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ВрачитаЛЛа
Frank H. Netter was born in 1906 in New York City. He studied art at the Art Student’s League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr Netter’s notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

Icon Learning Systems acquired the Netter Collection in July 2000 and continues to update Dr Netter’s original paintings and to add newly commissioned paintings by artists trained in the style of Dr Netter.

Dr Netter’s works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book Netter Collection of Medical Illustrations, which includes the greater part of the more than 20,000 paintings created by Dr Netter, became and remains one of the most famous medical works ever published. The Netter Atlas of Human Anatomy, first published in 1989, presents the anatomical paintings from the Netter Collection. Now translated into 11 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities, but more importantly, for their intellectual content. As Dr Netter wrote in 1949, “... clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration if it does not serve to make clear some medical point.” Dr Netter’s planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.

ABOUT THE AUTHORS

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We knew that this book was going to attain its goal when we began to work with James A. Perkins, MS, MFA. We had seen his artwork in previous publications, so his artistic talents were known, but the pleasant interactions and his contributions to the subject matter were an unexpected bonus. The arrival of each new illustration was something looked forward to. He and the other talented artists created illustrations that capture not only the visual aspect of the topic, but also its educational essence. It is anticipated that class after class of students will remember this artwork when they think of pharmacologic principles.

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Robert B. Raffa, PhD
Scott M. Rawls, PhD
Elena Portyansky Beyzarov, PharmD
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<tbody>
<tr>
<td>5-FU</td>
<td>5-fluorouracil</td>
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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
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<tr>
<td>5-ISMN</td>
<td>isosorbide-5-mononitrate</td>
</tr>
<tr>
<td>6-MP</td>
<td>mercaptopurine</td>
</tr>
<tr>
<td>6-TG</td>
<td>thioguanine</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>ACTH</td>
<td>corticotropin</td>
</tr>
<tr>
<td>ADH</td>
<td>antidiuretic hormone</td>
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<tr>
<td>ADME</td>
<td>absorption, distribution, metabolism, and elimination</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
</tr>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
</tr>
<tr>
<td>Asp</td>
<td>aspartate</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>ATPase</td>
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</tr>
<tr>
<td>AV</td>
<td>atrioventricular</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
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<tr>
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<tr>
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<td>Centers for Disease Control</td>
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<td>cGMP</td>
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<td>CHF</td>
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</tr>
<tr>
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<td>combination oral contraceptive</td>
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<tr>
<td>COPD</td>
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<td>cyclooxygenase</td>
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<tr>
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<td>cerebrospinal fluid</td>
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<tr>
<td>CTZ</td>
<td>chemoreceptor trigger zone</td>
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<tr>
<td>DM</td>
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</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRC</td>
<td>dose-response curve</td>
</tr>
<tr>
<td>DRSP</td>
<td>drug-resistant <em>Streptococcus pneumoniae</em></td>
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<td>DUMBELS</td>
<td>diarrhea, urination, miosis, bronchoconstriction, excitation (skeletal muscles and central nervous system), lacrimation, and salivation and sweating</td>
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<td>ED&lt;sub&gt;50&lt;/sub&gt;</td>
<td>median effective dose</td>
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<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>EPI</td>
<td>epinephrine</td>
</tr>
<tr>
<td>EPSP</td>
<td>excitatory postsynaptic potential</td>
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<td>ER</td>
<td>estrogen receptor</td>
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<tr>
<td>ESWL</td>
<td>extracorporeal shock wave lithotripsy</td>
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<tr>
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<td>growth hormone–releasing hormone</td>
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<td>G protein–coupled receptor</td>
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<td>LD₅₀</td>
<td>median lethal dose</td>
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<tr>
<td>LT</td>
<td>leukotriene</td>
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<td>mAChR</td>
<td>muscarinic cholinergic receptor</td>
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<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
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<tr>
<td>MoAb</td>
<td>monoclonal antibody</td>
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<tr>
<td>MPA</td>
<td>medroxyprogesterone acetate</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MTX</td>
<td>methotrexate</td>
</tr>
<tr>
<td>nAChR</td>
<td>nicotinic cholinergic receptor</td>
</tr>
<tr>
<td>NANC</td>
<td>nonadrenergic-noncholinergic</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NERD</td>
<td>nonerosive esophageal reflux disease</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
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<tr>
<td>NK</td>
<td>natural killer</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<tr>
<td>NNRTI</td>
<td>nonnucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal antiinflammatory drug</td>
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<tr>
<td>OC</td>
<td>oral contraceptive</td>
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<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
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<tr>
<td>PD</td>
<td>pharmacodynamic</td>
</tr>
<tr>
<td>PDE</td>
<td>phosphodiesterase</td>
</tr>
<tr>
<td>Ph</td>
<td>Philadelphia chromosome</td>
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<tr>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic</td>
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<td>PNS</td>
<td>peripheral nervous system</td>
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<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
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<td>PPI</td>
<td>proton pump inhibitor</td>
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<td>PRL</td>
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<td>PTU</td>
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<tr>
<td>PUVA</td>
<td>psoralen plus ultraviolet A light</td>
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<td>RAI</td>
<td>radioactive iodine</td>
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<td>SA</td>
<td>sinoatrial</td>
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<tr>
<td>SAR</td>
<td>structure-activity relation</td>
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<tr>
<td>SERM</td>
<td>selective estrogen receptor modulator</td>
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<tr>
<td>SNS</td>
<td>somatic nervous system</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>T₃</td>
<td>triiodothyronine</td>
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<td>T₄</td>
<td>thyroxine</td>
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<td>TCA</td>
<td>tricyclic antidepressant</td>
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<tr>
<td>TRF</td>
<td>thyrotropin-releasing factor</td>
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<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
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<td>thyroid-stimulating hormone</td>
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<td>UTI</td>
<td>urinary tract infection</td>
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<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>VC</td>
<td>vomiting center</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella-zoster virus</td>
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OVERVIEW

Pharmacology is the study of drug action at both the molecular and the whole-organism levels. At the molecular level, drug action refers to the mechanism by which a drug or other molecule produces a biologic effect. At the whole-organism level, drug action refers to the therapeutic effects of a drug and its unwanted (ie, adverse, or side) effects. Drugs can produce biologic effects in several ways, eg, killing harmful invading organisms such as bacteria and viruses; killing the body's own cells that have gone awry (eg, cancer cells); neutralizing acid (mechanism of action of antacids); modifying ongoing underactive or overactive physiologic processes. In the last case, direct replacement of chemicals (eg, insulin) or indirect or more subtle modulation of biochemical processes (eg, inhibition of enzyme action) may be required.

Drugs can be said to modify the communication system within an organism. The modification should not interfere with the fidelity of the signal and should not activate unwanted compensatory responses. Drugs should selectively target specific cellular components that function in the normal signaling process. The study of molecular, biochemical, and physiologic effects of drugs on cellular systems and drug mechanisms of action is termed pharmacodynamics.

Equally important to drug action are the absorption, distribution, metabolism, and elimination (ADME) of drugs. The study of these processes (which involves the movement of the drug molecules through various physiologic compartments) and how they affect drug use and usefulness is termed pharmacokinetics. Complete understanding of the action of a drug involves knowledge of both pharmacodynamic (PD) and pharmacokinetic (PK) properties. In addition, the physical characteristics of an individual patient (eg, age, sex, weight, liver function, kidney function) dictate how the PD and PK characteristics of the drug are manifested.

Pharmacognosy is the study of drugs from natural sources. Pharmacy is the clinical practice devoted to the formulation and proper and safe distribution and use of therapeutic agents.

Therapeutic drug action involves interaction between an exogenous chemical and the endogenous biochemical target. The study of chemical structures of drugs and the study of normal and abnormal physiology are thus interrelated. Only by a clear understanding of the anatomy, physiology, and pathology of the organism can the proper drugs be designed and administered. The study of pharmacology therefore involves broad-based knowledge of the drug molecule, the organism, and the interaction between them.
Invading organisms such as bacteria, viruses, fungi, and helminths can threaten the health of the host. Cancer cells are abnormal and differ from normal cells in terms of chromosome alterations, uncontrolled proliferation, dedifferentiation and loss of function, and invasiveness. Drug therapy (chemotherapy) aims to kill invading organisms or aberrant cells directly or to reduce their numbers to a level that can be managed by a host-mounted defense. Typical drug targets for invading organisms include biochemical processes.
needed for cell wall synthesis or integrity. Drug targets for abnormal cells include cell-cycle regulation and enzymes involved in protein synthesis, so as to inhibit cancer cell replication. In both cases, optimal treatment occurs when a drug or combination of drugs displays selectivity against invaders or cancer cells. Such therapy—with separation between a desired therapeutic effect and unwanted (adverse or side) effects—minimizes harmful drug effects.
When the amount of an endogenous substance is insufficient for normal functions, it may be possible to supply it from sources outside of the body (exogenous supply). Examples include insulin used for diabetes and dopamine used for parkinsonism. The exogenous material may originate from humans, animals, microorganisms, or minerals or it may be synthesized—a product of technology. It can be the substance itself or a precursor metabolized to the substance (e.g., levodopa is metabolized to dopamine). Excess amounts can also be harmful, e.g., excess stomach acid can cause or exacerbate ulcer formation. Gastric acid levels can be reduced directly by using an antacid (a base such as calcium carbonate or magnesium hydroxide). An alternative approach—inhbiting acid secretion—can be achieved by antagonizing the action of histamine on H₂ receptors of parietal cells (e.g., with cimetidine) or by interfering with the proton pump that transports acid across parietal cells (e.g., with omeprazole).

**Figure 1-2 Replenish or Neutralize Endogenous Chemicals**
Drugs use different mechanisms to modify normal homeostatic and biochemical communication in cellular and physiologic processes. They mimic (e.g., carbachol) or block neurotransmitters that transmit information across synapses. Chemical substances such as hormones also act over long distances in the body. Drugs that mimic hormones include oxandrolone; mifepristone blocks hormone action. Drugs selectively modify physiologic processes by targeting enzymes, DNA, neurotransmitters, or other chemical mediators or components of signaling processes such as receptors. The total effect depends on whether a drug promotes or reduces endogenous activity. Drugs with other mechanisms of action are chelating agents (contain metal atoms that form chemical bonds with toxins or drugs), antimetabolites (masquerade as endogenous substances but are inactive or less active than these substrates), irritants (stimulate physiologic processes), and nutritional or replacement agents (e.g., vitamins, minerals).
Communication (transmission of information) across synapses occurs via chemical messengers—neurotransmitters—stored in vesicles in presynaptic neurons. Action potentials at presynaptic axon terminals initiate steps that release neurotransmitter molecules into a synapse, which cross the synaptic cleft and bind reversibly to postsynaptic receptors. Receptor activation leads to cellular response. Receptor activators (eg, drugs) are agonists; antagonists are drugs that combine with but do not activate receptors. Transmitters are removed from synapses by enzymatic destruction, diffusion, and active reuptake into presynaptic neurons. Major peripheral neurotransmitters are acetylcholine and catecholamines (eg, epinephrine, dopamine). In the brain and spinal cord, major excitatory neurotransmitters are glutamate and aspartate; major inhibitory neurotransmitters are GABA and glycine. 5-HT, or serotonin, and neuropeptides are other neurotransmitters.
**Figure 1-5 Synapse Morphology**

A **synapse** is a region including the axon terminal of a presynaptic neuron, the plasma membrane of the postsynaptic (receiving) cell, and the physical space between the cells (synaptic cleft). Postsynaptic cells can be neurons or other cells (e.g., effector cells in muscle). At synapses, electrical transmissions—action potentials along presynaptic neurons—are translated into chemical signals, which lead to postsynaptic cell responses: increase (excitation), decrease (inhibition), or modulation of neuron activity or biochemistry. Synaptic transmission involves many steps, all possible drug targets. Steps occur in presynaptic neurons (e.g., neurotransmitter synthesis and storage in vesicles), at presynaptic membranes (e.g., vesicle docking with membranes, neurotransmitter exocytosis), in synaptic clefts (e.g., enzymatic reuptake), on postsynaptic membranes (e.g., binding to receptors, change in ion channel function), and in postsynaptic neurons (e.g., effects on second-messenger transduction).
Receptors are the first molecules in or on a cell that respond to a neurotransmitter, a hormone, or another endogenous or exogenous signaling molecule (ligand) and transmit messages (via transduction) from the molecule to the cell machinery. Receptors ensure fidelity of the intended communication by responding only to the intended signaling molecule or to molecules with closely related chemical structures (such as drugs with the required shape). Receptors are composed primarily of long sequences (typically hundreds) of amino acids. The body has dozens of receptor types to maintain communication pathways that must be differentiated from each other and serve different purposes. An individual cell may express one or many types of receptors, with the number depending on age, health, or other factors.
**Figure 1-7 Receptor Subtypes**

Receptors can be classified into subtypes, as first noted for receptors for the structurally related catecholamines epinephrine, isoproterenol, and norepinephrine. The order of potency (structure-activity relation, or SAR) of these drugs in some tissues is epinephrine > isoproterenol > norepinephrine; in other tissues, it is the reverse. Catecholamine receptors (adrenergic) exist in pharmacologically distinct types (α and β) and subtypes (eg, α₁, α₂, and so on). Subtypes are differentiated by amino acid sequence and post-translational processing, as shown for dopamine receptor subtypes. A clinical example of receptor subtype targeting involves asthma treatment. Activation of adrenoceptors in the lung relaxes smooth muscles and dilates bronchioles to ease breathing. To avoid stimulation of heart adrenoceptors, β₂-selective drugs (eg, salbutamol, metaproterenol, ritodrine, terbutaline) were developed to activate only lung adrenoceptors; β₁-selective drugs would affect the heart.
Certain molecules have physiochemical and stereochemical (3-dimensional) characteristics that impart affinity for a receptor, affinity being the quantifiable tendency of a drug molecule to form a complex with (bind to) a receptor. Binding involves interaction between a ligand molecule (L) and a receptor molecule (R) to form a ligand-receptor complex (LR): L + R ↔ LR. Affinity is quantified by the reciprocal of the equilibrium constant of this interaction and is commonly reported (often designated $K_d$ or $K_i$); the greater the affinity is, the smaller the $K$ value is. Drugs can activate receptors and thus elicit a biologic effect (ie, have intrinsic activity, or efficacy). Such molecules have shapes complementary to receptor shapes and somehow alter the activity of a receptor. Full agonists possess high efficacy and can elicit a maximal tissue response, whereas partial agonists have intermediate levels of efficacy (the tissue response is submaximal even when all receptors are occupied).
Figure 1-9 Antagonists

Some molecules have physiochemical and stereochemical traits that impart affinity for a receptor but cannot activate it. Such molecules bind to (occupy) receptors and block access of agonists, thereby reducing the effects of agonists. Such pharmacologic antagonists do not elicit biologic effects directly; they modify the physiologic process that is maintained by agonist action (e.g., by neurotransmitters). Examples of drugs that are receptor antagonists are atropine (muscarnic cholinergic), d-tubocurarine (nicotinic cholinergic), atenolol (adrenoceptor), spironolactone (mineralocorticoid), diphenhydramine (histamine H1), ondansetron (5-HT), flumazenil (benzodiazepine), haloperidol (dopamine), and naloxone (opioid). Chemical antagonism (e.g., neutralization of gastric acid by chemical bases) or physiologic antagonism, in which an effect of one drug opposes an effect of another agent (e.g., epinephrine used to counteract the histamine response to a bee sting), of drug effects can also occur.
One enantiomer fully occupies the receptor binding pocket...

... while the other enantiomer is only a partial match.

**Figure 1-10 Stereochemistry and 3-Dimensional Fit**

One enantiomer of a racemic pair is often observed to bind more avidly to (has greater affinity for) a receptor than does the other enantiomer of the pair. Because the only difference between them is the stereochemistry, the 3-dimensional shape of a molecule must be a crucial characteristic for binding affinity. The relation between chemical structure and biologic response is known as the SAR and is a common focus of drug discovery efforts. Computer modeling of the ligand-receptor fit provides a visual representation of the fit of a ligand into the receptor pocket. It can also be used for virtual screening for goodness of fit of potential drug candidates before they are synthesized.
**Figure 1-11 Receptor-Effecter Coupling**

In most cases, a drug activates or inhibits only 1 molecule in a long series of biochemical reactions. When a drug binds to a receptor on a cell membrane, the extracellular drug signal must be passed to the intracellular physiologic processes, i.e., it must be converted (transduced) to an intracellular message, the process termed signal transduction, which occurs via many mechanisms. The effect of a drug depends on its receptors, the transduction pathways to which it is coupled, its level of receptor expression in cells, and its cellular response capacity. In the simplest case (A), a drug binds to 1 receptor coupled to 1 effector (transduction pathway) and produces 1 effect. A drug can bind to 1 receptor coupled to more than 1 effector (B) so it produces more than 1 effect in the same or different cells. A drug can also have affinity for more than 1 receptor (C), with each receptor coupled to a different effector. Effect 2 can be a therapeutic end point or an adverse effect.
Figure 1-12 Signal Transduction and Cross Talk

Receptors provide specificity for cell responses to only certain extracellular chemical signals. Different receptor types can have 1 or more intracellular second-messenger transduction mechanisms without loss of ligand specificity. Different ligands acting through different receptors can thus have the same or different effects via 1 messenger system. All ionotropic (ion channel) receptors shown here regulate Cl⁻ influx; neurons and cells are hyperpolarized (transmembrane potential is more negative) and are less likely to fire (generate action potentials). The effect depends on ligand concentration, cell type, and expression of receptor and second messenger system components. Integrated communication between and within cells thus occurs. A cell with multiple receptor types can be regulated by various ligands and by interaction among receptor types. Interaction among receptor types constitutes receptor cross talk, which allows cells diverse and sophisticated response possibilities.
Figure 1-13  Second-Messenger Pathways

Signal transduction commonly occurs by means of several general mechanisms: (1) ligand-gated ion channels modulate the influx or outflow of ions that alter transmembrane potential or modulate intracellular biochemical reactions (e.g., the calcium-calmodulin system); (2) ligand binding to GPCRs modulates enzyme activity (e.g., adenylyl cyclase or phospholipase C); (3) ligand binding activates a catalytic portion of the receptor (e.g., tyrosine kinase activity); (4) a ligand enters the cell nucleus and alters protein (receptor) synthesis; and (5) a ligand amplifies or attenuates nitric oxide synthesis and the subsequent production of cGMP.
Figure 1-14 Ligand-Gated Ion Channels

Some drugs bind to molecules (ion channels) that form transmembrane pores for ions (usually Na⁺, K⁺, Ca²⁺, Cl⁻), the channels being composed of many subunits. A drug’s binding to 1 or more subunits modifies the receptor function (ion passage), i.e., the channels are ligand gated. A single ion channel can accommodate multiple drugs, with each drug binding to a different subunit or site on or within (extracellular, transmembrane, or intracellular) the channel. Membrane-bound channels include nicotinic cholinergic, ionotropic glutamate, GABAₐ, 5-HT₁ (serotonin), and glycine receptors. Intracellular channels include those for Ca²⁺ on the sarcoplasmic reticulum, endoplasmic reticulum, and mitochondria. Barbiturates, for example, bind to sites on the GABAₐ receptor complex, which increases Cl⁻ influx and produces increased resting transmembrane potential difference and decreased cell excitability. One drug that modifies activity of an intracellular ligand-gated ion (Ca²⁺) channel is caffeine.
Some drugs bind to receptors whose transduction involves a physical association of a receptor with G proteins—the GPCRs. GPCRs, a large family of receptors, mediate effects of neurotransmitters, hormones, and drugs. GPCRs are large proteins that span a cell membrane many times; many drug-related GPCRs, the 7-TM GPCRs, do this 7 times (amino terminus is outside the cell, carboxy terminus is inside). Examples are receptors for epinephrine, norepinephrine, dopamine, 5-HT, ACh (muscarinic), histamine, adenosine, purines, GABA, glutamate, opioids, and vasopressin. Binding of an agonist (drug or endogenous ligand) to a GPCR activates associated G proteins by GTP-GDP exchange, which stimulates dissociation of α from βγ subunits. Inherent GTPase activity within the α subunit restores the initial conditions. One receptor can be coupled to more than 1 type of G protein. Some G proteins activate and others inhibit biochemical steps in signal transduction.

