoxycytosine analogs.
      i. Both can be coadministered with AZT in HAART.
      ii. Both drugs cause peripheral neuropathy and should not be coadministered with one another.
   d. **Abacavir** (*Ziagen*) is a deoxyguanosine analog.
   e. **Didanosine** (*Videx*) is an adenosine analog and can also cause peripheral neuropathy. It should not be coadministered with zalcitabine.
   f. **Tenofovir** (*Viread*) is the first nucleotide analog (most other NRTIs are nucleoside analogs). It is an adenosine-5'-monophosphate analog.
3. **Nonnucleoside reverse transcriptase inhibitors (NNRTIs)** are **allosteric inhibitors of HIV-RT.**
   a. Thus, there is no cross resistance between NRTIs and NNRTIs.
   b. The three NNRTIs currently in use are **efavirenz** (*Sustiva*), **nevirapine** (*Viramune*), and **delavirdine** (*Rescriptor*).
4. **Protease inhibitors** were introduced in 1995 and have greatly reduced deaths due to HIV infection. They act by **inhibiting the protease** that cleaves viral protein precursors.
   a. Protease inhibitors can cause a characteristic "buffalo hump" deposit of fat on the upper back. They inhibit cytochrome P450 enzymes, leading to accumulation of some drugs.
   b. Most protease inhibitors are peptidomimetics or peptides.
      i. **Ritonavir** (*Norvir*) is used in combination with drugs such as AZT and didanosine for the treatment of HIV. It can also be used to increase the bioavailability of other protease inhibitors.
      ii. **Atazanavir** (*Reyataz*) can be given once daily instead of requiring multiple doses like the other protease inhibitors do.
      iii. **Lopinavir/ritonavir** (*Kaletra*) is a coformulation of two protease inhibitors.
      iv. Others common protease inhibitors include **saquinavir** (*Invirase*), **indinavir** (*Crixivan*), and **nelfinavir** (*Viracept*).
5. **Enfuvirtide** (*Fuzeon*) is the first **viral fusion inhibitor.** It is a peptide that binds to gp41 and **prevents fusion of viral and host cell membranes.** Its biggest drawback is its high cost.

Chapter **11**

Cancer Chemotherapy

I Principles of Cancer Chemotherapy

A. Chemotherapy is useful for disseminated cancers that cannot be removed by surgery or as supplemental treatment after surgery or radiation.

1. Using surgery or radiation to shrink the tumor before chemotherapy increases the number of dividing cells, which increases the effectiveness of chemotherapy.

2. Most anticancer drugs **affect cell division.**

a. They act preferentially on **rapidly proliferating cells.**

b. **Smaller tumors have a higher growth fraction.**

i. Consequently, they are more susceptible to the anticancer drugs.

ii. **Adjuvant chemotherapy** is used with surgery or radiation to treat undetectable metastases when they are small and highly sensitive to anticancer drugs.

c. A greater proportion of nondividing cells **will survive** chemotherapy compared to dividing cells.

B. CELL CYCLE SPECIFICITY OF ANTICANCER DRUGS

1. Some drugs are **cell cycle phase specific.** They are only effective against replicating cells, particularly malignancies with a high growth fraction.

a. The cell cycle phases include:

i. G_1, the phase after mitosis. Some G_1 cells can move into a resting, non-dividing state, G_0.

ii. S, the DNA synthesis phase.

iii. G_2, the phase before mitosis.

iv. M, the mitotic phase.

b. Cell cycle phase specific drug classes include **antimetabolites, bleomycin peptide antibiotics, vinca alkaloids (microtubule inhibitors), and etoposide.**

i. The folic acid analog **methotrexate** (MTX) kills in **S-phase** (DNA synthesis phase).

ii. **Vincristine and vinblastine** kill in **M-phase** (mitotic phase).

2. Other drugs are **cell cycle phase nonspecific.**

a. They are effective at killing nondividing cells as well as dividing cells.

b. Cell cycle phase nonspecific drug classes include **alkylating agents, most anticancer antibiotics, cisplatin, and nitrosoureas.**

C. CELLS ARE KILLED IN A FIRST-ORDER MANNER (a constant percentage is killed with each course of therapy). Because of this **log kill,** additional rounds of chemotherapy are necessary in order to completely eradicate the tumor.

D. There are many **standard toxicities** that occur with most anticancer drugs.

1. Myelosuppression is common because the bone marrow is a rapidly proliferating tissue.
   a. This is usually the dose-limiting side effect.
   b. The leukopenia is greater than the thrombocytopenia, which is greater than the anemia.
   c. The drugs for which bone marrow depression is not the dose-limiting toxicity include:
      i. Hormones
      ii. Vincristine
      iii. Bleomycin
      iv. Asparaginase
      v. Cisplatin
      vi. Monoclonal antibodies (MAbs)

2. Other rapidly proliferating cells that are affected include:
   a. **GI epithelium**
   b. **Germinal epithelium**
   c. **Hair follicles**

3. Nausea and vomiting are common side effects that can be managed with antiemetics, including:
   a. Phenothiazines such as prochlorperazine (*Compazine*)
   b. Cannabinoids such as dronabinol (*Marinol*)
   c. Dopamine receptor antagonists such as metoclopramide (*Reglan*)
   d. Ondansetron (*Zofran*), a 5-HT_3 antagonist
   e. Glucocorticoids, such as dexamethasone
   f. Antihistamines, such as diphenhydramine (*Benadryl*)
   g. Benzodiazepines, such as lorazepam (*Ativan*)