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**Figure 1-15  G PROTEIN–COUPLED RECEPTORS**

α-Adrenergic receptor, a G protein–coupled receptor with 7 transmembrane α helices.
FIGURE 1-16  **Trk Receptors**

Some drugs bind to receptors that are composed of an extracellular ligand-binding domain, a transmembrane region, and an intracellular domain that has tyrosine kinase (tk) activity. When activated, these receptors catalyze the intracellular phosphorylation of tyrosine residues in target proteins that are important for cellular growth and differentiation and responses to metabolic stimuli. Examples of ligands (and drug mimetics) that bind to trk receptors include insulin, nerve growth factor, platelet-derived growth factor, cytokines, and other growth factors. It is hypothesized that agonists cause a change in the conformation of the receptor, thereby promoting its action as a tyrosine kinase.
**Figure 1-17 Nuclear Receptors**

Some drugs produce their effects by binding to receptors located in the cytoplasm or the nucleus of the cell. For example, steroid hormones, thyroid hormone, corticosteroids, vitamin D, and retinoids diffuse through the plasma membrane of the cell and bind to their respective receptors in the cytoplasm. The complex or activated receptors then act as transcription factors by entering the nucleus and binding to DNA hormone-response elements within the nucleus. The DNA-binding domain recognizes certain base sequences, which leads to promotion or repression of particular genes. Regulation of gene transcription by this mechanism can lead to long-term effects. One class of nuclear receptors functions in increased expression of drug-metabolizing enzymes induced by many drugs.
Figure 1-18 Up-regulation and Down-regulation of Receptors

The type and number of receptors that a cell expresses are the net effect of simultaneous receptor synthesis and destruction. In addition to other factors, the number of receptors is modified by long-term exposure to drugs. Chronic stimulation by agonists tends to decrease receptor number (down-regulation), whereas chronic inhibition by antagonists tends to increase the number of receptors (up-regulation). The cellular response opposes the drug-induced effect and may be a defense mechanism. Also, the effect of subsequent administration of drug is greater (or less) than that of initial exposure, and abrupt withdrawal of drug leaves the cell overresponsive or underresponsive to the endogenous ligand. Downregulation is one mechanism by which pharmacologic tolerance can occur, in which increasing doses of a drug must be used to achieve the same effect.
Figure 1-19 Dose-Response Curves

A direct relation exists between the concentration or dose of a drug and the magnitude of its biologic effect. As a graph, this relation is commonly referred to as a DRC. A DRC can be plotted by using a continuous (graded) or binary (quantal) measure of effect and a linear or logarithmic representation of dose (the latter producing the familiar S-shaped DRC). Each of a drug's usually multiple effects can be represented by a DRC. When the effect is mediated by receptors, the shape of the DRC is consistent with a reversible interaction between ligand (L) and receptor (R): \( nL + mR \rightleftharpoons L^nR^m \), where \( m \) and \( n \) usually equal 1. The general relation between ligand [L] (drug concentration) and effect \( E \) is given by

\[
E = \frac{E_{\text{max}} \cdot [L]}{[L] + [L]_{50\% \text{ effect}}}
\]
**Figure 1-20 Potency**

Potency is the drug quantity required for a specified level of a specified effect. For the drug with a DRC given by line A (A), potency is 1 mg/kg for the 50% level of effect A. The 50% level is usually used, with potency shown as an ED\textsubscript{50} value. Potency represents ADME and PD properties. Potency for desirable and adverse effects can be established: the potency of one drug for effects A, B, and C (A) is 1, 10, and 100 mg/kg. Potency is thus related to the relative position of a DRC along the horizontal axis. Potency is also used to compare drugs with similar effects (B): 1 mg/kg of drug A is needed for 50% of the effect. Ten times the amount of drug B (10 mg/kg) is required for this level, so drug A is more potent than drug B; both are more potent than drug C. Potency is clinically important only if a drug is expensive or the amount needed is too large. The ED\textsubscript{50}/LD\textsubscript{50} ratio (therapeutic index) is used to compare potency (ED\textsubscript{50}) with lethality (LD\textsubscript{50}).

**Figure 1-21 Efficacy**

At a molecular level, efficacy is the ability of a drug to produce an effect (agonists have positive efficacy, and antagonists have zero efficacy) and the degree of effect per drug molecule bound. At an organism level, it refers to the maximum effect of a drug. Maximum effects of drugs whose DRCs are given by lines A, B, and C is 100%, 50%, and 25%, with the order of efficacy being A > B > C. Efficacy is thus associated with the position of a DRC along the vertical axis. Drugs with a maximal possible effect are full agonists; partial agonists are drugs whose effect is less than maximal. Some agonists elicit this effect by occupying less than 100% of available receptors, and the other receptors are called spare receptors. Efficacy is associated with the molecular actions of a drug, not its PK properties. Efficacy can be determined for each of a drug’s effects. Unlike potency, efficacy is relatively important clinically because it indicates the maximum attainable effect of a drug.
Drug receptors were first thought to be binary switches—either on (activated) or off (resting). Agonists turned the switch on; antagonists blocked agonists’ access to receptors. Today, a receptor is viewed as a continuous switch, with the resting state between on or off. Two types of agonists can exist at these receptors: those that move the receptor from resting toward on and those that move it toward off. Both types are agonists, because both have affinity and intrinsic activity. For example, the channel pore of a ligand-gated ion-channel receptor may have a certain resting diameter; some agonists bind to the receptor and increase pore size (increase ion flux), whereas others decrease pore size (decrease ion flux). Which agonist is said to be the inverse of another is arbitrary and depends on which was discovered first. Classic examples of inverse agonists reduce Cl⁻ flow through a GABA₄ receptor and cause rather than inhibit anxiety. The same antagonist should block both types of agonist.
**Figure 1-23 Antagonists: Surmountable (Reversible) and Nonsurmountable (Irreversible)**

The ability of an antagonist to alter an agonist effect depends on the affinity of the antagonist for the shared receptor. With weak, reversible antagonist binding (e.g., hydrogen bonds), thermal agitation causes some antagonist molecules to uncouple from receptor and agonists successfully compete for receptor sites. The agonist DRC with surmountable antagonists shifts to the right along the horizontal (dose) axis—the same maximal effect can occur. If antagonist molecules bind to a receptor irreversibly (e.g., covalent chemical bonds) or irreversibly alter receptor sites, those sites are unavailable for agonist molecules. Antagonist molecules do not uncouple from a receptor; agonist molecules cannot compete for unoccupied sites. Fewer drug-receptor complexes mean diminished drug effect. The agonist DRC with irreversible antagonists shifts to the right along the dose axis and downward. The same maximal effect cannot be achieved by the agonist at any dose (nonsurmountable antagonism).
Figure 1-24 Routes of Administration

The oral route is generally the most convenient, economic, and safe. Most drugs are rapidly and well absorbed along the GI tract, although some (e.g., insulin) are not because of inactivation by enzymes. Drugs given intravenously enter the systemic circulation rapidly; drugs given intra-arterially reach a target site in high concentration. Subcutaneous and intramuscular routes rely on diffusion of the drug into the bloodstream, which can be influenced by warming or cooling the area or by other drugs. Inhalation produces a rapid response to a drug because of the large surface area of the lungs and their extensive blood supply. Transdermal application is becoming an increasing popular mode of administration. Other routes or sites of drug administration include dermal (for local action), mucous membranes (for systemic action), insufflation (lungs), intraneural (nerves), optic (eyes), otic (ears), intraperitoneal (abdomen), and epidural (spinal cord).
Drugs that are administered into the GI tract (orally or rectally) are subject to a first-pass effect. Venous drainage of blood from most portions of the GI tract enters the portal circulation, which delivers blood to the liver. In the liver (sometimes the gut wall), drug molecules can be biotransformed (term preferred to metabolized) to less active substances (usually). The amount of active drug that enters the systemic circulation after GI administration is thus less—by the amount of the first-pass effect—than that after another route of administration. The magnitude of this effect on a drug’s systemic bioavailability ($F$) is expressed as the extraction ratio ($ER$):

$$F = f \times (1 - ER) = f \times (1 - \frac{C_{liver}}{Q})$$

where $f$ is the extent of absorption, $C_{liver}$ is the hepatic clearance, and $Q$ is the hepatic blood flow (normally approximately 90 L/h in a 70-kg person). Two related drugs that have comparable bioavailability and similar $t_{max}$ (time to peak concentration) are said to be bioequivalent.
**Figure 1-26 Membrane Transport**

The biologic membrane is a phospholipid bilayer, a hydrophobic core (lipid layer) between 2 hydrophilic portions (phospho groups). Small molecules can pass through membrane pores. Drugs can pass across membranes by passive diffusion (through lipid or aqueous channels), by active transport (combining with carriers), or by pinocytosis. To cross membranes, most drugs must be both water soluble (hydrophilic or lipophilic) and fat soluble (lipophilic or hydrophobic), which is achieved by weak acids (HA ↔ H⁺ + A⁻) and weak bases (BH⁺ ↔ B + H⁺), whose charged (hydrophilic) and uncharged (lipophilic) forms are in equilibrium. The extent of drug absorption is a function of pH of the drug and pH of the local environment. Equations for determining distribution of protonated and nonprotonated forms of a drug across a membrane are:

- **Acids:** \[ pK_a = pH + \log(\frac{HA}{A^-}) \]
- **Bases:** \[ pK_a = pH + \log(\frac{BH^+}{B}) \]

For reference, pH values in the stomach are 1.0 to 1.5; that in blood plasma is approximately 7.4.
After absorption, drugs enter the systemic circulation and are distributed widely in the body; they leave the bloodstream and enter cells, with the amount entering depending on local blood flow, capillary permeability, and relative drug lipophilicity. Drugs in the blood are either unbound or bound reversibly to plasma proteins (e.g., albumin) in equilibrium. The unbound portion is bioactive. Binding of drugs to these proteins is determined by affinity between drug and protein and protein binding capacity. Only a few binding sites are available, so a high dose can saturate binding sites, and additional drug circulates unbound in the bloodstream. If 2 or more drugs have affinity for the same binding sites, the one with highest affinity will bind, which increases plasma concentration of displaced drug. These effects, which may have clinical consequences, must be considered for the dosing regimen. Drugs with high plasma protein binding (≥95%) include lithium, midazolam, and warfarin (99%).
Because of various anatomical and physiologic features, endothelial cells of the capillaries can limit passage of drugs from the bloodstream to tissues. For example, endothelial cells of brain capillaries, whose tight junctions merge into a continuous wall, are highly impermeable to many substances. Thus, a blood-brain barrier is established that generally limits accessibility of a good number of drugs, many of which are ionized in the blood at pH 7.4, to the brain. Water-soluble drugs, polar drugs, and ionized forms of drugs cannot cross this blood-brain barrier because they cannot pass through slit junctions and have difficulty traversing the lipid cell membrane. Lipid-soluble drugs pass more readily through cell membranes. In the liver, large fenestrations allow most drugs free access to the hepatic interstitium (with subsequent metabolism of the drugs). The placenta limits but does not prevent entry of drugs into the fetal circulation.
**Figure 1-29 Metabolism (Biotransformation) of Drugs**

Drugs undergo biotransformation by many of the same reactions as endogenous compounds. Drugs are usually metabolized to less active and more ionized (water-soluble) forms, but equally or more active metabolites can also be created. An inactive parent drug that forms active metabolites is called a prodrug. Although drug metabolism occurs in almost all tissues, including the GI tract, the liver is the major site because of its strategic place in the portal circulation and its many metabolic enzymes. Two general types of drug metabolic reactions occur: phase 1, involving chemical modification, typically by oxidation, reduction, or hydrolysis; and phase 2, in which an endogenous chemical is covalently attached (conjugated) (glucose conjugation, or glucuronidation, the most common). Drugs often undergo multiple phase 1 and 2 reactions, which produces many metabolites, each with its own pharmacologic profile. Liver disease alters drug metabolism, so appropriate dosage adjustment is required.

<table>
<thead>
<tr>
<th>Conjugation Reaction</th>
<th>Endogenous Conjugant</th>
<th>Intracellular Sites</th>
<th>Common Substrates</th>
<th>Drug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylation</td>
<td>Acetyl-CoA</td>
<td>Cytosol</td>
<td>–OH, –COOH, –NH₂, –NR₂ –SH</td>
<td>Clonazepam, dapsone, isoniazid, sulfonamides, valproate</td>
</tr>
<tr>
<td>Glutathione conjugation</td>
<td>Reduced form of γ-Glu-Cys-Gly (the most common intracellular thiol)</td>
<td>Cytosol and microsomes</td>
<td>Electrophilic benzylic halides, aliphatic nitrate esters, epoxides, and quinines</td>
<td>Acetaminophen, ethacrynic acid</td>
</tr>
<tr>
<td>Gly (amino acid) conjugation</td>
<td>Gly, Glu, others</td>
<td>Mitochondria</td>
<td>–COOH</td>
<td>Benzoic and salicylic acid</td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>UDPGA (uridine-5′-diphospho-D-glucuronic acid)</td>
<td>Microsomes</td>
<td>Hydroxyl, amino, or sulphydryl groups</td>
<td>Acetaminophen, codeine, diazepam, disulfiram, ethylnl estradiol, fentanyl, gaantamine, lorazepam, modafinil, morphine, propanolol, paroxetine, sulfonamides</td>
</tr>
<tr>
<td>Methylation (N, O, and S)</td>
<td>CH₃ from 5-adenosylmethionine (SAM)</td>
<td>Cytosol (eg, COMT)</td>
<td>–OH, –NH₂, –SH</td>
<td>Oxprenolol (N-), clomethiazole and isoproterenol (O-), captopril (S-)</td>
</tr>
<tr>
<td>Sulfate conjugation</td>
<td>3′-Phosphoadenosine-5′-phosphosulfate (PAPS)</td>
<td>Cytosol</td>
<td>–OH, –NH₂</td>
<td>Acetaminophen, ethylnl estradiol, methyldopa, paxoxetine, steroids, trimaterene</td>
</tr>
</tbody>
</table>
CYP Substrate

1A2 Acetaminophen, antipyrine, caffeine, clomipramine, olanzapine, ondansetron, phenacetin, riflozole, ropinirole, tamoxifen, theophylline, warfarin

2A6 Coumarin

2B6 Artemisinin, bupropion, cyclophosphamide, S-mephobarbital, S-mephenytoin, (N-demethylation to nirvanol), propofol, selegiline, sertraline

2C8 Pioglitazone

2C9 Carvedilol, celecoxib, fluvastatin, glimepiride, hexobarbital, ibuprofen, losartan, mefenamic acid, meloxicam, montelukast, nateglinide, phenytoin, tolbutamide, trimethadone, sulfaphenazole, warfarin, ticrynafen, zafirlukast

2C19 Citalopram, diazepam, escitalopram, esomeprazole (S isomer of omeprazole), irbesartan, S-mephenytoin, naproxen, nirvanol, omeprazole, pantoprazole, proglasil, propranolol

2D6 Almotriptan, bustranol, bupropranolol, carvedilol, clomipramine, clozapine, codeine, debrisoquin, dextromethorphan, dexamethasone, fluoxetine (S-norfluoxetine), formoterol, galantamine, guanoxan, haloperidol, hydrocodone, 4-methoxy-amphetamine, metoprolol, mexitilene, olanzapine, oxycodone, paroxetine, phenformin, phentoiazines, propoxyphene, risperidone, selegiline, (deprenyl), sparteine, thioridazine, timolol, tolterodine, tramadol, tricyclic antidepressants, type 1C antiarrhythmics (eg, encainide, flecainide, propafenone), venlafaxine

2E1 Acetaminophen, chloroxazone, enfurane, halothane, ethanol (minor pathway)

3A4 Acetaminophen, alfentanil, almotriptan, amiodarone, astemizole, becloethasone, beclometasone, bepoterone, benzodione, S-bupivacaine, carbamazepine, citalopram, cocaine, cortis, cyclosporine, dapson, delavirdine, diazepam, diltiazem, escitalopram, ethyl estradiol, fentanyl, finasteride, fluticasone, galantamine, gestodone, imatinib, indinavir, irtraconazole, letrozole, lidocaine, loratadine, losartan, lovastatin, macrolides, methadone, miconazole, midazolam, mifepristone (RU-486), montelukast, oxybutynin, paclitaxel, pimecrolimus, pimozone, pioglitazone, progesterone, quinidine, rabeprazole, rapamycin, repaglinide, ritonavir, saquinavir, spinololone, sulfamethoxazole, sufenilant, tacrolimus, tamoxifen, terfenadine, testosterone, tetrahydrocannabinol, tiagabine, triazolam, troleandomycin, verapamil, vinca alkaloids, ziprasidone, zonisamide

27 Dorsocuriciferal (activated)

No/ minimal involvement zolendronic acid

**FIGURE 1-30 CYTOCHROME P-450 (CYP450) ENZYMES**

A major enzyme system that catalyzes phase 1-type drug metabolism reactions is the microsomal CYP450 mixed-function oxidase (monooxygenase) system located in lipophilic membranes of the endoplasmic reticulum in liver, GI tract, lungs, kidney, and other tissues. These enzymes catalyze an oxidation-reduction process that requires CYP450, CYP450 reductase, NADPH (reducing agent), and O2. The enzymes have little substrate specificity; the only common feature of the many drugs metabolized by this pathway is lipid solubility. Drugs can be metabolized by the CYP3A, CYP2D6, CYP2C9, and CYP1A2 isozymes. Known polymorphisms in these enzymes require a drug dosage adjustment. If 2 drugs are metabolized by the same CYP isozyme, they can interfere with each other's normal route or rate of metabolism, and a drug interaction may decrease or increase plasma drug concentrations. An example is PK interaction between fluoxetine (a selective serotonin reuptake inhibitor) and St John's wort.
Multiple factors, including drugs, can either increase or decrease metabolic enzyme activity. Long-term administration of drugs often induces CYP450 activity dramatically by enhancing the rate of synthesis or reducing the rate of degradation of these hepatic microsomal enzymes. Enzyme induction results in more rapid metabolism of the drug and all other drugs metabolized by the same enzymes. As a result, plasma levels and biologic effects of the drugs decrease (except for prodrugs, whose biologic effects increase). Barbiturates are well-known strong inducers of CYP450 enzymes. Other substances can inhibit CYP450 enzymatic activity. In this case, the metabolism of other drugs through this pathway is reduced, which results in increased blood levels of these other drugs. The clinical consequences of the altered blood levels can be greater biologic effects (except for prodrugs) or increased toxicity.
The major route of drug elimination is through the kidneys, which receive one fifth to one fourth of the cardiac output. Other routes are feces and lungs (especially for anesthetic gases). The rate of elimination of most drugs follows first-order kinetics (exponential decline). The time for the plasma levels of a drug to reach half the initial value is the half-life (t½). A notable exception is ethanol, which follows zero-order (linear) kinetics at subintoxicating concentrations. The clearance of a drug from the body is the sum of clearances from all elimination routes, e.g., clearance from the kidney is given by the volume of plasma that is completely cleared of the drug per unit time (usually 1 minute). In this case, the amount of drug in urine is measured. Kidney clearance of drug X (Cₘ) is calculated from drug concentrations in urine (Uₘ) and plasma (Pₘ), and urine volume (V): $CL_X = \frac{(U_m \times V)}{P_m}$. A kidney disorder alters the rate of drug elimination, so the dosage must be adjusted.
CHAPTER 2

DRUGS USED TO AFFECT THE AUTONOMIC AND SOMATIC NERVOUS SYSTEMS

OVERVIEW

The nervous system functions as a major communication system within the body. Information is transmitted by electrical conduction along axons of neurons to (via afferent nerves) and from (via efferent nerves) the central nervous system (CNS). Between neurons or between neurons and target cells are gaps termed synapses across which the signal is transmitted chemically rather than electrically (with some exceptions). The endogenous chemical substances that transmit these signals are termed neurotransmitters. Accuracy of signal transmission requires that the postsynaptic cell reliably receive the intended message from the presynaptic cell. The fidelity is ensured by neurotransmitter-specific receptors located on the postsynaptic cell membrane.

Because an action potential, or the change in membrane potential occurring in excitable tissue during excitation, relies on a chemical process (ion flux across the membrane) and the transmission across synapses is primarily chemical, exogenously administered chemicals or drugs can modify physiologic processes mediated by the nervous system. The major neurotransmitters in the periphery are acetylcholine (ACh) and norepinephrine, and drugs can be designed either to mimic or to inhibit their actions. The integrated arrangement of the nervous system and the special distribution of neurotransmitter receptors allow for a targeted drug effect. In most cases, the actual action of the drug—and even much of its unwanted action—is predictable on the basis of the anatomy and physiology of the nervous system. It is convenient for the understanding of drug action to subclassify the peripheral nervous system (PNS) into 2 components: the somatic nervous system (SNS) and the autonomic nervous system (ANS).

The nerves of the SNS innervate skeletal muscles, and drugs that act on this system thus affect skeletal muscle function such as tone (eg, muscle relaxants given before surgery). Because all skeletal neuromuscular junctions contain ACh as the neurotransmitter, ACh and its receptors are targets for drugs intended to modify skeletal muscle function. The cholinergic receptors at these skeletal neuromuscular junctions are sufficiently different structurally (3-dimensional shape) from those at other sites to allow drugs to be designed to bind to only this type (nicotinic) of cholinergic receptor.

The nerves of the ANS innervate the organs of the body and can be further classified into sympathetic and parasympathetic subdivisions. Sympathetic activity is increased by drugs that mimic or enhance the action of norepinephrine. Parasympathetic activity is increased by drugs that mimic or enhance the action of ACh. Both systems are tonically active. Hence, antagonism of one system results in enhanced activity of the other. The SNS and ANS together provide a mechanistic framework for understanding the effects (good and bad) of drugs.

Elucidation of additional roles for neurotransmitters and identification of other receptor subtypes will likely lead to development of more selective drugs. Such drugs will be found by using, for example, high-throughput screening assays or molecular modeling techniques—or even by serendipity. However they are discovered, they should permit more selective targeting of the therapeutic end point with fewer unwanted effects.
FIGURE 2-1 ORGANIZATION OF THE NERVOUS SYSTEM

The actions of many drugs can be understood as the modulation of the nervous system's control of physiologic processes. The CNS and PNS communicate via afferent and efferent neurons. As a result of this anatomical organization, drugs can affect sensory input (e.g., local anesthetics for pain), skeletal muscle activity (e.g., muscle relaxants for surgery), or autonomic output (e.g., drugs that act on blood vessels or the heart to reduce high blood pressure).
### Figure 2-2 Action of Drugs on Nerve Excitability

Efficient and effective transmission of neuronal action potentials relies on the unequal distribution of positive (primarily Na⁺ and K⁺) and negative (primarily Cl⁻) ions across the axonal membrane. Selective, voltage-sensitive permeability of the membrane to these ions establishes the unequal distribution of the ions according to the Nerst equation and gives rise to a resting transmembrane potential difference. Drugs that alter the ion flux affect the resting transmembrane potential difference. The larger this difference, the further the neuron is from its firing threshold and the less likely that it will fire (ie, initiate an action potential). The smaller the transmembrane potential difference, the more likely it is that the neuron will reach this threshold and fire.
Spinal nerve pairs enter and exit along segmented caudal, thoracic, lumbar, and sacral portions of the spinal cord and distribute throughout the body. Somatic afferent neurons transmit sensory information about normal status (e.g., proprioception) or pathologic states (e.g., heat and mechanical damage) to the spinal cord and brain. Efferent neurons carry motor signals from the spinal cord and brain to the somatic (striated or skeletal muscles: effectors) and autonomic (smooth muscle, cardiac muscle, glands) divisions of the PNS. Drugs can selectively modulate the activity of afferent or efferent pathways: those that excite afferent nociceptive neurons produce pain; those that inhibit afferent nociceptive neurons are analgesic. Those that excite efferent, or neuromuscular, junctions produce tetanus; those that inhibit these junctions cause paralysis.
**Figure 2-4 Neuromuscular Transmission**

Neurons innervate skeletal muscles at the neuromuscular junction (A). The axon-muscle interface forms at a synaptic trough, which has extensive foldings that increase the surface area of exposure to a neurotransmitter (B). ACh, the neurotransmitter at neuromuscular junctions, is synthesized in the presynaptic neuron from mitochondrial acetyl-CoA and extracellular choline via an enzymecatalyzed reaction. ACh is stored in presynaptic vesicles (C) until release in response to an action potential in the presynaptic neuron (D), a Ca$^{2+}$-dependent process. ACh diffuses across the synaptic cleft and binds reversibly to specific receptor sites on the postsynaptic membrane. Ion flux then increases and the postsynaptic membrane depolarizes (E), which triggers an action potential that leads to muscle contraction. Released ACh is eliminated from the synapse by cholinesterase action (F).
Figure 2-5 Nicotinic Acetylcholine Receptor

Drugs that block cholinesterases prolong the ACh residency time in the synapse and enhance the effect of ACh. Receptors at neuromuscular junctions are termed nicotinic cholinergic receptors (nAChRs) because nicotine is a relatively selective agonist at these sites. In an nAChR, 5 subunits (α, β, γ, δ) form a cluster around a central cation-selective pore. Two ACh-binding sites are in the extracellular part of the receptor between α and the other subunits. When ACh binds to the sites, the receptor conformation changes: α subunits swing out, and the channel opens. Charged amino acids lining the pore select ions that can pass into the cell.
**Figure 2-6 Physiology of the Neuromuscular Junction**

As Loewi demonstrated in the 1920s, a gap (synapse) exists between an ANS neuron's axon terminal and the adjacent neuron or effector cell. Information is transmitted across this gap via chemical transmitters (neurotransmission). Neurotransmitters are commonly stored in presynaptic vesicles; arrival of an action potential stimulates a Ca²⁺-dependent neurotransmitter release into the synapse. The neurotransmitter crosses the gap and binds to highly selective receptor molecules on the postsynaptic cell, thereby modifying the activity of the postsynaptic cell. Neurotransmission provides fidelity of signal transmission. ANS neurotransmitters are simple organic molecules, and exogenous chemicals (drugs) can modify (mimic or antagonize) the action of the endogenous ANS neurotransmitters.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Supply of ACh in Terminal</th>
<th>Effect on Amount of ACh Released in Terminal by Action Potential</th>
<th>Effect of Amplitude on Endplate Potential</th>
<th>Effect of Muscle Response to Application of ACh</th>
<th>Direct Effect on Muscle Membrane Resting Potential</th>
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<tr>
<td>Hemicholinium</td>
<td>Decreased</td>
<td>Decreased (smaller quanta)</td>
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<td>—</td>
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<tr>
<td>ACh release blockers</td>
<td>(Botulinum toxin)</td>
<td>Decreased (fewer quanta)</td>
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<td>—</td>
<td></td>
<td>Paralysis (low Ca²⁺ concentration may also produce tetany by direct action on nerves)</td>
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<td>Low Ca²⁺ or High Mg²⁺</td>
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<td>Strongly depolarized</td>
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<td>Increased; prolonged</td>
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<td>Muscle power and duration of contraction increased</td>
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**Figure 2-7 Pharmacology of the Neuromuscular Junction**

Pharmacologic agents can induce effects at the neuromuscular junction by altering steps involved in ACh synthesis, storage, release, receptor binding, and elimination from the synapse. They can also have direct actions on skeletal muscle. For example, inhibitors of choline uptake limit ACh synthesis and depress neuromuscular functioning (e.g., paresis). Inhibitors of ACh release, such as botulinum toxin (food poisoning) and nAChR antagonists, have the same effect. With sufficient suppression of ACh, complete paralysis results. Neuromuscular stimulation is produced by substances that enhance ACh action or mimic its action at cholinergic receptor sites (cholinomimetics).
Figure 2-8 MECHANISM OF ACTION OF ACETYLCHOLINESTERASE INHIBITORS

Enhancement of endogenous ACh action results from increasing ACh release or inhibiting degradation of ACh by AChE. ACh binds to active subsites (choline, catalytic, and acyl) on AChE, choline is released by hydrolysis, acetylated enzyme is formed and rapidly hydrolyzed, and active enzyme is reformed by hydrolysis. Only nAChR agonists or antagonists selectively modify ACh action at the skeletal neuromuscular junction. Neostigmine and other reversible inhibitors bind to the active site and form a carbamoylated enzyme that is hydrolyzed slowly by AChE; irreversible inhibitors such as organophosphates (eg, isofluorophate) form a stable, phosphorylated enzyme that is very slowly hydrolyzed. Effects of AChE inhibition persist until new enzyme is synthesized.
Muscle relaxants inhibit ACh transmission at the skeletal neuromuscular junction; categorization as nondepolarizing or depolarizing agents depends on mechanism of action. The former (e.g., pancuronium, atracurium, vecuronium, and now rarely used tubocurarine [curare] and gallamine) are reversible nAChR antagonists that bind to postsynaptic membrane nAChRs, block ACh access to nAChRs, and cause muscles to relax. Increasing nAChR occupation directly (via cholinomimetics) or indirectly (via AChE inhibitors) overcomes drug action. Adverse effects are hypotension, tachycardia, and bronchospasm. Depolarizing agents are nAChR agonists and, like ACh, depolarize membranes (cause muscle twitching). These agents are not degraded by AChE; they stimulate nAChRs, muscle depolarization persists, and muscles relax. Cholinomimetics or AChE inhibitors do not affect these agents. Only succinylcholine is used currently. Unwanted effects are bradycardia, prolonged paralysis, and malignant hyperthermia.
In contrast to SNS nerves, which innervate skeletal muscles, ANS nerves distribute to smooth muscle, cardiac muscle, and glands. The somatic division mainly controls the stability and voluntary movement of the body; the ANS primarily controls more autonomous internal body functions. The ANS consists of efferent (from CNS to periphery) and afferent (from periphery to CNS) components and is subclassified on the basis of anatomy and physiology into sympathetic and parasympathetic divisions.

Sympathetic or parasympathetic fibers innervate almost all organs. The knowledge that most organs are innervated by both sympathetic and parasympathetic ANS neurons aids in understanding selective actions and adverse effects of drugs. Sympathetic neurons mediate fight or flight responses (pupil dilation, bronchodilation, increased heart rate). Parasympathetic neurons usually mediate the opposite response and control daily functions such as peristalsis, saliva flow, and near vision accommodation.
Activation of these responses by a real threat elicits a beneficial, magnified, short-term response; prolonged activation (stress) has harmful effects. Most available sympathomimetics—i.e., drugs or other chemicals that mimic fight or flight responses—target a subset of fight or flight responses. For example, phenylephrine, a common component of decongestants, produces vasodilation of nasal blood vessels but has relatively little effect on the heart. Some substances are sympathomimetic because they amplify epinephrine or norepinephrine release. Examples include ephedrine (the active ingredient of ephedra, or Ma-huang, recently banned in the United States because of adverse effects), amphetamines (synthesized in the 1930s as an alternative to ephedra), and tyramine (present in fermented foods). Interconnections among organs through ANS neurons explain some adverse effects of drugs on organs other than the intended targets.
Drugs affect organs innervated by the ANS and SNS by mimicking or antagonizing neurotransmitter action. Knowing the identity and synaptic distribution of neurotransmitters can offer insight into the therapeutic action or adverse effects of a drug, which can often be predicted. ACh is the neurotransmitter at neuromuscular junctions, preganglionic synapses (sympathetic and parasympathetic), and postganglionic parasympathetic synapses. Norepinephrine, or noradrenaline, is the neurotransmitter at most postganglionic sympathetic synapses. Drugs that mimic or potentiate norepinephrine produce sympathetic effects that resemble fight or flight responses such as increased heart rate. Drugs that mimic or potentiate ACh produce parasympathetic effects such as decreased heart rate. Nonadrenergic-noncholinergic (NANC) neurotransmitters in the ANS also exist, including peptides, nitric oxide, and serotonin.
Figure 2.13 Example of Cholinergic and Adrenergic Drug Treatment: Glaucoma

Certain types of glaucoma (excess intraocular pressure) can be treated with drugs that modify the activity of sympathetic or parasympathetic nerves in the eye. Parasympathetic activity opens pores in the trabecular meshwork and enhances outflow of aqueous humor into the canal of Schlemm. Sympathetic activity on the ciliary epithelium increases the secretion of aqueous humor. Cholinergic agonists such as pilocarpine, which enhance aqueous humor outflow, and adrenergic antagonists such as timolol, which decrease aqueous humor inflow, ameliorate symptoms of glaucoma. Adrenergic agonists such as apraclonidine that reduce aqueous humor production and irreversible AChE inhibitors such as echothiophate, an organophosphate, are also used.
FIGURE 2-14 CHOLINERGIC RECEPTORS

Cholinergic receptors are classified into 2 major types: nicotinic (nAChR) and muscarinic (mAChR), each having several subtypes. nAChRs are ligand-gated ion channels, and mAChRs are GPCRs. The receptors were named on the basis of selective actions of nicotine and muscarine (from the mushroom Amanita muscaria).

Muscarinic agonists mimic the actions of ACh at the postganglionic mAChRs in synapses of the parasympathetic subdivision of the ANS; antagonists inhibit these actions. Nicotinic agonists mimic the actions of ACh at nAChRs at skeletal neuromuscular junctions (SNS; detailed earlier); antagonists inhibit these actions.
The pupils in poisoning

Miosis (pinhole pupils)
Seen in poisoning by morphine and morphine derivatives, some types of mushrooms, cholinesterase inhibitors, parasympathomimetics, nicotine, chloral hydrate, sympatholytics, and some other compounds

Mydriasis (pupils dilated and not reactive)
Seen in poisoning by barbiturates, carbon monoxide, methyl and other alcohols, oxalid acid, cocaine, belladonna derivatives, camphor, cyanide, sympathomimetics, parasympathomimetics, and a number of other compounds

Figure 2-15 Cholinergic Drugs

Acetylcholine is rapidly broken down by cholinesterases in the blood and AChE in the synaptic cleft. AChE inhibitors (drugs such as phystostigmine or poisons) enhance actions of ACh by decreasing its enzymatic breakdown and prolonging its synaptic residency time. Muscarinic agonists such as pilocarpine amplify parasympathetic actions and, for example, decrease pupil diameter (miosis), decrease heart rate, increase gastrointestinal motility and secretion, contract bronchiolar and urogenital smooth muscles, and stimulate...
glandular secretions. Muscarinic antagonists such as atropine (derived from Atropa belladonna) and scopolamine have the opposite effects. Nicotinic agonists such as succinylcholine stimulate, and nicotinic antagonists such as pancuronium inhibit skeletal muscle contraction.
Myasthenia Gravis
Pathophysiologic Concepts

Normal neuromuscular junction: Synaptic vesicles containing acetylcholine (ACh) form in nerve terminal. In response to nerve impulse, vesicles discharge ACh into synaptic cleft. ACh binds to receptor sites on muscle sarcolemma to initiate muscle contraction. Acetylcholinesterase (AChE) hydrolyzes ACh, thus limiting effect and duration of its action.

Myasthenia gravis: Marked reduction in number and length of subneural sarcolemmal folds indicates that underlying defect lies in neuromuscular junction. Anticholinesterase drugs increase effectiveness and duration of ACh action by slowing its destruction by AChE.

Clinical Manifestations

Regional distribution of muscle weakness

- 95%
- 60%
- 30%
- 10%

Ptosis and weakness of smile are common early signs.

Improvement after edrophonium chloride

In early stages, patient may feel fine in the morning but develops diplopia and speech slurs later in the day.

Patient with chin on chest cannot resist when physician pushes head back.

Figure 2-16 Example of Cholinergic Drug Treatment: Myasthenia Gravis

Myasthenia gravis is characterized by progressive weakening of skeletal muscles. It preferentially affects women and is lethal if untreated. Symptoms are caused by an autoimmune-induced decrease (70-90%) in the number of nAChRs at the neuromuscular junction. In early stages of the disease, AChE inhibitors such as edrophonium produce a rapid recovery of function, which is diagnostic, and can be continued for therapy. Adverse effects of AChE inhibitors are those of excess ACh, known as DUMBELS: diarrhea, urination, miosis, bronchoconstriction, excitation (skeletal muscles and CNS), lacrimation, and salivation and sweating.
Adrenergic receptors (adrenoceptors) are classified into 2 major types, α and β, each with multiple subtypes that differ in terms of their mechanism of signal transduction (e.g., increased or decreased cAMP). All adrenoceptors are 7-transmembrane GPCRs: they cross the cell membrane 7 times (with the amino terminus of the receptor on the extracellular side) and are coupled to a guanine nucleotide-binding protein (G protein). When an agonist binds to a GPCR, it enhances the association of a receptor with a G protein, which then stimulates (e.g., $G_s$) or inhibits (e.g., $G_i$) a step in the second-messenger pathway, such as adenyl cyclase, phospholipase C, or an ion channel. The same adrenergic agonist (e.g., epinephrine, norepinephrine, or drug) can produce various effects depending on the G protein coupling in a cell. Effects of receptor activation include muscle contraction ($\alpha_1$, $\alpha_2$) and relaxation ($\alpha_1$, $\alpha_2$, $\beta_2$), increased heart rate and force ($\beta_1$), and lipolysis and thermogenesis ($\beta_3$).
\(\alpha_1\)-Adrenoceptor agonists (eg, phenylephrine) elicit vasoconstriction and mydriasis and are used as nasal decongestants and in eye examinations. \(\alpha_2\)-Adrenoceptor agonists (eg, clonidine) bind to presynaptic receptors and activate a negative feedback loop that inhibits further release of norepinephrine; they serve as antihypertensive agents. \(\alpha_1\)-Adrenoceptor antagonists (eg, doxazosin) are also used to treat hypertension. \(\beta_1\)-Adrenoceptor agonists (eg, dobutamine) augment sympathetic innervation of the heart and are used as cardiac stimulants. \(\beta_1\)-Adrenoceptor antagonists (eg, atenolol) attenuate sympathetic innervation of the heart and function as antihypertensive agents. \(\beta_2\)-Adrenoceptor agonists (eg, albuterol) stimulate bronchodilation and are used to treat asthma. Certain drugs (eg, isoproterenol and labetalol) affect multiple receptor types. Adverse effects include vasoconstriction, vasodilation, and tachycardia.
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<tr>
<td></td>
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**Figure 2-19 Drugs that Act on the Autonomic Nervous System**

Actions of drugs affecting the PNS can be organized on the basis of ANS anatomy and the neurotransmitter receptors that mediate physiologic responses to endogenous ACh and norepinephrine. Sympathetic effects can be produced by drugs that either enhance sympathetic tone (sympathomimetics such as adrenoceptor agonists) or depress parasympathetic tone (cholinergic receptor antagonists). Parasympathetic effects can be produced by drugs that either enhance parasympathetic tone or depress sympathetic tone. Drugs enhancing neurotransmitter action by activating receptors are known as direct acting; drugs enhancing neurotransmitter action by some other means, e.g., by inhibiting enzymes that degrade the neurotransmitter, are known as indirect acting.
Figure 2-20 Drug Side Effects

The organization of the ANS permits an understanding of effects that drugs can have on organs other than those that are the intended targets of drug action. For example, drugs that are designed to reduce heart rate by activating mAChRs on the heart activate mAChRs throughout the ANS unless subtypes of mAChR were identified on the heart and the drug selectively activates that subtype. The therapeutic and adverse effects of a drug are sometimes a function of intended use. The same drug (e.g., an mAChR antagonist) in one clinical setting may be given to treat diarrhea and cause sensitivity to light (miosis) as an adverse effect; in another clinical setting, the drug may be used therapeutically for an eye examination, but it could cause constipation as an adverse effect. The drug-induced effects are the same in both cases. Also, drugs that have different therapeutic targets can share a similar side effect.
CHAPTER 3

DRUGS USED IN DISORDERS
OF THE CENTRAL NERVOUS SYSTEM
AND TREATMENT OF PAIN

OVERVIEW

There is something special and inherently compelling about drugs that affect behavior or cognitive processes. However, in many ways the pharmacology of drugs that have effects (wanted or unwanted) on the CNS is similar to the pharmacology of drugs that have effects on peripheral organs. The properties of the CNS, like the properties of peripheral organs, are mediated by neurochemical transmitters acting at receptor sites. Hence, at the molecular level, the fundamental mechanisms of action of drugs affecting the CNS differ little from the mechanisms of action of drugs that act on the PNS.

Neurotransmitter pathways exist in the CNS (brain and spinal cord) just as they do in the PNS, although more CNS than PNS neurotransmitters have been identified, and amino acid transmitters and peptides play a more preeminent role in the CNS than they do in the PNS. As in the ANS, the CNS consists of opposing neurotransmitter systems. The major excitatory neurotransmitters are the amino acids glutamate (Glu) and aspartate (Asp); the major inhibitory neurotransmitters are GABA and glycine (Gly).

The etiology of CNS functional disorders is often difficult to determine. Psychosocial influences are important in many disorders, so they are best treated with a combination of pharmacotherapy and psychosocial intervention. Drug treatment of these disorders developed partly as the result of serendipity and, more recently, targeted drug discovery efforts. Many CNS disorders are imperfectly treated with current medications, and basic research findings continuously provide promising leads for new drugs.

More is also being learned about the disorders themselves. For example, it is now recognized that clinical depression and clinical anxiety are biochemically distinct from normally experienced feelings of sadness or apprehension. Schizophrenia is now known to consist of what are known as positive and negative symptoms. Pain is seen as multifaceted. Neuronal atrophy is implicated in conditions in which it was not previously suspected.

Drugs targeted to CNS disorders, like drugs used for conditions affecting the PNS but to a much larger extent, are subject to abuse—sometimes by patients but more often by nonpatients. Such abuse can adversely affect the availability of these drugs (such as opioids for relief of severe pain) to patients in need.
The nervous system, derived from ectoderm, begins with embryonic disk formation. The neural tube develops bulges, bends, and crevices that form mature brain structures and ventricles. Three major bulges appear by approximately day 28 of gestation: the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). At approximately day 36, the posterior (caudal) portion of the forebrain develops into the diencephalon; the anterior part develops into the telencephalon (eventually cerebral hemispheres). The cerebral cortex has a specific outline by 6 months but develops sulci and gyri only in the 3 months before birth. The developing brain is affected, especially in the first trimester, to injuries caused by various chemicals such as drugs. Various neurotransmitters and growth hormones play critical roles in development of normal CNS function and restoration of function after injury. Efforts aimed to identify these substances and design drugs that will facilitate or enhance their actions are ongoing.
Cerebral hemispheres are separated by a fissure and falx cerebri but are connected by commissures and other structures. The medial brain surface reveals complex, highly organized, structures of the hemispheres. The spinal cord and the brain (ie, the CNS) merge at the level of the brainstem. The major connection between the 2 hemispheres is the corpus callosum. Important sites of CNS drug effects are in the limbic system—communicating structures involved with smell, memory, and emotion. Four communicating cavities (ventricles) in the brain contain CSF produced by choroid plexuses. CSF circulation—from ventricles to central canal of spinal cord to drainage in venous sinuses—provides protection against trauma and a way to communicate chemically. Structures respond to circulating substances (eg, neurotransmitters, neuropeptides, hormones), as evidenced by introducing substances into CSF. The central action of a drug is studied by direct injection into ventricles.
Although many, if not most, brain functions involve coordinated interaction among multiple brain structures and each portion of the brain is connected to almost every other portion, some functions are loosely associated with certain regions. For example, the somatosensory (motor-sensory and sensorimotor) regions of the frontal and parietal lobes and the premotor cortex of the frontal lobe are involved with initiation, activation, and performance of motor activity and reception of primary sensations.