4. Tissue necrosis may occur at the site of injection.

5. Some anticancer drugs have **unique organ toxicities.**
   a. **Anthracyclines** (doxorubicin, daunorubicin, idarubicin, epirubicin and mitoxantrone) **are cardiotoxic.**
   b. **Bleomycin induces pulmonary fibrosis.**
   c. **Vinca alkaloids** (vincristine, vinblastine and vinorelbine); **platinum compounds** (cisplatin, carboplatin and oxaliplatin); and **taxanes** (paclitaxel and docetaxel) are **neurotoxic.**
   d. **Cisplatin, carboplatin,** and **methotrexate** are **nephrotoxic.**

6. Adverse side effects can be minimized by a variety of techniques including:
   a. Local perfusion of tumors
   b. Removing marrow pre-treatment and reimplanting it afterward
   c. Diuresis to prevent bladder toxicity
   d. Administering leucovorin (folinic acid) for megaloblastic anemia and prevention of MTX toxicity
   e. Urine alkalinization for MTX excretion
   f. Administering G-CSF (filgrastim) for neutropenia
   g. Administering **allopurinol** (*Zyloprim*) or **rasburicase** (*Elitek*) to **treat hyperuricemia** associated with tumor lysis syndrome, especially in leukemia and lymphoma patients.

E. OTHER PROBLEMS WITH CHEMOTHERAPY

1. Immunocompromised patients usually have poorer responses to anticancer treatment.

2. The centers of large tumors and the CNS can serve as **pharmacologic sanctuaries.**

3. Some chemotherapeutic agents, particularly alkylating agents, can cause new, treatment-induced cancers up to several years after treatment. **Teratogenicity and carcinogenicity** can also occur, again especially with the alkylating agents.
4. **Resistance** can develop.
   a. Some cancers are inherently resistant to certain agents; other cancers can develop resistance by mutation, especially after long-term administration of low doses of the drug.
   b. Resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs.
   c. Multidrug resistance occurs due to stepwise selection for the **permeability glycoprotein (P glycoprotein).**
      i. P glycoprotein actively pumps drugs out of the cell.
      ii. Because P glycoprotein is a multidrug efflux pump, its activity provides cross-resistance for several structurally unrelated drug classes.
      iii. Some organs naturally express high levels of P glycoprotein, including the **kidneys, intestines, liver, and pancreas.** Cells of these organs are therefore more resistant to chemotherapy.

F. COMBINATION THERAPY is common and is often more effective against a wider variety of cell lines.
1. Each drug in the combination should be **active** against the tumor to provide maximum cell killing within the range of tolerance.
2. The drugs should have **different mechanisms** of action to kill the maximum number of cells in heterogeneous tumors.
3. The drugs should have **different toxicities** so that they can all be given at full strength and emergence of resistance can be delayed**.**
4. The drugs are usually administered in treatment cycles and time must be allowed for host tissue recovery between cycles.

II Anticancer Drugs

A. ALKYLATING AGENTS are usually cell cycle **phase non-specific,** but they are most toxic to rapidly dividing cells**. They react with nucleophilic groups on nucleic acids and may cause secondary cancers like leukemias several years after treatment.**
1. **Nitrogen mustards** form a very reactive **immonium** intermediate.
   a. The intermediate attacks nucleophilic groups, especially **guanine,** leading to
      i. **Cross-linking of DNA**
      ii. **Linking of bases in the same DNA strand**
      iii. **Linking of bases to water or other molecules**
   b. Compounds with **2 reactive sites** have **greater activity.**
   c. The cells will not replicate normally.
   d. The cells can repair the DNA; thus, the mustards are **proliferation-dependent** because rapidly dividing cells have less time to repair the DNA before DNA replication occurs.
   e. **Resistance** occurs due to:
      i. **Reduced drug uptake** by the cancer cells
      ii. **Increased rate of DNA repair**
   f. **Cross-resistance** between alkylating agents is common.
   g. **Bone marrow depression** is the dose-limiting side effect for these drugs.
   h. The nitrogen mustards include:

i. **Mechlorethamine** (*Mustargen*), which is a potent **vesicant** with a **very short half-life** (a few minutes).
   (a) It reacts with tissues quickly, especially those near the site of injection.
   (b) It cross-links guanine residues in DNA, facilitating breakage.
   (c) **Phlebitis** occurs at the injection site.

ii. **Cyclophosphamide** (*Cytoxan*), which is a **prodrug** that is metabolized to the active forms by CYPs in the liver.
   (a) It is the most commonly used alkylating agent.
   (b) **Phosphoramide mustard** and **acrolein** are two active alkylating metabolites.
   (c) Since the prodrug form is inactive, it can be given **orally,** and it is not a vesicant.
   (d) The metabolites are eliminated in the urine, which can irritate the bladder, leading to a **sterile hemorrhagic cystitis.** Sufficient hydration and the administration of mesna (*Uromitexan*) to protect the bladder can help alleviate this side effect.

iii. **Chlorambucil** (*Leukeran*), is effective after oral administration and is the slowest-acting and least toxic alkylating agent.

iv. **Melphalan** (*Alkeran*) is another oral agent with moderate toxicity.

2. The nitrosoureas also alkylate and crosslink DNA. They include:

a. **Lomustine** (*CCNU, CeeNu*), which can be given orally; and **carmustine** (*BiCNU*), which must be given by IV. Both are **highly lipophilic.**
   i. They can **penetrate to the CSF.**
   ii. Unlike most other cytotoxic drugs, they are useful to treat CNS cancers or metastases in the CNS.

b. **Streptozocin** (*Zanosar*) accumulates in the **beta cells of the pancreas** and can produce **insulin shock,** an unusual side effect for an anticancer drug. It is useful for treating insulinomas but can cause diabetes.