Interconnections among parietal (integration and interpretation of sensory information), temporal (reception and interpretation of auditory information), and occipital (vision) lobes provide an organized, integrated system. The prefrontal cortex is involved with higher mental functions. Association pathways provide added organized communication via intrahemispheric and interhemispheric connections.
Figure 3-4 Resting Membrane and Action Potentials

The CNS comprises many types of neurons. In general, myelinated neurons conduct impulses more rapidly than do nonmyelinated neurons. The magnitude of the electrical potential difference across the neuronal membrane in the resting state, termed the resting membrane potential, depends on the relative intracellular and extracellular concentrations of Na⁺ and Cl⁻ (higher on the outside) and K⁺ (higher on the inside). The cytoplasmic electrical potential is more negative than the extracellular fluid by approximately −70 mV. The potential difference is partly maintained by an Na⁺/K⁺ active transport exchange mechanism (ion pump). If the membrane is depolarized from its resting potential to approximately −40 mV (threshold potential), an action potential develops; the membrane potential continues to increase to approximately +20 to +30 mV and then returns to its resting level, in approximately one thousandth of a second. The frequency of a neuron’s firing is one mechanism by which information is encoded within the CNS.
Synaptic activation can either excite or inhibit a postsynaptic cell. During chemical synaptic transmission, neurotransmitters change postsynaptic membrane permeability to ions. For example, increased permeability to Na⁺ produces excitation, and increased permeability to K⁺ and Cl⁻ produces inhibition. The former manifests as a depolarizing change in the transmembrane potential (EPSP), and the latter manifests as a hyperpolarizing change (IPSP). Each neuron receives input from many other neurons, so a membrane potential is a net influence of EPSPs and IPSPs. Excitatory neurotransmitters such as Glu and Asp produce EPSPs; inhibitory neurotransmitters such as GABA and Gly produce IPSPs. Drugs that enhance Glu or Asp action (or otherwise enhance EPSPs) (eg, low nicotine doses) have excitatory effects in the CNS; drugs that enhance GABA or Gly action (or otherwise enhance IPSPs) (eg, diazepam) have inhibitory CNS effects.
Figure 3-6 Central Nervous System Neurotransmitters, Receptors, and Drug Targets

Many substances within the CNS modulate neurotransmitter actions. ACh and norepinephrine (NE), predominant in the PNS, also function in the CNS. Dopamine and 5-HT (serotonin)—more prominent in the CNS—and peptides such as endorphins are important in CNS function. Transduction mechanisms for neurotransmitter action are similar to those in the PNS: ionotropic types include voltage-gated ion channels (respond to membrane potential changes) and ligand-gated ion channels (alter membrane ion permeability in response to ligands such as neurotransmitters or drugs). Metabotropic types include GPCRs and involve second-messenger pathways (affect ion channels or biochemical reactions). Drugs affect various sites along neuronal pathways, including neurotransmitter synthesis, storage, and release; receptor activation and inhibition; modulation of intrasynaptic neurotransmitter metabolism or reuptake; and direct second-messenger pathway effects.
**Figure 3-7 GABA<sub>α</sub> Receptor Complex and Sedative-Hypnotic Drugs**

Many CNS depressants, including alcohols, barbiturates, benzodiazepines, and carbamates, produce sedation (reduction of anxiety) or hypnosis (induction of sleep). Sedative-hypnotics show considerable chemical diversity but share an ability to modulate Cl⁻ influx via interaction with the GABA<sub>α</sub> receptor-Cl⁻ channel complex, a heterologeric glycoprotein comprising 5 or more membrane-spanning subunits. Various subunit combinations give rise to multiple receptor subtypes. GABA enhances Cl⁻ influx by binding to α or β subunits. Cl⁻ influx hyperpolarizes the neuron and makes it less likely to fire in response to stimulation (EPSPs). Barbiturates depress neuronal activity by facilitating and prolonging inhibitory effects of GABA and Gly by interacting with Cl⁻ channel sites and increasing the duration of GABA-mediated channel opening. Benzodiazepines (see Figure 3-9) bind to specific receptor sites on the complex and increase the frequency of GABA-mediated channel opening.
Figure 3-8 Clinical Anxiety

To experience anxiety is normal. However, clinical anxiety is tension or apprehension that is grossly disproportionate to an actual or perceived stimulus. The source of anxiety may not be apparent and indeed may not be external; an underlying biochemical defect and genetic predisposition are hypothesized. Clinical anxiety, whether chronic or in the form of a panic attack, often produces somatic symptoms, impedes normal functioning, and adversely affects the quality of life. The disorders are approximately twice as common (possibly more often reported) in women than in men. The age at onset is usually between 20 and 30 years. Both endogenous and external factors likely contribute to susceptibility and expression of the clinical problem. Common adult anxiety disorders include generalized anxiety disorder, social phobia, OCD, panic disorder, and posttraumatic stress syndrome. Drugs for treating anxiety disorders, or anxiolytics, include benzodiazepines and buspirone.
Two main categories of anxiolytics are benzodiazepines and miscellaneous (e.g., buspirone, zolpidem, zaleplon). Subclassification of benzodiazepines is based on speed of onset or duration of action, metabolism, and adverse effects. Benzodiazepines cross the blood-brain barrier and bind to specific receptors on the GABA\textsubscript{A} complex; these receptors occur in many brain regions. The drugs do not bind to the same sites as does GABA but potentiate GABA action. Benzodiazepines are safer than barbiturates (largely obsolete); adverse effects include dependence, ataxia, and drowsiness. Diazepam, chlordiazepoxide, prazepam, and the prodrug clorazepate undergo hepatic metabolism to the intermediate oxazepam. Alprazolam, flurazepam, lorazepam, and triazolam directly undergo conjugation before excretion. Zolpidem and zaleplon resemble benzodiazepines in pharmacology but differ chemically. Buspirone (an azapirone) acts on 5-HT\textsubscript{1A} receptors. These last drugs have fewer adverse effects and less abuse potential.
<table>
<thead>
<tr>
<th>Drugs for Treatment of:</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic and partial seizures</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, phenytoin</td>
<td>Block voltage-gated Na⁺ channels in neuronal membranes and prolong neuronal refractory period</td>
</tr>
<tr>
<td>Primidone</td>
<td>Structural analog of phenobarbital, converted to phenobarbital (see below)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Blocks voltage-gated Na⁺ channels in neuronal membranes and prolong neuronal refractory period (high dose); inhibits T-type Ca²⁺ channels, particularly in the thalamus; may also enhance K⁺ flux</td>
</tr>
<tr>
<td>Absence seizures</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Inhibits T-type Ca²⁺ channels, particularly in the thalamus</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Blocks voltage-gated Na⁺ channels in neuronal membranes and prolongs neuronal refractory period (high dose); inhibits T-type Ca²⁺ channels, particularly in the thalamus; may also enhance K⁺ flux</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Allosterically modulates GABA action at GABA&lt;sub&gt;A&lt;/sub&gt; receptors, which increases frequency of Cl⁻ influx and hyperpolarizes neurons</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Diazepam, lorazepam</td>
<td>Allosterically modulates GABA action at GABA&lt;sub&gt;A&lt;/sub&gt; receptors, which increases frequency of Cl⁻ influx and hyperpolarizes neurons</td>
</tr>
<tr>
<td>Additional drugs</td>
<td></td>
</tr>
<tr>
<td>Felbamate, gabapentin</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Blocks voltage-gated Na⁺ channels in neuronal membranes and prolongs neuronal refractory period</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Blocks voltage-gated Na⁺ channels in neuronal membranes and prolongs neuronal refractory period (high dose); may be antagonism of Glu receptors</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Inhibits GABA transporters and may increase synaptic levels of GABA</td>
</tr>
<tr>
<td>Topiramate</td>
<td>May be antagonist of Glu receptors; may block Na⁺ channels and potentiate GABA</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Irreversibly blocks GABA transaminase (enzyme that terminates the action of GABA), enhancing its action</td>
</tr>
</tbody>
</table>

**Figure 3-10 Causes of Seizures and Their Treatment**

Seizures have various causes, both internal (intracranial) and external (extracranial). However, many seizures, perhaps the majority, are idiopathic. Internal causes include congenital defects, inborn errors in metabolism, infection, trauma, fever, intracranial hemorrhage, and malignancy. External causes include metabolic, electrolyte, and other biochemical disorders; anoxia; and hypoglycemia as well as excess doses of drugs or abrupt cessation of drugs. Approximately 10% of the US population has a seizure by the age of 80 years. Epilepsy, a type of seizure disorder, is a heterogeneous symptom complex characterized by recurrent, unprovoked seizures and affects approximately 1% of the population. For optimal drug therapy, the specific type of epilepsy should be identified. The principal mechanism of action of most current antiepileptic drugs involves action on voltage-gated ion channels or on inhibitory or excitatory neurotransmitter function.
Primary generalized seizures, the most common type being generalized tonic-clonic (grand mal) seizures, involve both cerebral hemispheres. The seizure begins with tonic stiffening of the limbs in an extended position, with arching of the back, followed by synchronous clonic jerks of muscles of the limbs, body, and head. The tongue may be bitten, and incontinence may occur. A period of postictal lethargy, confusion, and disorientation follows the seizure. An unbroken cycle of seizures—termed status epilepticus—can develop. Generalized tonic-clonic status epilepticus is a life-threatening emergency and almost always requires intravenous medication for seizure control. Drugs for tonic-clonic (and partial) seizures include carbamazepine, phenytoin, valproic acid, and primidone; those for status epilepticus include diazepam and lorazepam. Adverse effects such as sedation, confusion, and hepatic toxicity and drug interactions occur.
**Absence (Petit Mal) Seizures**

- **Between seizures**: patient normal
- **Seizure**: vacant stare, eyes roll upward, eyelids flutter (3/sec), cessation of activity, lack of response

**EEG normal between seizures**

|-------|-------|-------|-------|-------|-------|-------|-------|

**Absence seizure**

(3/sec generalized spike-and-wave discharges)

Patient is unresponsive, blinks eyes

---

**FIGURE 3-12 EPILEPSY: PARTIAL AND ABSENCE SEIZURES**

Partial-onset seizures start in localized brain regions and may affect nearly any brain function, from motor or sensory involvement to complex repetitive, purposeless, undirected, and inappropriate motor activities. Patients can be unaware of these automatisms.

Symptoms often represent the function of the underlying affected brain region. Postictal confusion and disorientation often occur. Drugs for these seizures include carbamazepine, phenytoin, valproic acid, and primidone. Absence (petite mal) seizures, characterized...
Simple Partial Seizures

- **Somatosensory**: Tingling of contralateral limb, face, or side of body
- **Central**
  - Postcentral sulcus
  - Precentral gyrus
- **Focal motor**: Tonic-clonic movements of upper (or lower) limb
- **Grimacing**
- **Contraversive**: Head and eyes turned to opposite side
- **Autonomic**: Sweating, flushing or pallor, and/or epigastric sensations
- **Auditory**: Hears ringing or hissing noises
- **Visual**: Sees flashes of light, scotomas, unilateral or bilateral blurring

**EEG**: Focal motor seizure, left arm and hand

- Fp1-F3
- F3-C3
- C3-P3
- P3-O1
- Fp2-F4
- F4-C4
- C4-P4
- P4-02
- Repetitive sharp waves over right central region

Complex Partial Seizures

- **Dreamy state**: Blank, vacant expression; déjà vu; jamais vu; or fear
- **Formed auditory hallucinations**: Hears music etc
- **Formed visual hallucinations**: Sees house, trees that are not there
  - Bad or unusual smell
- **Psychomotor phenomena**: Chewing movements, wetting lips, automatisms (picking at clothing)
- **Olfactory hallucinations**: Dysphasia

**EEG**: left temporal lobe seizure

- Fp1-F7
- F7-T3
- T3-T5
- T5-O1
- Fp2-F8
- F8-T4
- T4-T6
- T6-O2
- Repetitive sharp waves over left temporal region

**Figure 3-12 Epilepsy: Partial and Absence Seizures (continued)**

by periods of vacant staring or inattention (absence), occur without warning and last approximately 20 seconds. Hundreds may occur daily. Patients often have no memory of the events. These seizures usually occur in children, are often outgrown in adolescence, can disrupt academic performance, and are treated with ethosuximide and valproic acid and with clonazepam. Side effects of these drugs include sedation, leukopenia, and hepatic failure.
Antidepressants

The Face of Depression

"Doctor, what's wrong with me?"

Depression is a biochemically mediated state most likely based on abnormalities in metabolism of 5-HT and norepinephrine.

Clinical syndrome characterized by withdrawal, anger, frustration, and loss of pleasure.

5-HT, NE

Depressed mood with feelings of worthlessness and guilt

Associated Symptoms and Comorbidities

Poor concentration

Fatigue

Withdrawal

Substance abuse is a common comorbidity.

Weight loss may result from poor nutritional habits.

Sleep disturbance is a common complaint.

Increased suicide risk

Figure 3-13 Clinical Depression

Clinical (endogenous) depression, a heterogeneous biopsychologic disorder with genetic predisposition, can occur at any time in life, unrelated to obvious stressors. Treatment is required: approximately 15% of these patients commit suicide. Severe (major depression) and mild (dysthymic disorder) forms exist. Findings that clinical depression may be related to an imbalance in endogenous amines (5-HT or NE) in the CNS led to the amine hypothesis of etiology and spurred efforts to enhance synaptic action of these amines. Antidepressants are classified according to a presumed mechanism of action or chemical structure. TCAs and heterocyclics nonselectively inhibit both 5-HT and NE. SSRIs enhance drugs metabolized via the cytochrome P-450 pathway. MAOIs inhibit amine metabolism. Adverse effects (eg, mania, agitation, serotonin syndrome) and drug interactions (MAOIs used with TCAs or SSRIs) do occur.
Most antidepressants primarily enhance the action of endogenous amine neurotransmitters; they act indirectly, not binding to 5-HT or NE receptors but enhancing neurotransmitter action by inhibiting metabolism or removing neurotransmitters from synapses. Increased synaptic 5-HT or NE levels then counteract the abnormally low levels that produce depression. 5-HT enhancement may be more important than enhancement of NE, so SSRIs have become popular. MAOIs inhibit metabolism of 5-HT and NE, thus increasing amine levels. Mechanisms of newer drugs include direct binding to 5-HT or NE receptor subtypes (eg, antagonism at presynaptic α₂-adrenoceptors stimulates NE release). The action of bupropion does not seem to involve 5-HT or NE and therefore may represent a novel mechanism. The long-term mechanism of antidepressant action is unknown. All these drugs modify neurochemical pathways and can elicit adverse effects (eg, sedation and excitation).
Bipolar disorder is characterized by alternating periods of mania and depression. The manic phase can be productive but can also be disruptive and physically exhausting. Bipolar disorder often responds to treatment with lithium, which is rapidly absorbed from the GI tract and is distributed throughout the body. Lithium may reduce neuronal activity by inhibiting cellular phosphoinositide pathways involving the second messengers inositol triphosphate and diacylglycerol. Compulsive behaviors impair social interaction and disrupt daily activities. OCD affects at least 2% of the population (males and females approximately equally), with a genetic predisposition. The TCA clomipramine and SSRIs are usually chosen for OCD therapy. Other drugs, given individually or as combination therapy, include different TCAs, lithium, buspirone, clonazepam, dopamine antagonists (eg, haloperidol), and trazodone. Drugs used together with behavioral or psychosocial therapy are usually optimal.
Psychoses are psychogenic mental disorders involving a loss of contact with reality. The most common is schizophrenia, in which perception, thinking, communication, social functioning, and attention are altered. Caused by genetic and environmental factors, it affects approximately 10% of the population. Symptoms are called positive (e.g., delusions, hallucinations) or negative (e.g., flat affect, apathy); cognitive dysfunction may occur. Interest in dopamine, 5-HT, and Glu neurotransmitters led to most early drugs’ targeting the dopamine system, primarily as dopamine D2 receptor antagonists. Typical antipsychotics (e.g., chlorpromazine, haloperidol) are better for treating positive signs than negative signs. For treating negative signs, the newer (atypical) antipsychotic drugs (e.g., clozapine, risperidone) target other receptors, particularly 5-HT. Neurologic (e.g., dystonia, parkinsonism), anticholinergic (e.g., blurred vision), and antiadrenergic (e.g., hypotension) adverse effects can occur.
FIGURE 3-17 MOTOR TRACTS, BASAL GANGLIA, AND DOPAMINE PATHWAYS

Several major neuronal tracts coordinate somatic motor functions. One is the pyramidal tract, whose direct motor component goes from the precentral gyrus through the internal capsule and midbrain and terminates on motor neurons in the anterior horn of the spinal cord. Extrapyramidal tracts (eg, rubrospinal, reticulospinal, and corticoreticulor) are also important for motor control. The basal ganglia (including caudate nucleus, putamen, and globus pallidus) are subcortical masses found between the cerebral cortex...
and thalamus that, together with the substantia nigra, help to coordinate movement. A major pathway, the nigrostriatal, originates in the substantia nigra and connects with basal ganglia and other structures. The substantia nigra receives reciprocal input from these structures plus others. Efferent pathways (nigrostriatal) are dopaminergic; afferent input is from neurons containing 5-HT, GABA, and substance P. Defects in these pathways lead to motor incoordination or incapacity.
**Clinical Signs of Parkinson Disease**

- **Stage 1:** unilateral involvement; blank facies; affected arm in semillexed position with tremor; patient leans to unaffected side

- **Stage 2:** bilateral involvement with early postural changes; slow shuffling gait with decreased excursion of legs

- **Stage 3:** pronounced gait disturbances and moderate generalized disability; postural instability and tendency to fall

- **Stage 4:** significant disability; limited ambulation with assistance

- **Stage 5:** complete invalidism; patient confined to bed or chair; cannot stand or walk even with assistance

**Neuropathology of Parkinson Disease**

- Normal: Excitatory cholinergic neurons (green) in striatum
- Parkinson Disease: Decreased dopamine

**Figure 3-18 Parkinsonism: Symptoms and Defect**

Parkinsonism is a progressive neurodegenerative disease that adversely affects motor neuron control. Major early symptoms are tremor at rest, bradykinesia, muscle rigidity, and flat facial affect. If untreated, the condition worsens, leading eventually to complete immobility and early mortality. The prevalence is approximately 2% in persons older than 65 years. A genetic predisposition seems likely, but environmental factors (including viral infections and neurotoxins) may play a role. The most distinctive neuropathologic finding is progressive loss of dopaminergic neurons of the pars compacta of the substantia nigra. Projections of dopaminergic neurons from the substantia nigra correlate with motor and cognitive deficits. Degeneration of dopaminergic neurons in the nigrostriatal tract causes loss of inhibitory dopamine action on striatal GABAergic neurons and leads to excessive cholinergic neuron excitation of these striatal neurons. Drugs such as levodopa (increases dopaminergic activity) can help.
**Figure 3-19 Parkinsonism: Levodopa, Carbidopa, and Other Drugs**

Treatment aims to replenish dopamine, or at least to reestablish the balance between dopamine and ACh influences on striatal neurons. Dopamine cannot cross the blood-brain barrier, so its metabolic precursor, levodopa, is used. Most of an oral dose is rapidly converted to dopamine by dopa decarboxylase located in blood vessel walls. Approximately 1% to 5% of the dose crosses the blood-brain barrier, enters metabolic pathways of dopaminergic neurons, and is converted to dopamine. To increase the amount of levodopa that enters the brain, it is usually given with an inhibitor of dopa decarboxylase (such as carbidopa) that does not easily cross the blood-brain barrier. Peripheral conversion of levodopa to dopamine is thus reduced, so more levodopa enters the brain. Adverse effects include the on-off effect, arrhythmias, and hypotension. Direct-acting dopamine receptor agonists, inhibitors of dopamine metabolism (eg, MAOIs), anticholinergic agents, and amantadine are other drug options.

<table>
<thead>
<tr>
<th>Class and Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine prodrugs</td>
<td>Are rapidly converted to dopamine by dopa decarboxylase (which is inhibited by carbidopa)</td>
</tr>
<tr>
<td>Levodopa</td>
<td></td>
</tr>
<tr>
<td>Levodopa + carbidopa</td>
<td></td>
</tr>
<tr>
<td>Direct-acting dopamine</td>
<td>Bind to dopamine receptors and mimic the action of dopamine</td>
</tr>
<tr>
<td>agonists</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td></td>
</tr>
<tr>
<td>pergolide</td>
<td></td>
</tr>
<tr>
<td>pramipexole</td>
<td></td>
</tr>
<tr>
<td>ropinirole</td>
<td></td>
</tr>
<tr>
<td>Indirect-acting dopamine</td>
<td>Increases dopamine release and reduces dopamine reuptake into dopaminergic nerve terminals of substantia nigra neurons (by unknown mechanism)</td>
</tr>
<tr>
<td>agonist</td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Inhibits only type B isozyme</td>
</tr>
<tr>
<td>Selegiline</td>
<td></td>
</tr>
<tr>
<td>Muscarinic antagonists</td>
<td>Have central activity (brain) as anticholinergic agents</td>
</tr>
<tr>
<td>benztropine</td>
<td></td>
</tr>
<tr>
<td>Biperiden</td>
<td></td>
</tr>
<tr>
<td>Orphenadrine</td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 3-20 HUNTINGTON DISEASE AND TOURETTE SYNDROME

Various tremors (rhythmic oscillations around a joint), tics (repetitive, sudden, coordinated, abnormal movements), and chorea (irregular, unpredictable, involuntary muscle jerks) are components of disorders of coordinated movement. Gilles de la Tourette syndrome (which includes involuntary verbal outbursts) is a disorder of unknown cause. Current therapy consists primarily of haloperidol and other dopamine D2 receptor antagonists. Huntington disease is a dominantly inherited disorder characterized by progressive chorea and dementia. It is typically associated with an adult onset and a shortened lifespan. GABA and enzymes for ACh and GABA synthesis are deficient in the basal ganglia of patients with Huntington disease. Current therapy consists usually of amine-depleting drugs, such as tetrabenazine, or haloperidol or other dopamine D2 receptor antagonists. Hypotension, depression, sedation, restlessness, and parkinsonism are the most common adverse drug effects.
**Possible Factors in Development and Progression of Alzheimer Disease**

**Major predisposing factors**
- Genetic factors
  - 1, 14, 19, 21
- Aging
- Female gender
- Head

**Additional predisposing factors**
- NO
- AI
- Free radicals
- Toxic factors

**Possible factors include**
- Altered neuronal metabolism
- Chromosome 19 (APOE4)
- Chromosomes 21, 14, 1
- Toxins
- Hypoxia

**Formation of paired helical filaments**

**Dementia typical of Alzheimer disease may result from**
- Selective loss or dysfunction of projection neurons, resulting in cortical, limbic, and subcortical dysfunction and decrease in neurotransmitters.

<table>
<thead>
<tr>
<th>Phase and Dysfunction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early phase</td>
<td>“Where is my checkbook?”</td>
</tr>
<tr>
<td>Memory loss</td>
<td>“Could you direct me to my office? I have the address written down here somewhere, but I can’t seem to find it.”</td>
</tr>
<tr>
<td>Spatial disorientation</td>
<td>“Circumlocution” (Asks husband, “John dear, please call that woman who fixes my hair.”)</td>
</tr>
<tr>
<td>More advanced phase</td>
<td>Sloppily dressed, slow, apathetic, confused, disoriented, stooped posture</td>
</tr>
<tr>
<td>Terminal phase</td>
<td>Bedridden, stiff, unresponsive, nearly mute, incontinent</td>
</tr>
</tbody>
</table>

**Figure 3-21 Alzheimer Disease: Symptoms, Course, and Pathology**

Alzheimer disease is a neurodegenerative disorder characterized by progressive impairment of short-term memory and other memory, language, and thought processes. Functions are typically lost in the reverse order in which they were attained. In advanced stages, patients cannot perform simple activities of daily life. Diagnosis is usually made 3 years or more after symptom onset, and life expectancy is approximately 7 to 10 years after diagnosis. Gross brain atrophy accompanies the progression of the disease, with characteristic high numbers of neuritic plaques (fragments of insoluble amyloid, type Aβ, protein) and neurofibrillary tangles (abnormal τ microtubule complexes), particularly in the hippocampus and posterior temporoparietal lobe areas. Predisposing factors include aging and genetics, with a possible contribution from environmental toxins. The neurodegeneration results in loss or dysfunction of neurotransmitter pathways.
Alzheimer disease: pathology

Regional atrophy of brain with narrowed gyri and widened sulci, but precentral and postcentral, inferior frontal, angular, supramarginal and some occipital gyri fairly well preserved; association cortex mostly involved

Senile plaque (center) made up of argyrophil fibers around core of pink-staining amyloid (Bodian preparation); neurons decreased in number, with characteristic tangles in cytoplasma

Section of hippocampus showing granulovacuolar inclusions and loss of pyramidal cells

Section of brain schematically demonstrating postulated normal transport of acetylcholine (ACh) from basal nucleus of Meynert (substantia innominata) to cortical gray matter

**Figure 3-22 Alzheimer Disease: Cholinergic Involvement and Drugs**

Although many neurotransmitter systems become disrupted in Alzheimer disease, cholinergic pathways become especially damaged. Functional cholinergic deficits, such as impairment in short-term memory, become apparent even in the early stages of the disease. Medication strategies to ameliorate the decline in cholinergic function include the administration of precursors (e.g., lecithin); direct-acting cholinergic receptor agonists; and indirect-acting cholinomimetics. Indirect-acting agents, specifically
Pharmacologic Management Options in Alzheimer Disease
Cholinergic Approaches

Cholinergic therapies attempt to boost cholinergic function diminished by loss of cholinergic projections from basal forebrain to frontal cortex, amygdala, and hippocampus.

**Cholinesterase inhibitors** prevent hydrolysis of acetylcholine and increase cholinergic action.

**Precursor loading** to increase acetylcholine levels ineffective

**Muscarinic agonists** under study (postsynaptic muscarinic receptors usually preserved after loss of projection neurons)

---

**Figure 3-22 Alzheimer Disease: Cholinergic Involvement and Drugs (continued)**

Cholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, are currently the most commonly used. Ongoing research is investigating other potential targets, such as enzymes responsible for synthesis or degradation of Aβ or τ protein, and other postulated mechanisms responsible for the etiology or progression of the disease.
Figure 3-23 Stroke: Symptoms and Drug Treatment

Strokes are cerebrovascular accidents with CNS effects. Strokes can be categorized as ischemic (inadequate oxygen) or hemorrhagic (excess blood). Most ischemic strokes are caused by thrombi or emboli caused by cardiac or cerebrovascular disease, such as arteriosclerosis involving cerebral blood vessels. Early treatment intervention reduces subsequent neuronal damage and functional loss. The most common current drug therapies for ischemic stroke involve use of intravenous thrombolytic agents, such as alteplase or reteplase (tissue plasminogen activators), anistreplase (prodrug: streptokinase plus recombinant human plasminogen), streptokinase, and urokinase (all plasminogen activators). The most important adverse effect of these drugs is bleeding (cerebral hemorrhage). Low-dose aspirin (COX-1 inhibitor) is given for stroke prevention. Hemorrhagic stroke requires anticoagulant or surgical intervention. Research efforts now focus on drugs that may limit the extent of CNS damage after stroke.
Figure 3-24 Motor Neurons and Drugs

Skeletal muscle spasticity often results from neuronal, not muscle, deficits. The reflex arc involved in coordinated skeletal muscle action involves several neurons, including interneurons, in the spinal cord. These spinal polysynaptic reflex arcs are depressed by a number of drugs, including barbiturates. However, nonspecific depression of synapses is not desirable because normal muscle function can be disrupted. More specific agents, including CNS-acting drugs, are preferred. Benzodiazepines allosterically facilitate GABA-mediated Cl⁻ influx (Figure 3-9) throughout the CNS, including the spinal cord. They are used for muscle spasm of almost any cause but can also produce excess sedation. Baclofen is a GABA₉ receptor agonist that hyperpolarizes neurons by increasing K⁺ conductance. Other CNS-acting antispasmodic agents include α₂ adrenoceptor agonists (e.g., tizanidine), GABA₆ and GABA₉ receptor agonists, and the inhibitory amino acid Gly.
Figure 3-25 Pain Pathways

Tissue injury can lead to cellular changes involving release of chemicals (e.g., histamine) that start or quicken neuronal impulses that are interpreted as pain. Many neuronal pathways transmit pain sensation. For example, pain from peripheral injury reaches the CNS via primary afferent neurons, whose cell bodies form the DRG. Disorders such as phantom limb pain may involve abnormal DRG structure or function. Primary afferents end mainly in the dorsal horn of the spinal cord. Secondary neurons cross the spinal cord and ascend in pathways to the thalamus, the cerebral cortex, and other sites. A descending system of opioid (endorphins, enkephalins), 5-HT (e.g., from raphe nuclei), and noradrenergic (e.g., from locus ceruleus) pathways can lessen afferent signals. Drugs that act at pathways mediating pain sensation or perception are local (e.g., lidocaine) and general (e.g., halothane) agents, opioids (e.g., morphine), and nonopioids (e.g., aspirin and acetaminophen).
Local anesthetics cause temporary loss of pain sensation without loss of consciousness by blocking conduction along sensory nerve fibers. Some selectivity for pain afferents is achieved partly by using the agent close to target neurons. All currently used drugs block voltage-dependent Na⁺ channels in excitable cells, which decreases the likelihood of an action potential. The target site of the drugs is on the cytoplasmic side of the neuron membrane, so drug molecules must pass through the membrane. They are both lipophilic and hydrophilic and are weak bases (amides or esters) that exist in equilibrium between ionized (hydrophilic) and nonionized (lipophilic) forms. The latter diffuse more readily through the membrane; the former diffuse more readily through cytoplasm. Esters are metabolized by plasma cholinesterases; amides are hydrolyzed in the liver. Because they act on all excitable cells, local anesthetics can cause toxicity, including fatal cardiovascular effects or seizures.
General anesthetics (inhalational and intravenous agents) have a rapid, smooth onset of action and clinically desirable rapid reversal of effect. Concentrations of inhalational agents in the body and the pharmacokinetics depend on the drugs' partial pressure in the lungs and solubility in blood and brain tissue. Induction of anesthesia is more rapid for drugs with high partial pressure in the lungs and high solubility in blood (e.g., nitrous oxide, desflurane, sevoflurane). Onset of anesthesia is slowed when pulmonary blood flow is reduced. The site of drug action is the brain; the exact mechanism is unknown but may be related to lipid solubility and activation of GABA<sub>A</sub> receptors (enhanced Cl<sup>-</sup> influx, hyperpolarization of neurons). Elimination from brain and exhalation from lungs stop the effect of the drug. Redistribution to other tissues delays elimination and may increase occurrence of adverse effects. Intravenous agents include barbiturates, benzodiazepines, ketamine, opioids, and propofol.
Figure 3-28 OPIOIDS: ENDOGENOUS OPIOID PATHWAY

Morphine and related compounds (opioids) mimic the effects of the endogenous opioid neurotransmitters—endorphins and enkephalins. Endogenous opioid receptors are located throughout the pathways that relay the pain signal from its source to higher CNS centers for processing, evaluation, and response (such as via the spinoreticular tract [see Figure 3-25]). Descending pathways, including endogenous opioids, NE, and 5-HT, modulate the transmission of the incoming pain signal. These pathways can be activated subconsciously or consciously, which may account for a large analgesic placebo effect. Opioids alter the perception of pain. Such modulation of the affective component of pain can improve a patient’s quality of life even in the presence of a continuing sensation of pain.
Selected Opioid Analgesics

- Alfentanil
- Buprenorphine
- Butorphanol
- Codeine
- Dezocine
- Fentanyl
- Hydromorphone
- Meperidine
- Methadone
- Morphine
- Nalbuphine
- Oxycodone
- Oxymorphone
- Pentazocine
- Propoxyphene
- Remifentanil
- Sufentanil

**Figure 3-29 Opioids: Receptor-Transduction Mechanisms**

Opioids activate 7-transmembrane GPCRs located presynaptically and postsynaptically along pain transmission pathways. High densities of opioid receptors—known as μ, δ, and κ—are found in the dorsal horn of the spinal cord and higher CNS centers. Most currently used opioid analgesics act mainly at μ-opioid receptors. Opioids have an onset of action that depends on the route of administration and have well-known adverse effects, including constipation, respiratory depression, and abuse potential. Cellular effects of these drugs involve enhancement of neuronal K⁺ efflux (hyperpolarizes neurons and makes them less likely to respond to a pain stimulus) and inhibition of Ca²⁺ influx (decreases neurotransmitter release from neurons located along the pain transmission pathway). Brainstem opioid receptors mediate respiratory depression produced by opioid analgesics. Constipation results from activation of opioid receptors in the CNS and in the GI tract.
Nonsteroidal antinflammatory drugs have good analgesic efficacy (but often less than that of opioids), relatively rapid onset, and adverse effects (eg, possibly fatal gastrointestinal bleeding and disturbed salt and water balance). All NSAID effects—analgesic, antinflammatory, antipyretic, and antiplatelet—are thought to be due to decreased prostanoid biosynthesis via COX inhibition. Traditional NSAIDs inhibit both COX-1 and -2 isoforms, but newer COX-2 inhibitors are more selective. The analgesic efficacy of selective COX-2 inhibitors (coxibs) is approximately equal to that of traditional NSAIDs, but the adverse effects of COX-2 inhibition have yet to be fully characterized and are somewhat controversial. The ability to selectively inhibit COX-2 has been related to the difference in amino acids at position 523 of COX-1 and COX-2: isoleucine in COX-1, valine in COX-2. The mechanism of action of acetaminophen is uncertain but is thought to be via CNS effects.
Figure 3-31 Sumatriptans and Reuptake Inhibitors

Certain types of pain are sometimes successfully treated with drugs that are not analgesic for other types of pain. Two examples are sumatriptan and related compounds (triptans) and inhibitors of neuronal reuptake of NE or 5-HT. Triptans (eg, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and sumatriptan) are often the first-line therapy for treatment of acute severe migraine attacks. Reuptake inhibitors (eg, tricyclics and more selective NE or 5-HT reuptake inhibitors) are used for some patients with migraine and for some patients experiencing neuropathic pain with hyperalgesia (increased sensitivity to painful stimuli) or allodynia (painful sensitivity to non-painful stimuli). Neither the triptans nor the reuptake inhibitors are very effective against inflammatory or acute pain. Adverse cardiovascular effects can occur with the triptans, and numerous ANS effects can occur with the reuptake inhibitors.
CHAPTER 4

DRUGS USED IN DISORDERS OF THE CARDIOVASCULAR SYSTEM

OVERVIEW

The heart and circulatory system are mechanical marvels that must provide continuous, efficient, and reliable operation while adapting to short- and long-term physiologic changes. As with other organ systems, evolutionary adaptations have resulted in a cardiovascular system that is designed to meet its multiple requirements.

Drugs that are used to treat cardiovascular disorders constitute one of the largest categories of prescription drugs used. Two factors suggest that the use of these drugs will continue to increase: an aging population and the increasing use of drugs as prevention against future cardiovascular disease. These 2 factors work synergistically: as preventive care increases the average lifespan, the population has a greater risk of cardiovascular disease, and as life expectancy increases, greater emphasis is placed on earlier preventive intervention.

Certain cardiovascular disorders, such as cardiac arrhythmias and congestive heart failure (CHF), produce symptoms that are readily apparent to the person affected and have consequences long known to necessitate treatment. Other conditions, however, do not produce obvious symptoms and have become recognized as health problems only as a result of epidemiologic studies in relatively recent years. For example, blood pressures that had been considered normal because they were average (the age-appropriate mean) are now widely considered to fall into the hypertension category and are routinely treated with medication. Even more recently, cholesterol levels that were once deemed normal (or were even thought to be so insignificant that they went unmeasured) are now routinely treated with drugs.

For many years, the treatment of cardiovascular disorders primarily targeted the innervation of the heart and blood vessels by the 2 subclasses of the ANS. Parasympathetic innervation of the heart is principally via the vagus nerve (cranial nerve X) and is mediated by the action of acetylcholine (ACh) at muscarinic cholinergic receptors. Sympathetic innervation of the heart is mediated principally by the action of norepinephrine (NE) on $\beta$ adrenoceptors (more specifically, the $\beta_1$ subtype). The vasculature is controlled in a site-dependent manner by the parasympathetic subdivision mediated by ACh, which usually causes vasodilation, and by the sympathetic subclassification mediated by NE, which generally causes vasoconstriction. Hormones and local factors also contribute to overall vascular tone.

A major advance in treatment strategies for cardiovascular disorders occurred as a result of recognition of the significant contributions made by other neurotransmitter and hormone systems to normal and pathologic cardiovascular function. Targeting these systems, such as the renin-angiotensin system, has led to a broader variety of treatment options.

Cardiovascular drugs include some of the oldest medications, discovered by serendipity, and some of the newest, discovered by molecular modeling and screening technology. They include a wide variety of receptor agonists, receptor antagonists, and enzyme inhibitors.
Figure 4-1 Cardiovascular Function: Anatomy

The heart muscle pumps blood through the circulatory system. Each day, the heart beats 100,000 times and pumps 2000 gal of blood. The heart comprises 4 chambers (divisions): the upper two, the right and left atria; the lower two, the right and left ventricles. Blood is pumped through the chambers in only 1 direction, via 4 valves: the tricuspid, located between the right atrium and the right ventricle; the pulmonary, between the right atrium and the pulmonary artery; the mitral, between the left atrium and the left ventricle; and the aortic, between the left ventricle and the aorta. Dark blood, low in oxygen, returns from body tissues through veins, enters the right atrium, and then flows to the right ventricle, the pulmonary artery, and the lungs, where it is oxygenated. Blood returns by pulmonary veins to the left atrium and goes through the mitral valve into the left ventricle, which pumps oxygen-rich, bright-red blood through the aortic valve into the aorta and then into the circulation.
**Mechanism of Heart Adjustment to Body-Perfusion Requirements**

- Sympathetic stimulation: vagal inhibition
- Vagus nerves
- Sympathetic cardiac nerves
- SA node
- Coronary dilatation (increased O₂ supply and metabolite removal)
- Increased myocardial metabolism
- Increased force of contraction
- Frank-Starling effect
- Increased venous return
-Increased heart rate
- Increased cardiac output

**Effects of Resting Tension, Coronary Blood Flow, and Norepinephrine on Myocardial Contraction**

**Figure 4-2 Cardiovascular Function: Definition of Terms and Regulation**

Cardiac output is the total blood volume pumped by ventricles per minute (heart rate × stroke volume). Stroke volume is the blood pumped by the left or right ventricle per beat; in a resting adult, it averages 60 to 80 mL of blood. Systole is the contraction phase of the cardiac cycle, when ventricles pump stroke volumes. Diastole is the resting phase of the cycle, which occurs between heartbeats. End-diastolic volume is the blood volume in each ventricle at rest. End-systolic volume is the blood volume in each ventricle after contraction: 50 mL at rest. To maintain equal flow through pulmonary and systemic circuits, the left and right ventricles maintain the same cardiac output. The resting cardiac output is 4.8 to 6.4 L/min. Cardiac output increases (20-85%) during intense exercise to transport more oxygen to muscles. This greater blood flow is caused by higher blood pressure and arteriolar vasodilation in muscles, which is due to smooth muscle relaxation.
Norepinephrine and epinephrine (EPI), major catecholamine regulators of heart function, are released by the adrenal medulla after activation of preganglionic sympathetic nerves, which occurs during stress (e.g., exercise, heart failure, pain). More EPI (85%) than NE (15%) is released. A second source of NE is that from sympathetic nerves, especially those innervating cardiac pacemaker cells. The sympathetic effects increase heart rate and contraction force by activating $\beta_1$ adrenoceptors; vasoconstriction in systemic arteries and veins by activating $\alpha$-adrenoceptors; vasodilation in skeletal muscle at low concentrations by activating $\beta_2$ receptors; and vasoconstriction at high concentrations by activating $\alpha_1$ receptors. The overall cardiovascular response is greater cardiac output plus a small mean arterial pressure change. EPI release has similar cardiac effects. Heart rate, first increased by NE, usually decreases because of baroreceptor activation and vagal-mediated heart rate slowing.
Figure 4-4 Sympathetic and Parasympathetic Regulation of Heart Function

Sympathetic and parasympathetic systems innervate the heart and regulate function. Activation of the former increases heart rate and contraction force by increasing EPI and NE release. The latter system stimulates ACh release and reduces heart rate. The pacemaker cells of the SA node depolarize and promote atrial contraction. Ventricular contraction is due to impulses going from the AV node to the AV bundle to Purkinje fibers. Increased sympathetic drive activates β1 receptors in the SA node and increases pacemaker cell depolarization rate, heart rate, and contraction strength.