3. Busulfan (*Myleran*), **thiotepa** (*Thioplex*), **dacarbazine** (*DTIC*), **and temozolamide** (*Temodar, Temodal*) are other alkylating anticancer drugs.

a. **Busulfan** is an orally administered alkylating agent that can cause **myelosuppression** and **pulmonary fibrosis.**

b. **Thiotepa** is administered by IV and can be injected directly into the bladder to treat bladder cancer.

c. **Dacarbazine** is metabolized to methylhydrazine. It is given by IV and does not cross the blood–brain barrier (BBB). **Temozolamide** is an analog of dacarbazine and is also metabolized to methylhydrazine. However, it can be given orally and does cross the BBB.

4. Cisplatin (*Platinol*) **and carboplatin** (*Paraplatin*) are alkylating agents that bind to guanine in the DNA molecule.

a. They are not phase specific, but cells in the G_1 or S phases are the most susceptible to them.

b. **Nephrotoxicity** is the dose-limiting side effect. It can be reduced by aggressive hydration and diuresis or administration of **amifostine** (*Ethyol*).

c. **Oxaliplatin** (*Eloxatin*) is another cisplatin analog that is more water-soluble and does not have cross-resistance with cisplatin and carboplatin.

B. ANTIMETABOLITES are usually **phase-specific, especially S-phase–specific. They are structural analogs of normal metabolites and interfere with purine or pyrimidine synthesis,** as well as with **incorporation of nucleotides into nucleic acids.**

1. **Methotrexate** (*Trexall, Rheumatrex*) is an analog of folic acid which competitively inhibits the enzyme, **dihydrofolate reductase.**
   a. Tetrahydrofolate levels are decreased.
      i. Decreased DNA, RNA, and protein synthesis occurs.
      ii. The primary effect is a decrease of **thymidylate synthesis.**
      iii. The highest activity occurs in cells with low thymidine derivatives and normal RNA and normal proteins.
   b. Methotrexate is S-phase specific and **self-limiting** because it slows the movement of cells into the S-phase.
   c. It is metabolized to polyglutamate derivatives that also inhibit dihydrofolate reductase and that remain in the cells even in the absence of extracellular drug.
   d. Resistance can be due to
      i. Increased production of dihydrofolate reductase
      ii. Decreased affinity of the enzyme for methotrexate
      iii. Decreased active transport of methotrexate into the cancer cells
      iv. Low levels of dihydrofolate reductase in nonproliferating cells
   e. Due to low water solubility, **crystalluria and renal damage** can occur, but these problems can be prevented with urine alkalinization and aggressive hydration. Methotrexate is also **teratogenic.**
   f. Toxicity can be **reversed by leucovorin** (citrovorum factor, folinic acid) which is directly converted to tetrahydrofolate by an alternative pathway.
   g. Methotrexate can be given as an abortifacient, often along with **misoprostol.**
2. **Purine analogs** must be phosphorylated to their active form and are used to treat leukemias.
   a. **Fludarabine** (*Fludara*) inhibits DNA polymerase, ribonucleotide reductase, and DNA primase, thus preventing DNA synthesis.
   b. **6-Thioguanine** is converted to thioguanine monophosphate and deoxythioguanosine triphosphate, which is **incorporated into tumor cell DNA.**
      i. Thioguanine monophosphate also inhibits amidotransferases, which leads to reduced purine synthesis.
      ii. It is S-phase specific.
   c. **6-Mercaptopurine** (*Purinethol*) is the thiol analog of the purine hypoxanthine. It is converted to thioinosine monophosphate, which inhibits amidotransferase. Because inosine monophosphate (IMP) is converted to adenosine monophosphate (AMP) by the cell, this reaction is inhibited as well.
      i. It is **inactivated by xanthine oxidase.**
      ii. As a result, **allopurinol** will decrease the metabolism and increase the toxicity of mercaptopurine.
   d. Cross-resistance occurs between 6-mercaptopurine and 6-thioguanine. **Resistance** can occur due to **down-regulation of the enzyme that phosphorylates the drug, increased dephosphorylation, or increased metabolism of the drug.**
   e. 6MP and 6TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT deficiency is a common inherited genetic defect, and dose reduction or complete withholding may be necessary.
3. **Fluorouracil** (*Efudex, Adrucil*) is an important **pyrimidine analog.** It penetrates the CNS but is toxic to the GI tract.
   a. The phosphorylated form, fluorodeoxyuridine monophosphate, decreases the activity of thymidylate synthase.
   b. Fluorouracil is normally coadministered with **leucovorin** because leucovorin is required in a coenzyme for thymidylate synthesis. Thus, the effect of fluorouracil is enhanced by leucovorin; it is reversed by thymidine.

c. **Capecitabine** (*Xeloda*) is an oral fluoropyrimidine carbamate used to treat metastatic breast cancer. It is converted to fluorouracil in vivo.

4. **Gemcitabine** (*Gemzar*) is a fluorinated cytosine analog.
5. **Cytarabine (Ara-C)** is an arabinose analog of 2′-deoxycytosine that functions as a pyrimidine antagonist after being phosphorylated. It is S-phase specific.

C. SOME ANTIBIOTICS can be used as anticancer drugs. They interact with DNA and disrupt its function in a cell–cycle nonspecific fashion.