Parasympathetic impulses (through vagus nerves) reduce heart rate, AV node conduction, and contraction force. Increased ACh release and muscarinic M3 receptor activation mediate these effects. M3 receptor activation reduces cellular cAMP levels and increases K+ conductance, which leads to pacemaker cell hyperpolarization. Reduced heart rate and contraction force result.
Figure 4-5 Synthesis and Storage of Catecholamines

Norepinephrine synthesis starts with the amino acid tyrosine. Catecholaminergic nerves obtain it by active transport; tyrosine hydroxylase adds a hydroxyl group to form the catechol part of the molecule. Tyrosine hydroxylation is the rate-limiting step in catecholamine synthesis and is regulated by feedback inhibition. The product dihydroxyphenylalanine (dopa) is converted by aromatic amino acid decarboxylase into dopamine, one of 3 naturally occurring catecholamines. Dopamine enters synaptic vesicles via a catecholamine pump and is converted to NE by addition of a hydroxyl group. Synaptic vesicle catecholamine levels are much higher than surrounding cytosolic levels. Reserpine is a drug that inhibits the vesicular catecholamine pump, thus stopping vesicular catecholamine uptake and reducing catecholamine levels. The low cytosolic catecholamine level in nerves is maintained by the vesicular amine uptake pump and by mitochondrial monoamine oxidase, which degrades catecholamines.
Figure 4-6 Regulation of Norepinephrine Release

Vesicular release of NE depends on depolarization of the nerve terminal and the influx of Ca\(^{2+}\) ions. The influx of Ca\(^{2+}\) promotes the docking of synaptic vesicles at the plasma membrane and subsequent exocytosis of the vesicles. In the adrenal medulla, ACh acting as the neurotransmitter of the sympathetic ganglion acts on nicotinic receptors and promotes the release of catecholamines into the circulation. Certain drugs can also promote catecholamine release. Under certain experimental conditions, it is possible to mimic this nicotinic effect of ACh not only at the adrenal medulla, but also at the sympathetic ganglia. Thus, activation of cholinergic receptors by nicotinic agonists evokes substantial catecholamine release from postganglionic neurons and the adrenal medulla.
Figure 4.7 Inactivation of Norepinephrine

The primary NE inactivation mechanism is reuptake via a plasma membrane amine transporter, the amine uptake pump. This transporter is a member of a family of membrane proteins that transport different transmitter substances across the plasma membrane of the nerve terminal. The amine uptake transporter is driven indirectly by a sodium gradient, is selective for NE and EPI, and is inhibited by cocaine and tricyclic antidepressants such as imipramine. NE uptake is a major mechanism for ending sympathetic nerve transmission. Inhibitors of the amine transporter potentiate responses to stimulation of the sympathetic nervous system or to injected compounds that are taken up by sympathetic nerve terminals. In a sympathetically innervated tissue, such as the heart, the major uptake of catecholamines is neuronal uptake.
FIGURE 4-8 HYPERCHOLESTEROLEMIA: CAUSES

Cholesterol, a simple lipid found in cell membranes, is a precursor of steroids, bile acids, and vitamin D and a major part of atherosclerotic plaques. Most circulating blood cholesterol is synthesized from liver acetyl CoA and is excreted as bile salts. Only 25% of blood cholesterol is from the diet, but high-fat diets increase liver cholesterol production and blood cholesterol levels. HMG-CoA formation from HMG-CoA reductase, the rate-determining step in cholesterol synthesis, is regulated via feedback inhibition. When cholesterol uptake is low, the liver and small intestine increase cholesterol synthesis. The plaque-forming ability of cholesterol is related to LDLs, which promote plaque formation; HDLs remove cholesterol from arteries and transport it to the liver. HDLs remove cholesterol from plaques and slow atherosclerosis. Control of cholesterol and LDL levels is a major goal in heart disease therapy.
Primary goals of therapy are lower LDL levels and higher HDL levels. The best drugs for such therapy are statins: lovastatin, fluvastatin, pravastatin, simvastatin, and atorvastatin. They interfere with the cholesterol production of the liver by blocking HMG-CoA synthesis, so the liver can better remove cholesterol from circulating blood. Statins lower LDL cholesterol by 60%; side effects can occur. Nicotinic acid (or niacin) lowers total and LDL cholesterol and raises HDL cholesterol levels, but it can be toxic because the therapeutic dose is 100-fold greater than the recommended daily allowance. Resins (eg, cholestyramine and colestipol) bind intestinal bile acids and prevent recycling through the liver. The liver needs cholesterol to make bile, so it increases uptake of cholesterol from blood. Fibrin acid derivatives decrease triglyceride and increase HDL levels. Low doses of aspirin block platelet thromboxane A2 synthesis, which leads to reduced platelet aggregation and blood viscosity.
**Figure 4-10 Angina Overview**

Angina, or angina pectoris, is a gripping pain felt in the center of the chest that may move to the neck, jaw, and arms and is caused most often by exercise; emotion, eating, and cold weather are other causes. It occurs when the heart receives deficient oxygen because of blood vessel narrowing, which results mainly from aging and also from cigarette smoking, high cholesterol levels, obesity, and diabetes. The 3 types are stable angina (exertional or typical angina), caused by atherosclerosis, with treatment to reduce cardiac load and increase myocardial blood flow; vasospastic angina (variant or Prinzmetal angina), caused by severe coronary vessel contraction, with chest pain at rest and drugs aimed to stop vasospasm; and unstable angina (crescendo angina), in which pain occurs without stress. Nitrites and β blockers are used, as are calcium channel antagonists if the mechanism is vasospasm. Reducing platelet function and thrombotic episodes helps decrease mortality in unstable angina.
Nitrate Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Short acting&quot;</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, sublingual</td>
<td>10-30 minutes</td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>10-60 minutes</td>
</tr>
<tr>
<td>Amyl nitrate, inhalant</td>
<td>3-5 minutes</td>
</tr>
<tr>
<td>&quot;Long acting&quot;</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, oral sustained-action</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Nitroglycerin, 2% ointment</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow release, buccal</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow release, transdermal</td>
<td>8-10 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>1.5-2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, oral</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, chewable</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>6-10 hours</td>
</tr>
</tbody>
</table>

Side Effects

Headache, tachycardia (abnormal elevation in heart rate), orthostatic hypotension, facial flushing, and tolerance; contraindicated with sildenafil

*FIGURE 4-11 NITRATES FOR ANGINA TREATMENT: CLASSES, ADMINISTRATION ROUTES, PHARMACOLOGY, AND ADVERSE EFFECTS*

Organic nitrates are known as nitrovasodilators. The most commonly used nitrates are GTN, isosorbide dinitrate, and 5-ISMN. Another group of agents, organic nitrates (eg, amyl nitrite, isobutyl nitrite), contain the nitrate functional group. The final class of drugs—NO-containing agents (nitroglycerin, nitroprusside)—are often classed as organic nitrates, although the chemical structure differs, because of similar pharmacologic effects. Oral GTN is completely absorbed but undergoes extensive first-pass metabolism in the liver; dinitrate metabolites likely produce the therapeutic effects. 5-ISMN avoids first-pass metabolism and is 100% available orally. Sublingual dosing relieves acute attacks, whereas long-acting drugs (oral, transdermal) with a slow onset of action are used for prolonged prophylaxis. Loss of nitrate efficacy caused by tolerance can be reversed by use of sulhydryl-yielding agents such as N-acetylcysteine.
**Figure 4-12 Nitroglycerin in Angina Treatment**

Drugs that relax blood vessels, reduce the heart’s workload, and increase the amount of oxygenated blood to the heart are used for angina. Drugs are given long-term to reduce the number of attacks, just before certain activities to prevent acute attacks, and during attacks to relieve pain and pressure. Nitroglycerin (short-acting, long-acting, or intravenous form) is indicated for angina, AMI, and CHF. By releasing NO, nitroglycerin promotes venous dilation, inhibits venous return and cardiac preload, reduces intraventricular work, dilates large coronary arteries, and reduces systemic vascular resistance. Adverse effects include hypotension and headache. Nitroglycerin is more effective than nitroprusside, a similar organic nitrate, in reducing venous return but is less effective in expanding arteries. Nitroglycerin should not be used with sildenafil because of possible marked hypotension; it also interferes with anticoagulant actions of heparin.
Nitroglycerin produces vasodilation by releasing NO, which promotes blood vessel relaxation in cardiovascular and nervous systems. Drugs that release or induce NO release are important in treating hypertension, heart attacks, and other blood flow diseases. Heart attacks are caused by spasms or narrowing of blood vessels and occur when the blood cannot flow through the heart. NO relaxes the blood vessels and allows them to widen, thus increasing blood flow. NO released by nitroglycerin diffuses into cells and activates soluble guanylyl cyclase. This enzyme synthesizes the second messenger, cGMP, from GTP. cGMP modulates activity of protein kinase G, 2 cyclic nucleotide phosphodiesterases (PDE-2 and -3), and several ion channels. NO can also act through protein nitrosylation, interaction with transition metals, and direct modification of DNA. Thus, nitroglycerin promotes vasodilation and relief of the pressure associated with angina by activating the NO-cGMP pathway.
Calcium channel blockers (CCBs) reduce Ca²⁺ flow into heart cells by blocking L-type voltage-dependent calcium channels, which suppresses depolarization and reduces Ca²⁺-dependent conduction in the heart. Ca²⁺ binds to calmodulin in smooth muscle and troponin in the heart and affects muscle contraction. CCBs block these processes, thus reducing contraction. Three classes of CCBs are dihydropyridines (nifedipine, nimodipine, nicardipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem).

Blockade of slow calcium channels by the latter 2 drugs can have negative inotropic effects and thus reduce SA or AV conduction rate. Results are negative inotropic (force of contraction), chronotropic (rate), and dromotropic (conduction) effects. CCBs reduce afterload (not preload), coronary vascular resistance, and workload; help with oxygen delivery; and increase coronary blood flow. Adverse effects include vasodilation, hypotension, cardiovascular events, GI bleeding, and cancer.
## Summary of Pharmacologic Treatment of Patients With Chronic Stable Angina

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Which Patients</th>
<th>Effect on Cardiovascular Clinical End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>80-325 mg qd</td>
<td>All patients with vascular disease</td>
<td>Decreases the risk of death, myocardial infarction, and stroke</td>
</tr>
<tr>
<td>Statin drugs</td>
<td>Varies depending on particular drug</td>
<td>If LDL &gt;130; all patients who have extensive vascular disease. In patients with known CAD, LDL &gt;100</td>
<td>Decreases the risk of death in patients who have had a prior myocardial infarction</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Varies depending on particular drug; initial dosage will depend on blood pressure</td>
<td>All patients with vascular disease (in particular, any patient with vascular disease and hypertension or diabetes)</td>
<td>In the HOPE trial, ramipril 10 mg/qd reduced the rate of death, MI, and stroke in patients with vascular disease</td>
</tr>
<tr>
<td>β Blockers</td>
<td>Begin at low dose (eg, metoprolol 6.25 or 12.5 mg bid) and titrate depending on heart rate and blood pressure</td>
<td>Patients with prior myocardial infarction or with cardiomyopathy (caution is needed when initiating β blockers in patients with congestive heart failure)</td>
<td>Decreases the risk of death in patients who have had a prior myocardial infarction and improves outcomes in patients with dilated cardiomyopathy</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Sublingual or buccal spray can be used prn; longer acting oral and transdermal formulations are available</td>
<td>Patients with anginal symptoms</td>
<td>None</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Varies depending on particular drug; initial dosage will depend on blood pressure and heart rate</td>
<td>Patients with anginal symptoms</td>
<td>No beneficial effect; nifedipine worsens survival in acute coronary syndromes; diltiazem worsens survival in left ventricular dysfunction</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Varies depending on response; needs continual monitoring</td>
<td>Useful in selected patients with vascular disease</td>
<td>A meta-analysis demonstrates reduction in the risk of death, MI, or stroke if INR &gt;2 and used with concurrent ASA; bleeding increased by 1.9-fold</td>
</tr>
</tbody>
</table>

### Figure 4-15 Drug Summary for Angina

The aim of pharmacologic therapy for angina has changed from relieving symptoms to affecting survival. Drugs that improve survival and reduce the number of cardiovascular events include aspirin and statin drugs (HMG-CoA reductase inhibitors; eg, lovastatin); β blockers (eg, propranolol, metoprolol) reduce mortality in patients with previous myocardial infarction or left ventricular dysfunction. ACE inhibitors (eg, enalapril, captopril) are recommended when β blockers and diuretics are contraindicated, ineffective, or not tolerated. Nitrates (eg, nitroglycerin) and CCBs (eg, diltiazem) are used to treat symptoms without affecting survival. Warfarin can reduce the risk of serious cardiac events or death.
In heart failure, the most common cause of hospital stays of patients older than 65 years, the heart and circulation cannot meet peripheral metabolic demands while sustaining normal filling pressure. Systolic failure is the inability of the ventricle to empty normally; diastolic dysfunction is the inability of the ventricle to fill properly. Aging, smoking, obesity, fats, cholesterol, inactivity, viruses, and genetic defects promote heart failure; risk is also increased by hypertension and diabetes. Accumulation of fatty deposits in heart arteries leads to coronary artery disease. The normal heart tissue works harder because less blood is available. Previous myocardial infarctions cause oxygen and nutrient loss and heart damage. Abnormal heart valves that do not open or close completely during each heartbeat increase the workload. In COPD, abnormal lung function causes the heart to work harder to get oxygen to the body. Heart failure results when the workload is too great.
Heart failure caused by excessive workload is cured by treating the primary disease (e.g., thyrotoxicosis); surgery can help that related to anatomical problems. Acute myocardial infarction (AMI) results when reduced blood supply to the heart, caused by thrombus, leads to insufficient cardiac oxygen supply. The most common forms of heart failure—caused by damaged heart muscle—are treated with drugs to improve quality of life and survival. Combinations of at least 2 drugs are usually given. Diuretics reduce the amount of body fluid by decreasing salt and water retention. Glycosides increase heart contractility and contraction force by activating Na⁺-K⁺ pumps on heart cells. ACE inhibitors improve survival and slow the loss of heart-pumping activity by reducing blood pressure and workload. Organic nitrates are used when ACE inhibitors cannot be given. For AMI, thrombolytic drugs (e.g., alteplase) or plasminogen activators produce plasmin and dissolve blood clots by digesting fibrin.
**Figure 4-18 Heart Failure Treatment: β-Adrenergic Stimulators and Blockers**

β-Receptor activation augments sympathetic output, which increases heart contraction and rate. β Blockers blunt these actions. They block β₁-receptor activation by NE and EPI, thus reducing heart contractility and heart rate. β Blockers such as propranolol are especially useful for exertional angina but are ineffective against vasospastic angina. They are used in combination with calcium channel antagonists (eg, dihydropyridines, verapamil, diltiazem), organic nitrates, or both to treat cardiac symptoms that are resistant to a single drug. Because dihydropyridines do not alter SA or AV nodal conduction, they do not enhance the adverse effect of propranolol. Triple therapy (coadministration of 3 drugs) is sometimes used. The decrease in preload by nitrates, afterload by CCBs, and heart rate by β blockers is effective for treatment of angina that is not controlled by 2 types of antianginal agents. Dihydropyridines, but not diltiazem and verapamil, can be used in such a combination.
Cardiac glycosides inhibit the Na\(^+\),K\(^+\)-ATPase pump and increase intracellular Na\(^+\), thus slowing the rate of the Na\(^+\)/Ca\(^2+\) exchanger and increasing intracellular Ca\(^2+\). They are used in low-output heart failure with atrial arrhythmias. Digoxin is the most common digitalis preparation; digitoxin is used when a longer half-life is needed (7 days versus 1-2 days for digoxin). Improvement with digitalis depends on cardiac reserve; badly damaged hearts do not respond well. After digitalis restores heart function, its use is continued to prevent recurrence of heart failure. Digitalis may reduce the progression rate of heart damage in some patients, especially those in whom an increase in end-diastolic pressure and volume will occur. Digitalis reduces sympathetic tone by directly blunting the baroreceptor response. Because this drug has toxic effects, including ventricular tachyarrhythmias, GI distress, dizziness, and convulsions, its use by some patients should be avoided.
Arrhythmias is a disturbance of the heart rhythm. SA node malfunction usually triggers an abnormal electrical impulse rate. Because all heart tissue can start a beat, any part of the heart muscle can interrupt the electrical rhythm or take over as the heart’s pacemaker to produce an abnormal beat and arrhythmia. The term sinus arrhythmia is used when the changes are caused by spontaneous depolarization of SA node. The parasympathetic system normally slows the spontaneous discharge rate of the SA node from
100 beats/min to approximately 70 beats/min. Arrhythmias can range from entirely benign to immediately life-threatening. Most arrhythmias do not cause symptoms, but people may feel anxiety, lightheadedness, dizziness, fainting, heartbeat, and sensations of fluttering or pounding. Medical conditions (e.g., anemia, fever, heart failure, electrolyte imbalance) may cause arrhythmias. Synchronized electrical shock (defibrillation), electronic pacemakers, and radiofrequency ablation are nondrug treatments.
## Acute and Long-Term Management of Arrhythmias

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Acute Care</th>
<th>Long-Term Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia (&gt;100 bpm)</td>
<td>Treat underlying cause</td>
<td>If inappropriate, β blocker/calcium channel blocker. Persistent, consider RFA of the superior portion of the sinus node.</td>
</tr>
<tr>
<td>Sinus bradycardia (&lt;60 bpm)</td>
<td>If asymptomatic, no intervention.</td>
<td>If asymptomatic, no intervention.</td>
</tr>
<tr>
<td></td>
<td>If symptomatic and severe (rates &lt;40/min) with nonreversible cause, consider temporary pacing.</td>
<td>If symptomatic and severe (rates &lt;40/min) with nonreversible cause, consider permanent pacing.</td>
</tr>
<tr>
<td>Premature atrial complexes</td>
<td>If asymptomatic, no intervention.</td>
<td>If asymptomatic, no intervention.</td>
</tr>
<tr>
<td></td>
<td>Check potassium, magnesium.</td>
<td>Check potassium, magnesium.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If symptomatic, consider β blocker.</td>
</tr>
<tr>
<td>Premature ventricular complexes</td>
<td>If asymptomatic, no intervention.</td>
<td>Echo to assess LV and RV function, and LV wall thickness.</td>
</tr>
<tr>
<td></td>
<td>Check potassium, magnesium.</td>
<td>Normal echo: no intervention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β Blocker for symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal echo: Evaluate etiology and add β blocker.</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>No intervention, unless unstable</td>
<td>Permanent pacemaker. Allows the use of β blocker in patients with tachybrady syndrome.</td>
</tr>
<tr>
<td>Prolonged PR interval</td>
<td>No intervention</td>
<td>No intervention unless symptomatic</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>No intervention, unless unstable</td>
<td>Symptomatic patient, consider permanent pacemaker</td>
</tr>
<tr>
<td>Mobitz type 1 (Wenkebach)</td>
<td></td>
<td>Permanent pacemaker</td>
</tr>
<tr>
<td>Mobitz type 2 AV block</td>
<td>No intervention, unless unstable</td>
<td>Permanent pacemaker</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>Possible temporary pacemaker</td>
<td>Permanent pacemaker</td>
</tr>
<tr>
<td>Supraventricular tachycardia (SVT)</td>
<td>Control SVT with adenosine</td>
<td>WPPW with SVT needs EPS and RFA, because of risk of sudden death</td>
</tr>
<tr>
<td>Wolff-Parkinson-White syndrome and concealed accessory pathway</td>
<td>Control SVT with adenosine</td>
<td>Consider EPS and RFA for recurrent episodes</td>
</tr>
<tr>
<td>Atrioventricular nodal reentrant tachycardia</td>
<td>Control SVT with adenosine, metoprolol, diltiazem</td>
<td>Consider EPS and RFA for recurrent episodes</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>Control SVT with metoprolol, diltiazem</td>
<td></td>
</tr>
</tbody>
</table>

(continued)

**Figure 4-21 Cardiac Arrhythmias: Treatment**

Several drug strategies are used to treat arrhythmias. Warfarin, an anticoagulant, is used for atrial fibrillation to prevent stroke-inducing blood clots. The most common adverse effect of warfarin is bleeding, from mild nosebleed to life-threatening hemorrhage.

Antiarrhythmic drugs, such as amiodarone and sotalol, maintain the normal rhythm of the heart. Adverse effects include hypotension, AV block, various arrhythmias, and pulmonary toxicity (amiodarone) and bronchospasm (sotalol). β Blockers, such as
### Acute and Long-Term Management of Arrhythmias (continued)

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Acute Care</th>
<th>Long-Term Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Rate control</td>
<td>Warfarin with INR 2.0 to 3.0 in all at-risk patients. Consider pharmacologic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment and/or elective DC cardioversion</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>Rate control</td>
<td>Recurrent episodes need antiarrhythmic agent. Focal ablation for drug failures.</td>
</tr>
<tr>
<td>Persistent</td>
<td>Rate control</td>
<td>Cardioversion, addition of antiarrhythmic agent for recurrences. Focal ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for drug failures.</td>
</tr>
<tr>
<td>Permanent</td>
<td>Rate control</td>
<td>Rate control. Unsuccessful AV node ablation and permanent pacemaker.</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>Rate control</td>
<td>RFA for recurrent episodes</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>DC cardioversion if unstable or refractory to antiarrhythmic drugs</td>
<td>Echo to assess LV function. Ischemic evaluation ± revascularization. ICD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placement. Normal echo, consider RVOT or LV VT and ablation.</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>Emergent DC cardioversion</td>
<td>Rule out acute myocardial infarction. ICD placement in absence of acute myocardial infarction.</td>
</tr>
<tr>
<td>Nonsustained ventricular</td>
<td>Rate control</td>
<td>Low ejection fraction, need electrophysiology study. If positive, needs ICD.</td>
</tr>
<tr>
<td>tachycardia (3 to 30 beats)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>Primary prevention of sudden cardiac death</td>
<td>Previous myocardial infarction, LV ejection fraction &lt;30% require, ICD placement</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Treat as for arrhythmia</td>
<td>EPS for any ventricular tachycardia. If positive, needs IC.</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>Resuscitate as for arrhythmia</td>
<td>β Blocker/permanent pacemaker at 85 bpm/ICD</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Resuscitate as for arrhythmia</td>
<td>ICD placement. Asymptomatic and abnormal EKG, EPS ± ICD.</td>
</tr>
</tbody>
</table>

AV indicates atrioventricular; DC, direct current; EPS, electrophysiology study; ICD, implantable cardioverter defibrillator; INR, International Normalized Ratio; LV, left ventricular; RFA, radiofrequency ablation; RV, right ventricular; RVOT, right ventricular outflow tract; VT, ventricular tachycardia; WPW, Wolf-Parkinson-White syndrome.

**Figure 4-21 Cardiac Arrhythmias: Treatment (continued)**

acebutolol, esmolol, and propranolol, limit stimulating effects of EPI and NE on the heart, thus slowing the heart rate in atrial fibrillation. The selective β blockers have fewer central adverse effects than nonselective β blockers, such as propranolol. CCBs, such as verapamil and diltiazem, slow the heart rate and suppress tachycardia, although they can worsen ventricular tachycardia.
Figure 4-22 Cardiac Arrhythmias: Drug Classification

The standard classification was based on the 4 types of action of these drugs. Class I drugs block voltage-gated sodium channels and are classified into 3 subgroups on the basis of effects on phase 0 depolarization and repolarization: IA drugs have moderate potency at blocking the sodium channel and usually prolong repolarization (increase QRS). IB drugs are the least potent sodium channel blockers, do not alter action potential duration, and shorten repolarization. IC drugs are the most potent sodium channel-blocking agents but have little effect on repolarization (increase PR). Class II drugs act indirectly on electrophysiologic parameters by blocking β adrenoceptors (increase PR). Class III drugs prolong repolarization (increase refractoriness), with little effect on depolarization rate (QT). Class IV drugs are relatively selective AV nodal CCBs, primarily L-type channels (increase PR). In addition to these drug classes, cardiac glycosides act on arrhythmias.
Hypertension as Risk Factor for Cardiovascular Disease*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal subjects</th>
<th>Hypertensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>22.7</td>
<td>45.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>11.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>3.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.6</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Risk ratio: Men 2.0, Women 2.2; Men 3.8, Women 2.6; Men 2.0, Women 3.7; Men 4.0, Women 3.0

Excess Risk: Men 22.7, Women 11.8; Men 3.8, Women 2.6; Men 2.0, Women 3.7; Men 4.0, Women 3.0


Level of blood pressure is associated with cardiovascular events in a continuous, graded, and apparently independent fashion.†

Stroke

Stroke leading to intracerebral hemorrhage into putamen and ventricle

Coronary Heart Disease

Coronary heart disease and usual DBP

Cardiac hypertrophy and anteroseptal infarct with coronary heart disease

Angina

† Relative risk of stroke and coronary heart disease as a function of usual diastolic pressure in 420,000 individuals 25 years or older with a mean follow-up period of 10 years. Adapted from MacMahon S, Petro R, Cutter S, et al. Blood pressure, stroke, and coronary heart disease: part one. Lancet. 1990;335:765-767.

Figure 4-23 Hypertension Overview

Nearly 25% of adults have hypertension (high blood pressure)—increased arterial blood pressure that stays abnormally high for a long period. The heart pumps blood from the left atrium into the arteries. The blood flow exerts a force against arterial walls. This force, or blood pressure, is a measure of how much work is required by the heart to push blood through the arteries. The 2 numbers used to indicate blood pressure correspond to systole and diastole (e.g., 120/80 mm Hg). The systolic (top) number reflects pressure of blood against arterial walls that results from contraction of the heart. The diastolic number (bottom) reflects arterial blood pressure while the heart is filling and resting between beats. High blood pressure in adults is defined as a consistently increased blood pressure of 140/90 mm Hg or greater. Hypertension is called the “silent killer” because it causes serious complications without obvious symptoms. Some signs are headaches, dizziness, and blurred vision.
# Hypertension

## Causes of Hypertension

### Essential Hypertension
- Unknown etiology
- Glomerulonephritis
- Chronic pyelonephritis
- Diabetic nephropathy
- Interstitial nephritis
- Polycystic kidney disease
- Hydrenephrosis

### Renal disorders
- Atherosclerotic, thrombotic, or embolic obstruction
- Fibromuscular hyperplasia
- Aneurysm or dissecting aneurysm
- Hypoplasia

### Renovascular disease
- Mineralocorticoid excess (primary or idiopathic hyperaldosteronism, DOC-excess syndromes)
- Cushing or adrenogenital syndrome

### Adrenal disorders
- Cortical
- Medullary–Pheochromocytoma

### Neurogenic disorders
- Increased intracranial pressure
- Bulbar poliomyelitis
- Diencephalic syndrome
- Ganglioneuroma
- Neoblastoma

### Hematologic disorders
- Polycythemia
- Erythropoietin

### Parathyroid or thyroid disorders
- Hyperparathyroidism (also other causes of hypercalcemia)
- Myxedema

### Coarctation of aorta
- Thoracic
- Abdominal (with or without renal artery involvement)

### Toxemia of pregnancy
- Preeclampsia
- Eclampsia

### Drug- or diet-induced
- Oral contraceptives
- Estrogens
- Lecinone
- Cyclosporine
- Cocaine
- Amphetamines
- Sympathomimetics
- Monoamine oxidase inhibitors

### Increased left ventricular stroke volume
- Complete heart block
- Aortic regurgitation
- Patent ductus arteriosus
- Hyperthyroidism

### Decreased aortic distensibility
- Aortic arteriosclerosis
- Coarctation of aorta

---

**Figure 4-24 Hypertension: Causes**

Hypertension is classed as primary (essential) or secondary. The former cannot be directly related to a cause and constitutes 90% of hypertension cases. The latter occurs in less than 10% of hypertensive patients and is caused by liver and kidney disease, adrenal hormone overproduction, pregnancy, and sleep disorders as well as corticosteroids (eg, prednisone, cortisone), NSAIDs (eg, aspirin, ibuprofen), alcohol, nicotine, and caffeine. The renin-angiotensin system regulates all aspects of blood pressure control. ACE converts angiotensin I (AI) into angiotensin II (AII). Circulating AII increases sympathetic drive, constricts vascular smooth muscle, reduces bradykinin levels, and increases salt and water retention, all of which increase blood pressure and cardiac preload and afterload.
The goal for most patients is to decrease blood pressure to less than 140 mm Hg systolic and less than 90 mm Hg diastolic. Drug therapy involves 4 major drug classes: diuretics, ACE inhibitors, CCBs, and β blockers (used with drugs of another class). Diuretics have been the major antihypertensive drugs for decades and are still thought to be the best therapy for African-American and elderly patients and the best agents for preventing stroke. Diuretics also minimize blood clotting and reduce osteoporosis in the elderly. Three major types of diuretics are used. Thiazides (eg, chlorothiazide, chlorthalidone) are taken alone for moderate hypertension or used in combination with other drug types. Loop diuretics (eg, furosemide, bumetanide) block Na⁺ transport in the kidney. Their onset of action and potency are greater than those of thiazides. Potassium-sparing agents (eg, amiloride, spironolactone) increase potassium retention by kidneys and increase K⁺ levels in the body.
**Figure 4-26 Hypertension Treatment: Angiotensin-Converting Enzyme Inhibitors**

Angiotensin-converting enzyme converts the inactive form of angiotensin (AI) to the active AII. All causes arterial vasoconstriction and increases blood pressure. Blocking ACE with inhibitors (e.g., captopril, enalapril) inhibits AII formation, which reduces blood pressure, enhances the pumping efficiency of the heart, and improves cardiac output in heart failure patients. ACE inhibitors also slow progression of kidney disease, especially in diabetic patients. These agents are thus the best drugs for high blood pressure in cases that also involve chronic kidney failure in diabetic and nondiabetic patients, CHF, and heart attack, which damage heart muscle. Using only ACE inhibitors allows 60% of white patients to control hypertension; black patients need higher doses and use with a diuretic. All receptor antagonists are new drugs that decrease blood pressure by blocking AII from binding to receptors in vascular smooth muscle. Most adverse effects are mild; renal failure and fetol/neonatal morbidity may occur.
Hypertension Treatment: β and α Blockers

Emotional states and mental stress stimulate sympathetic nerves to vessels, adrenal medulla, and heart via hypothalamus, reticular formation, and pressor centers in medulla; affected by sedatives, sleep, rauwolfia, and cerebral blood supply.

Depressor nerves from baroreceptors in carotid sinuses (IX) and aorta (X) form afferent pathway in neurogenic regulation of blood pressure.

Intracranial pressure may affect blood supply to brain, thus influencing neural mechanisms.

Sympathetic nerves modify tension in peripheral and visceral vessels.

β₁ blockers

α blockers

Catecholamines from adrenal medulla affect tone of resistance in vessels as well as heart rate and output.

Vagus and sympathetic nerves affect heart rate and output.

Adrenal cortical stimulating hormones, produced by anterior pituitary, stimulate aldosterone output.

Parasympathetic efferents

Sympathetic efferents

Afferents

Humeral effects

Propranolol (a β blocker)

Terazosin (an α blocker)

β Blockers decrease cardiac output and blood pressure by reducing the frequency of spontaneous depolarizations in pacemaker cells. They prevent activation of β adrenoceptors by NE and EPI and block increased sympathetic effects on the heart. β Blockers are prescribed in combination with other antihypertensive agents to treat hypertension. They are excellent for patients with angina but should be avoided by patients with bradycardia (low heart rate), asthma, and chronic bronchitis. Main β blockers include propranolol, atenolol, acebutolol, metoprolol, pindolol, and nadolol. Side effects are fatigue, insomnia, nightmares, impotence, GI disorders, and limb cooling. α-Adrenergic antagonists (terazosin, doxazosin) decrease blood pressure by blocking sympathetic effects on α receptors in smooth muscle of peripheral arteries. These agents increase the risk of heart attack and stroke and are not the drugs of first choice for treating hypertension.
Minoxidil given orally is the most potent of the drugs that decrease blood pressure by dilating peripheral arteries. Topical minoxidil has garnered much attention for its ability to increase hair growth in men and women. Minoxidil, unlike α and β blockers, does not work through the peripheral sympathetic nervous system. Instead, it is a muscle relaxant that directly activates K⁺ channels in smooth muscle cells of the peripheral arteries. This effect increases K⁺ permeability and enhances K⁺ efflux, which causes hyperpolarization of the cell membrane and an overall reduction in blood pressure. Blood flow to the skin, skeletal muscle, and heart increases. This drug is used only in patients who do not respond to other antihypertensive agents. It is used in combination with β blockers or clonidine to reduce heart rate and is contraindicated during pregnancy. The most common adverse effects are fluid and salt retention and hair growth on the face, back, arms, and legs.
Hypertension Treatment: Clonidine

Emotional states and mental stress stimulate sympathetic nerves to vessels and heart via hypothalamus, reticular formation, and pressor centers in medulla.

Clonidine acts on the central sympathetic control center and is called a central α agonist. It reduces sympathetic drive from the brain and peripheral arterial resistance, which results in lower blood pressure via vasodilation. Clonidine is used only when other drugs have been unsuccessful. Adverse effects are dry mouth and fatigue. Clonidine can lead to bradycardia, so it should not be used with β blockers and calcium channel antagonists, which decrease heart rate. Clonidine also increases sedation caused by narcotic pain relievers, barbiturates, and alcohol. Abnormal heart rhythms can occur with clonidine plus verapamil. Also, cocaine, pseudoephedrine, phenylephrine, and amphetamine counteract the antihypertensive actions of clonidine.

Figure 4-29 Hypertension Treatment: Clonidine

Clonidine, an oral and topical drug, slows heart rate and reduces blood pressure. By stimulating adrenoceptors in the brain, it dampens signals that start in the CNS and are transmitted to the body by the sympathetic nervous system. Clonidine acts on the central sympathetic control center and is called a central α agonist. It reduces sympathetic drive from the brain and peripheral arterial resistance, which results in lower blood pressure via vasodilation. Clonidine is used only when other drugs have been unsuccessful. Adverse effects are dry mouth and fatigue. Clonidine can lead to bradycardia, so it should not be used with β blockers and calcium channel antagonists, which decrease heart rate. Clonidine also increases sedation caused by narcotic pain relievers, barbiturates, and alcohol. Abnormal heart rhythms can occur with clonidine plus verapamil. Also, cocaine, pseudoephedrine, phenylephrine, and amphetamine counteract the antihypertensive actions of clonidine.
The diagnosis of hypertension for all adults is based on the finding of systolic blood pressure of over 140 mm Hg with diastolic blood pressure of over 90 mm Hg, after 2 or more readings. Each reading must be performed after the person has been sitting for 3 minutes. A single reading with systolic blood pressure of over 210 mm Hg or diastolic blood pressure of over 120 mm Hg is consistent with hypertension.

**Etiology and pathogenesis**

- Reduced baroreceptor sensitivity
- Increased peripheral vascular resistance
- Lower renin levels
- Higher sensitivity to sodium
- Reduced glomerular filtration rates
- Decreased ability to maximally excrete sodium
- The most common secondary cause of hypertension for this age group is renal artery stenosis.

**Clinical presentation**

Most patients are asymptomatic but some present symptoms that reflect damage to cerebrovascular circulation, and those with end organ damage may experience dyspnea on exertion or chest pain.

**Postural hypotension** is common in older persons. Standing blood pressure readings should be measured after 3 minutes.

**Differential diagnosis**

"Pseudohypertension" should be considered in older persons with persistent elevated blood pressures, no evidence of end-organ damage, and near-syncope or syncopal symptoms with therapy. This condition is caused by advanced atherosclerotic changes in the upper extremities such as decreased arterial wall compliance and increased vascular stiffness.

Another differential diagnosis to be considered that presents increased prevalence in older persons is "white-coat" hypertension, especially among women.

**FIGURE 4-30 HYPERTENSION IN ELDERLY PATIENTS**

Older patients present a challenge in both drug selection and dosage adjustment to control blood pressure. One major concern is impaired drug-metabolizing ability, so toxic actions of agents must be considered. Diuretics are safe, effective, and well tolerated, but high doses can induce effects such as hypokalemia (low blood K⁺ levels) and hyperglycemia (high blood glucose levels). Thiazides expel water from the body, which makes them useful for reducing edema caused by heart, liver, or kidney disorders.

Potassium supplements or potassium-sparing agents can help to counter the K⁺ loss. Drugs other than diuretics can be given, but they are usually more costly and less effective. β Blockers are less effective than diuretics in preventing stroke, and CCBs have side effects such as postural hypotension, ankle swelling, and upset stomach. ACE inhibitors and AR blockers relieve hypertension but should not be given to patients with renal or carotid artery stenosis.
**Pheochromocytoma**

Tumor secretes increased amounts of catecholamines, usually epinephrine, and noradrenaline.

Increased dopamine secretion suggests malignant tumor.

**Hypertension may be episodic or sustained.**

Vasoconstriction increases peripheral resistance and blood pressure

_Pheochromocytoma_ is a chromaffin cell tumor secreting excessive catecholamines resulting in increased peripheral vascular resistance and hypertension.

**Clinical Features of Pheochromocytoma**

- Headache
- Sweating and flushing
- Anxiety
- Nausea
- Palpitations/chest pains
- Weakness
- Epigastric pain
- Tremor

Symptoms secondary to excessive catecholamine secretion and are usually paroxysmal.

More than 90% of patients with pheochromocytoma have headaches, palpitations, and sweating alone or in combination.

**Potential sites of pheochromocytoma**

- Sympathetic trunk
- Aortic arch
- Diaphragm
- Spleen
- Adrenal medulla
- Abdominal aorta
- Kidney
- Zucker's gland
- Body
- Ovary
- Bladder wall
- Testes

Most pheochromocytomas are adrenal in origin, but can occur in various sites and may be associated with multiple endocrine neoplasia (men) syndromes. Most are sporadic, but some are hereditary.

**Figure 4-31 Pheochromocytoma-Induced Hypertension**

_Pheochromocytoma_ is a rare tumor that arises from adrenal gland tissue. The tumor increases production of EPI and NE, thus increasing the level of catecholamines in blood, increasing sympathetic effects on cardiac cells and peripheral blood vessels, and increasing blood pressure and heart rate. Sweating, headache, anxiety, and tight often occur. Pheochromocytomas are normally benign, but they may be associated with malignant tumors in endocrine glands. Surgical removal of the tumor is usually needed to abolish the high catecholamine levels, increased sympathetic activity, hypertension, and cardiac dysfunction. However, before surgery and in cases in which surgery is not possible, drugs such as α and β blockers are used to block effects of the catecholamines. In cases of dangerous hypertension, organic nitrates such as nitroprusside or phentolamine are routinely given intravenously.
**Figure 4-32 Hypertension in Cushing Syndrome**

Cushing syndrome, or hypercortisolism, results from excessive cortisol production and is caused when adrenal glands overproduce cortisol or after prolonged corticosteroid use. The unique features of this syndrome are a fatty hump between the shoulders, a rounded face, and pink-to-purple striations on the skin. The syndrome can cause hypertension, diabetes, and bone loss. Therapy aims to decrease cortisol levels. If corticosteroid use is the cause, decreasing the dose may eliminate the syndrome while still controlling asthma, arthritis, and associated conditions. If a tumor causes the syndrome, total surgical removal or radiation therapy is preferred. When surgery and radiation do not normalize cortisol levels, therapy with drugs, most commonly ketoconazole and mitotane, can impede cortisol synthesis. They are taken orally. Antihypertensive agents can control the headache and high blood pressure that accompany Cushing syndrome, but they are not used to treat other conditions induced by the syndrome.
Peripheral Vascular Disease

Peripheral vascular disease can cause loss of limb or life and is characterized by chronic progression of symptoms such as intermittent claudication (leg pain produced by atherosclerosis) and sores that do not heal. Insufficient tissue perfusion resulting from atherosclerosis and compounded by emboli is the primary cause. Coronary artery disease, myocardial infarction, atrial fibrillation, stroke, and renal failure are additional causes. Risk factors are hyperlipidemia, smoking, diabetes, hyperviscosity, and autoimmune disorders. Conventional treatment includes antiplatelet (platelet-inhibiting) drugs (aspirin, dipyridamole, ticlopidine) and cholesterol-decreasing drugs (niacin, lovastatin, pravastatin), which are often used in combination with antiludication medications (cilostazol, pentoxifylline). Operations to restore blood supply or revascularization procedures (e.g., angioplasty, atherectomy, stent placement, and bypass) are reserved for patients with progressive symptoms.
CHAPTER 5

DRUGS USED IN DISORDERS OF THE ENDOCRINE SYSTEM

OVERVIEW

The endocrine system has often been viewed as more complex than other physiologic systems, primarily because the target organ is usually located relatively far from the site of release of the chemical mediator of the signal. However, it is now recognized that the signaling mechanisms—which use enzymes, neurochemical transmitters, hormones, and receptors—are similar (aside from distance) to those of other systems. Hence, the basic pharmacologic principles of therapy are the same. Some of the major applications of these drugs include treatment of hypothalamic and pituitary disorders, thyroid dysfunctions, disorders involving adrenal corticosteroids, and diabetes.

Hypopituitarism may be partial or complete and may result from hypothalamic disease (leading to deficiency of hypothalamic-releasing hormones) or intrinsic pituitary disease (causing pituitary hormone deficiency). Hypopituitarism may affect any of these pituitary hormones: thyrotropin, growth hormone (GH), luteinizing hormone, follicle-stimulating hormone, and corticotropin (ACTH). In targeting one of these hormones, therapy for GH deficiency aims to restore normal body composition, as well as, in children, to promote linear growth. Therapy for acromegaly, caused by excessive GH secretion, includes surgery and/or radiation, or use of a GH inhibitor.

Hypothyroidism can result from either thyroid or hypothalamic dysfunction. The treatment of choice is hormone substitution by using a synthetic hormone. Hyperthyroidism (thyrotoxicosis) is characterized by increased metabolism, and the primary treatment options include surgery, radioactive iodine, or drugs that inhibit the formation of thyroid hormones, such as by blocking the utilization of iodine.

The principal functions of glucocorticoids involve regulation of carbohydrate metabolism and a variety of other physiologic actions. Synthetic corticosteroids (e.g., hydrocortisone, prednisone, and dexamethasone) are widely used as therapeutic agents in treatment of cancer and autoimmune or inflammatory-type disorders. Pharmacologic treatment is also available for insufficient adrenal function, which is manifested as Addison disease, and excess glucocorticoid exposure, which results in Cushing syndrome.

Diabetes mellitus (DM) is a syndrome caused by a relative or absolute deficiency of insulin, with hyperglycemia being the hallmark medical finding. DM can occur as either an early onset form (type 1) or a gradual-onset form (type 2). In the former, insulin-producing β cells of the pancreas are destroyed or insufficiently active, and patients require lifelong treatment with exogenous insulin. In type 2 DM, adequate control of disease may be achieved by means of diet and exercise; if these methods fail, patients take oral hypoglycemic agents, which cause lower plasma glucose levels, improve insulin resistance, and reduce long-term complications (macrovascular and microvascular problems such as neuropathy, nephropathy, and retinopathy). Insulin is the sole treatment for type 1 DM and is sometimes also used for type 2 DM. For type 2 DM, drugs include sulfonylureas, which stimulate insulin secretion from pancreatic β cells; metformin, a biguanide that decreases blood glucose levels by reducing hepatic glucose production and glycogen metabolism in the liver and improving insulin resistance; meglitinides, which increase insulin secretion from pancreatic β cells; α-glucosidase inhibitors, which delay carbohydrate digestion and glucose absorption; and thiazolidinedione (TZD) derivatives (e.g., rosiglitazone and pioglitazone), which reduce insulin resistance.
<table>
<thead>
<tr>
<th>Hypothalamic Hormones</th>
<th>Pituitary Hormones</th>
<th>Target Organ</th>
<th>Specific Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin (-)</td>
<td>GH (growth hormone; somatotropin)</td>
<td>Liver</td>
<td>Somatomedins, IGFs</td>
</tr>
<tr>
<td>GHRH (growth hormone-releasing hormone) (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRH (corticotropin-releasing hormone)</td>
<td>ACTH (corticotropin)</td>
<td>Adrenal cortex</td>
<td>Glucocorticoids, mineralocorticoids, androgens</td>
</tr>
<tr>
<td>TRH (thrytropin-releasing hormone)</td>
<td>TSH (thyroid-stimulating hormone, or thyrotropin)</td>
<td>Thyroid</td>
<td>Thyroxine, triiodothyronine</td>
</tr>
<tr>
<td>GnRH (gonadotropin-releasing hormone)</td>
<td>FSH (follicle-stimulating hormone)</td>
<td>Conads</td>
<td>Estrogen</td>
</tr>
<tr>
<td></td>
<td>LH (luteinizing hormone)</td>
<td>Conads</td>
<td>Progesterone, testosterone</td>
</tr>
</tbody>
</table>

**Figure 5-1 Regulation of Hypothalamic and Pituitary Hormones**

The hypothalamus and pituitary control a complex neuroendocrine system that governs metabolism, growth, and reproduction. The hypothalamus produces both inhibitory and releasing neuropeptides and hormones, which reach the pituitary via a hypophysial portal system. Hypothalamic hormones trigger release of anterior pituitary hormones, which are sent to target organs where they induce hormone synthesis. Most of these endocrine-organ systems function via negative feedback, e.g., hypothalamic CRH stimulates
pituitary ACTH secretion, which stimulates adrenal cortisol secretion, which in turn inhibits CRH and ACTH secretion. Hypothalamic and pituitary hormones are used as tools in stimulation tests to diagnose hypofunctioning or hyperfunctioning endocrine states. For example, ACTH and CRH, which target the adrenal cortex, aid adrenal insufficiency diagnosis. Pituitary hormones are also used as replacement therapy for deficiencies such as hypopituitarism.
**Figure 5-2 Hypopituitarism**