1. **Dactinomycin** (*Cosmegen*), also called actinomycin D, **intercalates** between bases, especially guanine, in DNA.
   a. This reduces DNA-dependent RNA polymerase activity, which reduces RNA synthesis.
   b. It is cytotoxic at **all phases** of the cell cycle and is **not proliferation dependent.**
   c. Resistance occurs due to decreased drug entry and accumulation in cells.
2. **Doxorubicin** (*Adriamycin*) **and daunorubicin** (*Cerubidine*) also **intercalate** into DNA, but there is **no base specificity.** Additional mechanisms of action include **interfering with phosphatidylinositol activation and generation of oxygen radicals.**
   a. **Cumulative cardiotoxicity** occurs due to **superoxide anion.** Adding the iron chelator **dexrazoxane** (*Zinecard*) can help mitigate this. Another odd side effect of doxorubicin is that the patient's urine turns red.
   b. Resistance occurs due to decreased drug entry into the cells; there is cross-resistance between doxorubicin and daunorubicin and often with dactinomycin.
3. **Bleomycin** (*Blenoxane*) induces **fragmentation of DNA via an oxidative process.**
   a. Bleomycin is a mixture of copper-chelating glycopeptides. Unlike the other antibiotics, bleomycin is cell–cycle specific (G_2 phase).
   b. The effects of intercalating agents are enhanced.
   c. **Delayed pulmonary fibrosis** can be induced, but myelosuppression rarely occurs.

D. STEROID HORMONES can induce palliation of some cancers, either by adding or removing the appropriate hormone.

1. Their activity depends on the presence of the **steroid receptors** on the tumor cells (e.g., estrogen receptors).
2. Hormone-active substances include antiestrogens, estrogens, progestins, androgens, and corticosteroids.
   a. **Glucocorticoids** reduce inflammation and swelling that can cause pain.
      i. **Prednisone** (*Deltasone*) is an anti-inflammatory corticosteroid that is metabolized to its active form (prednisolone) by the liver. It is used to treat lymphomas and leukemias because it causes lymphocytopenia.
      ii. **Dexamethasone** (*Decadron*) can also be used.
   b. **Tamoxifen** (*Nolvadex*) is a **selective estrogen receptor modulator (SERM)** that is used to treat estrogen receptor–positive breast cancer.
      i. It is a competitive inhibitor of the estrogen receptor; thus, premenopausal women must also take a second drug to decrease their estrogen levels.
      ii. Side effects include hot flashes.
   c. **Aromatase inhibitors** are beginning to replace tamoxifen. **Aromatase** is the extra-adrenal enzyme that synthesizes estrogen from androstenedione. This is an important source of estrogen, especially in postmenopausal women.

i. **Aminoglutethimide** (*Cytadren*) was the first aromatase inhibitor used to treat breast cancers in postmenopausal women. It also inhibits hydrocortisone synthesis; thus, hydrocortisone must be coadministered.
ii. **Anastrozole** (*Arimidex*) and **letrozole** (*Femara*) are nonsteroidal aromatase inhibitors. They are more potent and selective than aminoglutethimide, do not require hydrocortisone supplementation, and do not have androgenic side effects.
iii. **Exemestane** (*Aromasin*) is a steroidal, irreversible aromatase inhibitor.

d. **Megestrol** (*Megace*) is a progestin used to treat breast and endometrial cancers. It is being replaced by aromatase inhibitors.
e. **Estrogens** were formerly used to treat prostate cancer but have now been largely replaced by gonadotropin-releasing hormone (GnRH) agonists. They block luteinizing hormone (LH) (and therefore androgen) production.
f. **Leuprolide** (*Leupron, Eligard*) and **goserelin** (*Zoladex*) are synthetic peptide GnRH agonists. They desensitize the GnRH receptor, leading to down-regulation of FSH (follicle-stimulating hormone) and LH. This then reduces both androgen and estrogen synthesis.
i. These drugs can be used to treat breast and prostate cancers.
ii. The effects are milder compared to treatment with estrogen.
g. **Flutamide** (*Eulexin*), **nilutamide** (*Nilandron*), and **bicalutamide** (*Casodex*) are synthetic, nonsteroidal antiandrogens used to treat prostate cancer. As competitive inhibitors of androgen receptors, they may be coadministered with GnRH agonists.

E. There are several **inhibitors of chromosomal function.**

1. **The vinca alkaloids, vincristine** (*Oncovin*), **and vinblastine** (*Velban*), enhance the **depolymerization** of the **tubulin in the mitotic spindles,** thereby disrupting spindle function.
a. **Mitosis is inhibited (M-phase specific).**
b. Vinblastine displays standard toxicity (myelosuppression); however, **peripheral neurotoxicity is the dose-limiting side effect of vincristine.**
c. **Resistance** is due to efflux of the drug or altered tubulins.
2. **Etoposide** (*VePesid*) **and teniposide** (*Vumon*) **inhibit topoisomerase II,** resulting in breaks of the DNA strands. Cells are arrested in the late S- or G_2-phases.
3. **Paclitaxel** (*Taxol*) **and docetaxel** (*Taxotere*) interfere with cell division by **enhancing microtubule formation** and stabilizing microtubules. This prevents chromosome desegregation in anaphase.
4. **Irinotecan** (*Camptosar*) **and topotecan** (*Hycamtin*) are S-phase specific agents that **inhibit topoisomerase I.** This leads to single-stranded breaks in the DNA that cannot be repaired.
5. **Procarbazine** (*Matulane*) causes breakage of DNA strands by an unknown mechanism. It also inhibits DNA, RNA, and protein synthesis and may alkylate DNA.

F. MAbs ARE DIRECTED AGAINST A PARTICULAR CANCER CELL ANTIGEN AND ARE HIGHLY SPECIFIC.

1. **Trastuzumab** (*Herceptin*) is used to treat breast tumors that overexpress the HER-2 receptor. It is usually coadministered with paclitaxel. The most serious side effect is congestive heart failure.
2. **Rituximab** (*Rituxan*) is specific for the CD20 antigen on B-cells, making it useful for treating B-cell lymphomas. It must be infused slowly because it activates complement.

3. **Bevacizumab** (*Avastin*) is an anti-angiogenesis MAb that binds vascular endothelial growth factor (VEGF) and prevents it from stimulating new blood vessel growth.
4. **Cetuximab** (*Erbitux*) targets the epidermal growth factor receptor (EGFR). It is used along with irinotecan to treat colorectal cancer.
5. **Gemtuzumab ozogamicin** (*Mylotarg*) is an MAb conjugated to a plant toxin. It binds to the CD33 cell–surface receptor, which is present on many leukemia cells.

G. SIGNAL TRANSDUCTION INHIBITORS interfere with cell signaling.

1. **Imatinib mesylate** (*Gleevec*) is a tyrosine kinase signal transduction inhibitor.
   a. It is used to treat myeloid leukemia blast crises caused by cells containing the BCR–ABL fusion tyrosine kinase (Philadelphia chromosome).
   b. Imatinib prevents phosphorylation of tyrosine on the kinase substrates, thus inhibiting cell proliferation.
2. **Gefitinib** (*Iressa*) targets the epithelial growth factor (EGF) receptor tyrosine kinase domain.

H. MISCELLANEOUS DRUGS have unique actions.

1. **Asparaginase** (*Elspar*) deaminates asparagine and glutamine, thereby depriving cells of essential amino acids.
   a. Tumors with no asparagine synthetase are sensitive to asparaginase because any asparagine taken up by the tumors will be metabolized.
   b. It has none of the standard anticancer drug toxicities.
   c. **Hypersensitivity** reactions can occur due to the proteinaceous nature of this drug.
2. **Mitotane** (*Lysodren*) induces adrenocortical necrosis and is useful to treat adrenocortical cancers.
3. **Interferons** bind to cell surface receptors and prevent proliferation.

III Immunomodulators

A. Immunosuppressants are used to suppress the rejection of transplanted organs.

1. The principle approach to immunosuppressive treatment is to alter lymphocyte function using drugs or antibodies against immune system proteins.
   a. To decrease toxicity, multiple agents are used together so that each can be administered at a lower dose.
   b. Immunosuppressants are also used to treat autoimmune disorders.
2. **Corticosteroids** bind to steroid receptors and affect transcription, leading to suppression of the immune response.
   a. They have **no cytotoxic activity.**
   b. **Anti-inflammatory** effects are very useful.
      i. **Prednisone** (*Deltasone*) and **methylprednisolone** (*Medrol*) are used in combination with other agents to prevent transplant rejection.
      ii. **Prednisone** and **prednisolone** (*Prelone*) are used to treat autoimmune disorders.
3. **Cytotoxic drugs suppress the bone marrow** and thereby reduce the immune reaction by disrupting cell metabolism and preventing lymphocyte proliferation. They have **no anti-inflammatory effects.**
   a. **Azathioprine** (*Imuran*) is a **purine analog** that is converted to mercaptopurine and reduces DNA synthesis. (See Section II.B.2.c on the antimetabolite mercaptopurine.)

i. Azathioprine is **S-phase specific** and predominantly affects rapidly dividing lymphocytes in an acute (but not chronic) immune response**.**
ii. The side effect profile is similar to the anticancer drugs (e.g., bone marrow suppression).

b. **Mycophenolate mofetil** (*CellCept*) is largely replacing azathioprine due to its safety and efficacy in prolonging graft survival for transplants.
i. It blocks the *de novo* synthesis of guanosine monophosphate, thus depriving rapidly dividing B- and T-cells of an essential nucleotide.
ii. This is effective because B- and T-lymphocytes lack the salvage pathway for purine synthesis and are wholly dependent on *de novo* purine production.

c. **Cyclophosphamide** (*Cytoxan, Neosar*) is a **phase-nonspecific** immunosuppressant and an alkylating agent. (See Section II.A.1.h.(ii) on cyclophosphamide.)

d. The antimetabolite **methotrexate** (*Folex*) is useful. (See Section II.B.1.)

4. **Cytokine inhibitors** block IL-2, a cytokine that activates helper T-cells. Thus, these drugs decrease the ability of helper T-cells to produce cytokines to activate the immune system, thereby preventing organ transplant rejection.

a. **Cyclosporine** (*Sandimmune*) is a **selective immunosuppressant** that is usually coadministered along with glucocorticoids to prevent transplant rejection**.**
i. **T-lymphocyte activation is reduced** as a result of decreased interleukin transcription and release.
ii. B-cell and mature T-cell functions are not affected.
iii. There is **no myelosuppression.**
iv. **Nephrotoxicity** is the major complication.

b. **Tacrolimus** (*Prograf*) is a macrolide given along with glucocorticoids to prevent transplant rejection.
i. It has better potency and fewer episodes of rejection in comparison to cyclosporine and works in a similar way.
ii. As with cyclosporine, nephrotoxicity is the major side effect, but tacrolimus can also cause type 1 diabetes post-transplant.

c. **Sirolimus** (*Rapamune*) is another macrolide that can be used together with cyclosporine for a synergistic anti-transplant rejection effect.
i. Unlike cyclosporine and tacrolimus, sirolimus does not affect IL-2 levels, but instead dampens the T-cells' response to IL-2.
ii. Hyperlipidemia can be a side effect.
iii. Sirolimus is also used in drug-eluting coronary artery stents due to its antiproliferative properties.

5. **Antibodies against T-cell surface antigens** can be monoclonal or polyclonal. MAbs are more homogeneous and specific than polyclonal antibodies are.

a. **Antithymocyte globulins** are polyclonal antibodies used to treat hyperacute graft rejection.
i. They cause immune-mediated destruction of T-cells.
ii. Side effects include profound immunosuppression and potential for an immune response causing formation of antibodies against antithymocyte globulins.

b. **Muromonab** (*Orthoclone*) is an anti-CD3 monoclonal mouse-derived antibody that is used to treat acute transplant rejection and to deplete bone marrow of T-cells before transplantation.
i. The patient should be premedicated with steroids to help lessen the cytokine storm that often occurs when MAbs first bind to the T-cells (cytokine release syndrome).
ii. Muromonab may cause anaphylactic shock-like symptoms.

c. **Basiliximab** (*Simulect*) and **daclizumab** (*Zenapax*) are two chimerized/humanized MAbs used to prevent acute transplant rejection.
   i. These MAbs are competitive IL-2 receptor antagonists that interfere with the proliferation of activated T-cells.
   ii. Both of these antibodies are well tolerated.

B. THE IMMUNE POTENTIATOR, LEVAMISOLE (*Ergamisol*), increases the proliferation of T-lymphocytes. It is useful in a combination regimen to treat colon cancer.

Chapter 12

Toxicology

I Emergency Toxicology

A. ROUTES OF EXPOSURE to toxins include **inhalation, transdermal absorption,** and **ingestion** (particularly in young children).

B. THE GOALS OF TREATMENT of a patient who has been exposed to a toxic substance are

1. **Stabilize the ABCDs**
   a. Open the **airway.**
   b. Check for adequate **breathing.**
   c. Monitor **circulation.**
   d. Give **dextrose** if the patient might be hypoglycemic.
2. **Control the symptoms,** including:
   a. Cardiovascular effects (hypotension, lethal arrhythmias)
   b. Loss of respiratory function
   c. Convulsions
   d. Muscle rigidity
   e. Acidosis
3. **Reduce the absorption** of the substance by decontaminating skin or GI tract.
4. **Administer an antidote** if warranted (see Table 12-1).
5. **Enhance the elimination** of the substance.

C. Several approaches are available to **reduce the systemic absorption of an ingested toxic substance.**

1. **Chemical adsorption with activated charcoal** can be utilized.
   a. Charcoal binds many, but not all, toxic substances.
   b. One limitation is that charcoal will also bind emetics, antidotes, and dietary substances.
2. **Emesis** can be induced.
   a. **Syrup of ipecac** acts as a local irritant on the gastrointestinal (GI) tract and stimulates the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS) to induce vomiting.
      i. It is sold without a prescription.
      ii. It should be administered as soon as possible and less than 4 hours after ingestion to maximize recovery of the toxic substance. Charcoal is usually a better choice unless ipecac can be given within 1 hour of ingestion.
      iii. Note that **extract of ipecac should not be used.**
   b. **Apomorphine** is much less useful as an emetic, because:
      i. Parenteral administration is required.
      ii. As with other narcotics, respiratory depression can occur.

TABLE 12-1 PHARMACOLOGICAL ANTIDOTES*

Toxins	Antidotes
Acetaminophen	N-Acetylcysteine (give within 8–10 hours after overdose)
Anaphylaxis (e.g., penicillin-induced)	Epinephrine
Anesthetic-induced malignant hyperthermia	Dantrolene
Anticholinergics	Physostigmine (not for tricyclic antidepressant overdose)
Arsenic	Dimercaprol, penicillamine, unithiol
Benzodiazepines	Flumazenil (can cause seizures)
Beta blockers (e.g., propanolol)	Glucagon to increase HR and BP
Calcium channel blockers	Calcium plus management of hypotension
Carbamates (cholinesterase inhibitors)	Atropine
Carbon monoxide	Fresh air and/or 100% oxygen
Competitive muscle relaxants	Neostigmine
Cyanide	Nitrite and thiosulfate
Digoxin	Digoxin-immune Fab
Ethylene glycol	Ethanol, fomepizole
Fibrinolytics	Aminocaproic acid
Heparin	Protamine
Hydrogen sulfide	Nitrite
Insulin-induced hypoglycemia	Glucagon
Iron	Deferoxamine, deferasirox
Isoniazid-induced neuritis	Pyridoxine
Lead	$CaNa_2EDTA$, dimercaprol, penicillamine, or succimer
Mercury	Dimercaprol, penicillamine, unithiol
Methanol	Ethanol, fomepizole
Methotrexate	Leucovorin
Muscarine	Atropine
Nitrate-induced methemoglobinemia	Methylene blue (speeds conversion to normal hemoglobin)
Opiates	Naloxone
Organophosphates (cholinesterase inhibitors)	Atropine and pralidoxime
Salicylate (aspirin)	Gut decontamination, $NaHCO_3$ to alkalize urine
Thyroxine	Propranolol
Tricyclic antidepressants	Norepinephrine for hypotension, $NaHCO_3$ for cardiotoxicity due to sodium channel blockade
Warfarin	Vitamin K

*Only given along with supportive care if benefits outweigh risks.

c. Emesis has several **contraindications,** including:
   i. Ingestion of a **strong acid or alkali**
   ii. Ingestion of a **low viscosity petroleum distillate** (e.g., kerosene), which could be aspirated during emesis
   iii. An **unconscious** patient or a patient who may become unconscious
   iv. Ingestion of substances that can cause convulsions or a patient who may otherwise have a seizure

d. The primary **complication** of emesis is **aspiration** of the stomach contents which can lead to pneumonitis.

3. Gastric lavage (pumping the stomach) can also be effective.

a. Lavage should be performed **as soon as possible,** as delayed lavage is not very helpful and increases the risk of aspiration.

b. **Contraindications are the same** as for emesis, except it can be performed using an endotracheal tube on a comatose patient.

c. **Aspiration of the stomach contents** can also occur with this method.

4. **Water can be used to dilute** a toxic substance, especially a strong acid or base.
5. Osmotic cathartics such as **polyethylene glycol** electrolyte solution (*GoLytely, Colyte*) will reduce the absorption of a toxic substance by enhancing its elimination in the feces, but this is often ineffective.

D. ELIMINATION of toxic substances from the circulation can occasionally be hastened.

1. **The rate of metabolism** of a toxic substance usually cannot be affected, although the hepatotoxicity of acetaminophen can be reduced by this mechanism.
   a. With an **overdose of acetaminophen,** glutathione will be depleted. This results in the buildup of a reactive intermediate that induces **delayed hepatotoxicity.**
   b. **Acetylcysteine,** administered shortly after exposure to acetaminophen, will substitute for glutathione, enhance conjugation of the reactive acetaminophen intermediate, and reduce hepatotoxicity.
2. **Urinary excretion** of a toxic substance can occasionally be enhanced by
   a. Osmotic or loop diuretics that will increase urine flow and enhance clearance of a toxic substance by the kidney (forced diuresis)
   b. **Changing the pH** of the urine will enhance the elimination of some toxic substances by ion trapping (converting the substance to the charged form, which cannot be reabsorbed across the nephron wall)
      i. To be effective, the **pK_a** of the toxic substance should be **near 7.5,** and the V_d must be small.
      ii. **Bicarbonate** enhances elimination of the **salicylates and phenobarbital** (weak acids).
      iii. **Ammonium chloride** enhances the elimination of **phencyclidine and amphetamines** (weak bases).
3. Hemodialysis or peritoneal **dialysis** can be effective if the toxin
   a. Is a small molecule and readily crosses membranes
   b. Has a small V_d, so that much of the substance is in the serum
   c. Has low protein binding, so that much of the substance is in free form
4. Hemoperfusion can also be performed.

II Heavy Metal Toxicity and Chelators

A. CHELATORS are flexible molecules containing nucleophiles (–NH, –SH, –OH) that bind heavy metals. When heavy metals have been absorbed, chelators should be administered as soon as possible after exposure. A metal–chelate complex is formed which is then excreted.

1. **Dimercaprol** (*BAL*) chelates arsenic, mercury, gold, and lead.
   a. It must be administered **parenterally.**
   b. Dimercaprol has multiple side effects and should not be used to treat chronic metal poisoning, as it may redistribute Ar and Hg to the CNS.
   c. **Unithiol** (*Dimaval*) and **succimer** (*Chemet*) are water-soluble derivatives of dimercaprol that chelate mercury, arsenic, and lead. They are administered orally or parenterally.
2. **Penicillamine** (*Cuprimine, Depen*) chelates arsenic, mercury, gold, lead, and copper.
   a. It can be administered **orally.**
   b. Because it is a penicillin derivative, a penicillin allergy can develop.
   c. Wilson's disease is an indication for use.
3. **Deferoxamine** (*Desferal*) and **deferasirox** (*Exjade*) chelate iron.
   a. Deferoxamine must be administered **parenterally,** but deferasirox can be administered **orally.**

b. Hemochromatosis is an indication for use.
c. An unusual side effect is that the urine turns red.

4. Edetate calcium disodium **(EDTA)** (*Calcium Disodium Versenate*) binds many heavy metals but is used primarily to treat lead and radionuclide poisoning.
   a. It must be administered **parenterally** because it is highly water soluble**.**
   b. **Nephrotoxicity** is a major limitation of this chelator, but it can be reduced by sufficient hydration.
   c. **Sodium EDTA is not used** because it will chelate endogenous calcium and can induce hypocalcemic tetany.
5. **Prussian blue** (*Radiogardase*) chelates radionuclides such as thallium and cesium. It is part of the Center for Disease Control and Prevention's strategic national stockpile.

B. HEAVY METALS FORM CHELATES WITH NATURAL SUBSTANCES IN THE BODY. It is this phenomenon that leads to their toxicity.

1. **Lead** is handled much like calcium in the body.
   a. **Accumulation** occurs first **in soft tissues** (e.g., kidney), and then **in bone, teeth, and hair.**
   b. Lead can be mobilized from bone by the parathyroid hormone.
   c. **Chronic poisoning** from lead is the most common problem, and the symptoms are diverse and nonspecific, including:
      i. **Neurological effects** (e.g., mental retardation, especially in children)
      ii. **Peripheral neuritis** (weakness in extensors [wrist drop])
      iii. **GI lead colic** (spasmodic contraction of intestinal walls)
      iv. **Nephropathy** (fibrosis and sclerosis)
      v. **Anemias** (lead interferes with heme synthesis)
      vi. **Reproductive effects** (risk factor for stillbirth and spontaneous abortion with large exposures)
      vii. **Cardiovascular** (hypertension)
   d. **Treatment** involves the use of chelators.
      i. Both **calcium disodium EDTA** and **dimercaprol** are used initially.
      ii. Long-term deleading is performed with **oral penicillamine** or oral **succimer** (*Chemet*), another lead chelator.
2. **Mercury** forms covalent bonds with sulfur-containing compounds. Elemental mercury, mercury salts, and organomercury compounds are all toxic and can remain in the body for months to years.
   a. **Cell membranes and enzymes** (e.g., cytochrome oxidase) are damaged.
   b. **Acute poisoning** can occur by several routes of exposure.
      i. Ingestion of mercury induces a **GI syndrome.**
      ii. Inhalation induces **pneumonitis.**
      iii. Absorption through the skin.
      iv. **Renal tubular necrosis** occurs with any route of exposure.
   c. **Chronic poisoning** leads to
      i. **Neurologic and psychological complications,** especially with methylmercury, which is very lipid soluble
      ii. **Nephrotoxicity** (renal tubular necrosis and failure)
      iii. **Fetal toxicity** (mental retardation, cerebral palsy)
   d. **Treatment** of acute mercury poisoning involves the administration of
      i. **Fluids** to help reduce nephrotoxicity
      ii. **Chelators**
         (a) **Dimercaprol** is used for mercury salt poisoning, but it should not be used for elemental mercury or alkyl mercury compounds.
         (b) **Penicillamine** is used for mercury vapor poisoning.

(c) **Succimer, unithiol,** or **N-acetylcysteine (NAC)** may be effective for methylmercury poisoning.

3. **Arsenic** binds sulfhydryl groups, leading to enzyme inhibition, or substitutes for phosphate in adenosine triphosphate (ATP). It binds to keratin and is deposited in hair, nails, and skin.
   a. Arsenic is still used as a drug to treat some cancers and trypanisomiasis. However, arsenic is a recognized carcinogen for lung, skin, and bladder cancers.
   b. **Acute** poisoning induces
      i. **GI syndromes**
      ii. **Circulatory collapse** (hypotension and shock)
      iii. **Pancytopenia**
      iv. **CNS neuropathies**
      v. A diagnostic feature is a **garlic odor** on the breath
   c. **Chronic** arsenic poisoning leads to **peripheral neuropathies, fatigue, skin changes,** and **anemia.**
   d. **Arsine gas poisoning** causes hemolysis and renal failure.
   e. **Treatment** of acute arsenic poisoning involves the administration of
      i. **Fluids**
      ii. **Vasopressors**
      iii. **Dimercaprol, unithiol,** or **succimer**
   f. **Treatment** of chronic arsenic poisoning involves the administration of **dimercaprol or penicillamine.**
4. **Iron** is very corrosive to the GI tract in high dosages, especially to young children.
   a. **Acute** ingestion induces a **hemorrhagic GI necrosis,** resulting in the development of **shock and metabolic acidosis.**
   b. **Treatment** involves
      i. **Lavage with bicarbonate,** which yields ferrous carbonate, a substance that is not absorbed
      ii. **Fluids**
      iii. **Correction of the acidosis**
      iv. **Deferoxamine** or **deferasirox,** two potent iron chelators

III Other Toxic Substances

A. CARBON MONOXIDE induces hypoxia that cannot be detected using a pulse oximeter.
1. **It acts by**
   a. **Forming carboxyhemoglobin.** The affinity of carbon monoxide for hemoglobin is 200 times greater than the affinity of oxygen for hemoglobin.
   b. **Decreasing the dissociation of oxygen** from oxyhemoglobin.
2. **Treatment for carbon monoxide** toxicity involves one of the following:
   a. Inhalation of fresh air
   b. Artificial ventilation
   c. 100% oxygen, which shortens the half-life of the carboxyhemoglobin

B. CYANIDE has a high affinity for ferric (Fe^{3+}) iron.
1. **Cytochrome oxidases** in mitochondria, which contain Fe^{3+}, are inhibited.
   a. Cellular respiration is decreased.
   b. Cytotoxic hypoxia is induced.
2. **Specific treatment** for poisoning includes administration of:
   a. **Nitrite** to induce **methemoglobinemia;** methemoglobin binds cyanide, drawing the cyanide off the cytochrome oxidases.

b. **Thiosulfate,** which converts the cyanide on the methemoglobin to thiocyanate. The thiocyanate is then excreted.

C. HYDROGEN SULFIDE also **inhibits cytochrome oxidases. Treatment** involves the administration of **nitrites** to induce **methemoglobinemia,** which binds the sulfide.

D. SULFUR DIOXIDE forms sulfurous acid, which irritates the eyes, mucous membranes, and skin. It also can cause bronchial constriction and respiratory irritation.

E. NITROGEN DIOXIDE AND OZONE are deep lung irritants that can cause pulmonary edema and respiratory irritation.

F. CARBON TETRACHLORIDE (a halogenated hydrocarbon) has many toxic effects.
1. **Acute** poisoning leads to
   a. **CNS depression** with respiratory depression
   b. **Arrhythmias,** due to sensitization of the myocardium to catecholamines
2. **Chronic** poisoning leads to a disruption of cell membranes, resulting in
   a. **Hepatotoxicity**
   b. **Nephrotoxicity**
3. Other halogenated hydrocarbons (e.g., chloroform) can also cause these symptoms to varying degrees.

G. ACUTE BENZENE EXPOSURE can lead to CNS depression, whereas chronic exposure can lead to bone marrow toxicity and leukemia. **Toluene** can also cause CNS depression, but the bone marrow toxicity seen with chronic benzene exposure does not occur with toluene exposure.

H. The pesticide dichlorodiphenyltrichloroethane **(DDT) is very lipid soluble.**
1. It is **concentrated in fat.**
   a. Elimination from the body is extremely slow (1%/day).
   b. It gets into the **food chain,** and biomagnification occurs.
      i. **Biomagnification** describes the increasing concentration of a toxic substance that is seen in predators at the higher levels of the food chain due to bioaccumulation.
      ii. **Bioaccumulation** occurs when the intake of a toxic substance exceeds the organism's ability to metabolize it, so that the toxin concentrates in the tissues.
2. **Acute** toxicity results from the **blockade of potassium permeability changes, inactivation of sodium channels,** and **interference with calcium transport** in nerve membranes. This can induce tremors and convulsions due to enhanced neuron excitability, although death does not occur in humans.

I. THE HERBICIDE PARAQUAT increases the formation of a **superoxide anion radical** that attacks lipids and produces **pulmonary injury.** This pulmonary toxicity may be delayed, such that several weeks pass between ingestion of paraquat and death.

J. ORGANOPHOSPHORUS PESTICIDES such as **malathion** are acetylcholinesterase inhibitors that have neurological and psychological effects. Some of these compounds also phosphorylate a neural esterase, leading to a delayed-onset neuropathy.

K. THALIDOMIDE is a teratogen that **alters organogenesis** (the action of most teratogens), leading to **phocomelia.**

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