Hypopituitarism may be partial or complete and may result from hypothalamic disease (leading to deficiency of hypothalamic-releasing hormones) or intrinsic pituitary disease (causing pituitary hormone deficiency). Patients may present with, for example, adrenal insufficiency or hypothyroidism. Clinical signs depend on the degree and rapidity of onset of the deficiency. For example, basal cortisol secretion is normal in partial ACTH deficiency, but during an illness, adrenal insufficiency may occur. In complete ACTH deficiency, cortisol secretion is always subnormal. Diagnosis of complete deficiency is relatively easy: most patients have symptoms, and serum levels of target-organ hormone (e.g., cortisol, thyroxine, and testosterone in men) and pituitary hormone (e.g., ACTH, thyrotropin, and luteinizing hormone, respectively) are low. Causes of hypopituitarism include pituitary tumor (most common); hypothalamic tumor or cyst; infiltrative, vascular, and other disorders; and pituitary or cranial radiotherapy.
FIGURE 5-3 GROWTH HORMONE DEFICIENCY AND TREATMENT

Growth hormone promotes linear growth by regulating endocrine and paracrine production of IGF-1. Besides disruption in growth, GH deficiency also causes increased subcutaneous visceral fat and reduced muscle mass, bone density, and exercise performance. Children have short stature and low growth velocity for age and pubertal stage. Adults, who usually have had pituitary tumors or head trauma, show low energy, reduced strength, weight gain, anxiety, reduced libido, and impaired sleep. GH therapy goals differ in children and adults. In adults, they are to improve conditioning and strength, restore normal body composition, and improve quality of life. In children, therapy promotes linear growth and restores body composition. Synthetic GH is effective for children with GH deficiency as long as epiphyses are not closed. Side effects include edema, muscle and joint pain, benign intracranial hypertension, hair loss, hypothyroidism, hypoglycemia or hyperglycemia, and the more serious risk of cancer.
Acromegaly is a disfiguring hormonal disorder caused by excessive GH secretion from a pituitary tumor. Signs of acromegaly include coarse facial features and enlarged hands, feet, tongue, and internal organs (which lead to heart disease, hypertension, diabetes, arthralgias). Therapy includes surgical removal of the tumor and/or radiation, or subcutaneous use of octreotide, a GH inhibitor, available in a long-acting depot form. Octreotide effects mimic those of the natural hormone somatostatin (inhibition of GH and IGF-1 levels; suppression of the response of luteinizing hormone to gonadotropin-releasing hormone). By normalizing levels of GH and IGF-1—both markers for acromegaly—octreotide controls clinical signs and symptoms. Common adverse effects are gastrointestinal; the more serious effects include cardiac arrhythmias, hypoglycemia or hyperglycemia, suppression of thyrotropin, pancreatitis, and biliary tract abnormalities.
The thyroid gland is responsible for regulating normal growth and development by maintaining a level of metabolism in body tissues that is optimal for normal function. The thyroid synthesizes, stores, and releases 2 major, metabolically active hormones: triiodothyronine (T₃) and thyroxine (T₄). T₃, the active form of the thyroid hormone, is 4 times more potent than T₄, but its serum concentration is lower. Approximately 80% of the gland's total daily production of T₃ results from conversion of T₄ to T₃ through deiodination of T₄. T₃ and T₄ exist in either free (active) or protein-bound (inactive) forms. More than 99% of circulating T₄ is bound to plasma proteins, so only a small fraction exists in free form. As a result, T₄ is metabolized very slowly and has a long half-life (7 days). T₃ is less bound to plasma proteins and thus undergoes faster metabolism and has a shorter half-life (1.5 days).
Thyroid hormones are synthesized and stored as amino acid residues of thyroglobulin. Major steps in synthesis and release include thyroid uptake of iodide, oxidation of iodide and iodination of tyrosyl groups of thyroglobulin, coupling iodotyrosine residues to produce iodothyronines, proteolysis of thyroglobulin, release of $T_4$ and $T_3$ into blood, and conversion of $T_4$ to $T_3$ in peripheral tissues and the thyroid. Hormone synthesis and release are controlled by a negative feedback mechanism (thyroid-hypothalamic-pituitary axis; autoregulation of iodide uptake). Low circulating hormone levels trigger hypothalamic release of thyrotropin-releasing factor (TRF), which induces pituitary secretion of thyrotropin (thyroid-stimulating hormone, TSH). Increasing TSH levels stimulate thyroid iodide uptake and hormone synthesis. Circulating hormones halt TRF and TSH secretion. The thyroid also regulates its own iodine uptake to protect against excess hormone production if extra iodide is ingested.
Figure 5-7 Hypothyroidism

Hypothyroidism, a syndrome that results from a deficiency of thyroid hormones, can be caused by either primary (thyroid gland) or secondary (hypothalamic/pituitary) dysfunction. The most common cause of primary hypothyroidism is Hashimoto thyroiditis, an autoimmune disorder in which unsuppressed T lymphocytes produce excessive amounts of antibodies that destroy thyroid cells. Certain drugs, such as lithium, nitroprusside, iodides, and sulfonamides, can also induce hypothyroidism. The condition is usually more prevalent in females and persons older than 60 years. It typically presents with symptoms of “slowing down” (e.g., weight gain, fatigue, sluggishness, cold intolerance, constipation, muscle aches). Goiter may be present. Patients with end-stage hypothyroidism or myxedema coma may experience hypothermia, confusion, stupor or coma, carbon dioxide retention, hyponatremia, and ileus. Laboratory findings include increased TSH and low free T4 levels.
**Figure 5-8 Hypothyroidism: Treatment of Choice**

The principal treatment goal for hypothyroidism is to achieve a euthyroid state with thyroid replacement therapy. The preparation of choice is levothyroxine, a synthetic $T_4$ formulation with advantages including stability, uniform potency, relatively low cost, once-daily dosing, and lack of foreign proteins. Levothyroxine may have innate metabolic activity, but most of its activity is due to its conversion to $T_3$. Patients should notice improvement in typical symptoms of hypothyroidism after 3 to 4 weeks of treatment. Toxicity is directly related to $T_4$ levels and manifests as nervousness, tachycardia, heat intolerance, and weight loss. Levothyroxine is available in various brands and generics, which may not be bioequivalent, so only 1 product should be used throughout treatment.
Liothyronine is a pure T₃ preparation that is not recommended for routine thyroid replacement. After oral ingestion, T₃ is absorbed more rapidly than T₄, which may produce supraphysiologic plasma T₃ levels, which can lead to thyrotoxicosis. Also, free T₄ levels remain low during T₃ administration and, if misinterpreted, could lead to incorrect use of more hormone. Therefore, T₃ levels must be monitored. Other disadvantages are the need for multiple doses, higher expense, and greater potential for cardiotoxicity. T₃ is therefore not better than T₄, which is converted to T₃ anyway. However, T₃ is recommended for acute severe myxedema. Liotrix (a stable synthetic) and desiccated thyroid contain T₄ plus T₃. Liotrix uses a physiologic ratio of 4:1 but has the same problems as T₃ and is more expensive. Desiccated thyroid, derived mostly from pork, is not recommended: product potency and composition vary and can result in toxic effects, including allergic reactions to animal protein.
Hyperthyroidism, or thyrotoxicosis, is due to excessive thyroid hormone production and is characterized by increased metabolism in all body tissues. The most common cause of hyperthyroidism is Graves disease, an autoimmune disorder in which an abnormal thyroid receptor binds to the TSH receptor and causes uncontrolled thyroid hormone production. Drugs such as amiodarone, iodides, and lithium can also cause hyperthyroidism. Like hypothyroidism, hyperthyroidism occurs more often in females than in males. Symptoms include goiter, exophthalmos, nervousness, heat intolerance, palpitations, weight loss, insomnia, and new or worsening cardiac findings (atrial fibrillation, angina). Untreated hyperthyroidism can progress to thyroid storm, a possibly fatal state with acute onset of high fever, exaggerated thyrotoxicosis symptoms, cardiovascular collapse, and shock. Laboratory findings include high serum levels of free $T_4$, undetectable TSH levels, or both.
Primary treatment options for patients with hyperthyroidism include thioamides, radioactive iodine (RAI), and surgery. Adjuncts to primary therapies include adrenergic antagonists and iodides. Surgery (subtotal or total thyroidectomy) is considered the treatment of choice in cases of suspected malignancy, esophageal obstruction, respiratory difficulties, presence of large goiter, or contraindications to other treatments. Of the pharmacologic options, thioamides (propylthiouracil, or PTU, and methimazole) are the preferred agents for children, pregnant women, and young adults with uncomplicated Graves disease. The agents can be used as long-term therapy or as short-term therapy to reduce thyroid hormone levels before RAI or surgery.
**Figure 5-12 Thioamides**

Thioamides inhibit formation of thyroid hormones by interfering with incorporation of iodine into tyrosyl residues of thyroglobulin and inhibiting coupling of iodothyrosyl residues to form iodothyronines. Thioamides also block the oxidative binding of iodide because they are iodinated and degraded within the thyroid gland, which diverts oxidized iodide away from thyroglobulin. PTU, but not methimazole, inhibits peripheral deiodination of T₄ to T₃, which causes a more rapid decline in T₃ levels in patients with thyroid storm. Methimazole is 10 times more potent than PTU, but both drugs are equally effective if given in equipotent dosages. Methimazole can be given once daily, whereas PTU must be given every 6 to 8 hours. PTU is preferred for pregnant women. A clinical response is usually seen after 6 to 8 weeks of therapy with thioamides. The duration of therapy is usually 12 to 18 months.
A pruritic maculopapular rash, without other systemic symptoms, is the most common adverse effect of thioamides. In mild cases, the rash resolves despite therapy, or another thioamide can be used (minimal cross-sensitivity exists). If systemic symptoms (eg, fever, arthralgias) occur, thioamide therapy should be stopped. Hepatotoxicity involves hepatocellular damage (with PTU) and obstructive jaundice (with methimazole). Liver function test (LFT) results should be watched if a history of liver disease or risk for hepatitis exists. Agranulocytosis (leukopenia with much lower polymorphonuclear leukocyte numbers) is the most serious adverse effect. Onset of symptoms (fever, malaise, sore throat) is quite sudden; high methimazole doses may lead to greater risk. If this disorder is diagnosed, thioamide administration should be stopped, and the patient should be monitored for infection. Other serious effects include peripheral neuritis, neuropathy, taste disorders, nephrotoxicity, myopathy, arthritis, and systemic lupus erythematosus.

Figure 5-13 Thioamides: Adverse Effects
Radioactive iodine is used for postadolescent patients, patients with Graves ophthalmopathy or history of thyroid surgery, poor surgical candidates, and those who do not respond to thioamides. It is the treatment of choice in older patients with heart disease and those with toxic multinodular goiter. The maximal effects of RAI do not occur for 3 to 4 months. $^{131}I$, used most often, is rapidly trapped by the thyroid; $\beta$ particles act mostly on parenchymal thyroid cells, with minimal damage to adjacent tissues. Effects of radiation depend on dosage, with larger doses causing cytotoxicity. Proper RAI doses can destroy the gland without injuring nearby tissues. The major adverse effect of RAI is hypothyroidism. Post-RAI hyperthyroidism, caused by hormones leaking from damaged thyroid, can occur but is minimized by use of thioamides or $\beta$ blockers before RAI (depletes the gland of hormones). Immediate adverse effects include mild thyroid pain and hair thinning; long-term effects include carcinogenesis and genetic damage.
Iodide (i.e., Lugol solution: 5% iodine and 10% potassium iodide) is the oldest known remedy for symptomatic relief of hyperthyroidism, and, before the advent of pharmacologic therapy, it was the sole treatment available. Today, iodide therapy has been mostly replaced by thioamides and β blockers. Iodides act by blocking organification of iodine, inhibiting release of thyroid hormones, and decreasing gland size and vascularity. Iodides act rapidly and produce symptomatic relief after 2 to 7 days. They are thus useful in patients with thyroid storm and those awaiting relief from thioamide therapy. Iodides are also routinely given, preferably with thioamides, 10 to 14 days before surgery to facilitate removal of the gland by reducing its size and vascularity. Iodide cannot be given before RAI because it can block retention of RAI by the gland. Major adverse effects of iodide include hypersensitivity reactions and the risk of hypothyroidism or worsening of hyperthyroidism.
FIGURE 5-16 ADRENERGIC ANTAGONISTS

Many signs and symptoms of hyperthyroidism are mediated through the sympathetic nervous system, so it seems logical to use adrenergic antagonists for symptomatic relief because these agents block the effects of thyroid hormones on catecholamines. Adrenergic antagonists do not affect the underlying disease process, so they are not used as primary therapy, but they are quite useful in providing rapid symptomatic relief before thioamides, RAI, or surgery can take effect. They can also be used as adjuncts to thioamides and RAI for neonatal thyrotoxicosis, thyrotoxicosis in pregnancy, and thyroid storm. The β blocker propranolol, which reduces conversion of T₄ to T₃, is the most widely used adrenergic antagonist; it relieves palpitations, tachycardia, anxiety, sweating, tremor, and neuro-muscular manifestations of hyperthyroidism. The calcium channel blocker diltiazem may be useful when propranolol should be avoided (eg, patients with asthma, CHF, diabetes).
Fig 5.17 Regulation of Adrenal Hormones

The 2 adrenal glands in the human body are responsible for producing mineralocorticoids (e.g., aldosterone), which regulate fluid and electrolyte balance, and glucocorticoids (e.g., cortisol), which are essential for carbohydrate metabolism. Aldosterone production is mediated primarily by the renin-angiotensin system; cortisol production is regulated by a feedback mechanism involving the hypothalamic-pituitary-adrenal (HPA) axis. First, the hypothalamus releases CRH in response to various stimuli including neurotransmitters, vasopressin, and catecholamines. CRH stimulates the anterior pituitary to release ACTH, which then stimulates the adrenal cortex to produce cortisol. As serum cortisol levels increase, synthesis and secretion of CRH and ACTH decrease via a negative feedback loop.
Mineralocorticoids enhance reabsorption of sodium and water from the distal tubule of the kidney and increase urinary potassium and hydrogen ion excretion. The principal function of glucocorticoids involves regulation of carbohydrate metabolism, but they are also involved in other physiologic actions, including gluconeogenesis, glucose utilization, lipid and bone metabolism, fluid and electrolyte homeostasis, alteration of levels of various immune cells, alleviation of the inflammatory response, and participation in neuropsychiatric functions. As a result of these functions—most notably immunosuppressive and antiinflammatory actions (a direct result of immunosuppressive effects)—glucocorticoids are widely used in treatment of cancer and autoimmune and inflammatory disorders such as asthma, inflammatory bowel disease, arthritis, and allergies.
Corticosteroids and Adrenocortical Dysfunction

**Figure 5-19 Corticosteroids**

Therapeutic corticosteroids (e.g., hydrocortisone, prednisone, dexamethasone), with different mineralocorticoid and glucocorticoid activities, are antiinflammatory and immunosuppressive via inhibiting immune cells. This reduces formation, release, and activity of inflammation mediators (e.g., cytokines, histamine, prostaglandins, leukotrienes). Short-term therapy adverse effects include insomnia, euphoria, and increased appetite, and long-term therapy effects include osteoporosis, hypertension, edema, hyperglycemia, and Cushing-like syndrome. Long-term drug use can suppress the HPA axis, and abrupt stopping of therapy can cause the possibly fatal acute adrenal insufficiency syndrome. Slow dosage tapering allows the HPA axis to begin functioning. To reduce systemic absorption and side effects, drugs can be given topically or by inhalation or nasal spray, intraarticular injection, or rectal suppository. Alternate-day and lowest effective dosing may limit side effects and adrenal atrophy.
Cushing syndrome is a group of clinical symptoms that result from prolonged exposure to excess glucocorticoids. The condition may be caused by exogenous factors, such as long-term corticosteroid use, or it may be of endogenous origin. The latter may be due to either excess ACTH secretion (ACTH dependent) or autonomous cortisol hypersecretion (ACTH independent). Conditions such as adrenocortical adenomas and carcinomas as well as ectopic ACTH and CRH syndromes are responsible for the endogenous syndrome. Clinical manifestations affect multiple organ systems and depend on the degree and duration of hypercortisolism. The most common sign is progressive obesity, which is seen in the face, neck, trunk, and abdomen. Facial fat accumulation produces a moon-face appearance, and an enlarged dorsocervical fat pad produces a buffalo hump. Other symptoms include weakness, muscle wasting, reduced arm muscle mass, osteoporosis, and cardiovascular and metabolic complications.
FIGURE 5-21 KETOCONAZOLE

Therapy for exogenous Cushing syndrome consists of minimizing exposure to glucocorticoids or ACTH. For the endogenous syndrome, therapy aims to reduce cortisol production in preparing patients for surgery or to maintain normal plasma cortisol levels until full effects of surgery or radiation are felt. The antifungal agent ketoconazole is used to treat paraneoplastic Cushing syndrome secondary to ectopic ACTH production. The agent is highly effective in decreasing cortisol by inhibiting adrenocortical cytochrome P-450-dependent enzymes. These enzymes catalyze formation of cortisol precursors such as pregnenolone as well as metabolizing drugs. Because ketoconazole inhibits the latter effect, it can increase levels of many hepatically metabolized agents such as cyclosporine, warfarin, digoxin, and phenytoin. Side effects include blood dyscrasias, headache, dizziness, fatigue, gynecomastia, GI symptoms, and rash. Patients respond to therapy after 4 to 6 weeks.
Metyrapone is used to treat Cushing syndrome when dose-limiting side effects occur with ketoconazole, and it can be used in combination with other agents. The agent can also be used as a test for adrenal function. Metyrapone reduces cortisol production by inhibiting 11-β-hydroxylation, the final step in glucocorticoid synthesis. This process leads to accumulation of adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone. Resultant adverse effects include water retention, hirsutism, GI disturbances, and dizziness. Dose reduction can limit these adverse effects. Metyrapone may take up to 4 months to produce a response.
Figure 5-23 Aminogluthimide

Aminogluthimide is used primarily for Cushing syndrome secondary to adrenal hyperplasia, ectopic ACTH production, or adrenal carcinoma. The drug seems most useful when given after pituitary irradiation or in combination with metyrapone. Aminogluthimide partially inhibits conversion of cholesterol to pregnenolone in the adrenal glands and blocks conversion of androstenedione (prehormone produced in the adrenals) to estrone and estradiol in peripheral tissues. This inhibition interrupts production of cortisol, aldosterone, and estrogens. A reflex increase in ACTH results, which partly or completely overcomes the blockade, but this reflex can be prevented by replacement amounts of hydrocortisone, but not dexamethasone, given concomitantly. Adverse effects include headache, sedation, dizziness, nausea, anorexia, rash, blood dyscrasias, tachycardia, and hypertension. This drug may take up to 4 months to produce a response.
Addison disease is due to autoimmune-mediated destruction of adrenal cortex, mycobacterial infection, adrenal metastases, or use of certain drugs. Symptoms, caused by reduced production of glucocorticoids, mineralocorticoids, and sex hormones, range from vague feelings of illness to acute syncope and mental status changes. Biochemical abnormalities (e.g., hyponatremia, hyperkalemia) usually exist. The life-threatening adrenal crisis, which occurs in cases of undiagnosed adrenal insufficiency and untreated stress, mimics septic shock and presents with severe anorexia, dehydration, and hypotension; IV fluids and high-dose IV glucocorticoids are used for therapy. Chronic disease is managed with a glucocorticoid (hydrocortisone) plus a mineralocorticoid (fludrocortisone), with dosage tailored to avoid Cushing syndrome or inadequate therapy. Patients should be monitored for fludrocortisone side effects (e.g., electrolyte changes, hypertension, edema, and hyperglycemia).
**Relative density of distribution of islets in various parts of pancreas**

Section of an islet surrounded by acini (×220); Gomori aldehyde fuchsian and Ponceau stain; β granules stain deep purple; α cells, orange-pink

Portion of islet greatly magnified (×1200); Gomori aldehyde fuchsian and Ponceau stain

Dextrose injected (5 g/kg body weight); this stimulates output of insulin

<table>
<thead>
<tr>
<th>1/2</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Hours</th>
</tr>
</thead>
</table>

1/2 hour after intraperitoneal dextrose injection: β cells depleted of insulin granules

6 hours after injection: insulin granules restored in β cells; islet section has resting stage appearance

**Figure 5-25 The Pancreas and Insulin Production**

The pancreas is the principal organ involved in production and secretion of hormones that maintain normal blood glucose levels, or euglycemia. The pancreatic β cells of the islets of Langerhans produce, store, and secrete insulin. The pancreas first produces a parent protein called proinsulin, which is then cleaved to form the smaller compound proinsulin. Proinsulin is then cleaved to form insulin and peptide C. The pancreas also produces glucagon, a hormone that increases blood glucose levels, and somatostatin, a hormone that inhibits both insulin and glucagon secretion. Ingestion of carbohydrates prompts an increase in the release of insulin and a concomitant decrease in plasma glucagon levels. Glucagon is released in response to low blood glucose levels and protein ingestion. It stimulates insulin secretion, which in turn inhibits glucagon release in a negative feedback loop.
Insulin secretion is a highly regulated process that varies throughout the day. In a postprandial setting (after a meal), a burst of insulin secretion normally occurs in response to a transient increase in the plasma glucose level. In a postabsorptive period, the pancreas reduces insulin secretion, which maintains low basal levels of circulating insulin. Insulin is the key to the body's use of glucose. It promotes the uptake of glucose, fatty acids, and amino acids, and it facilitates their conversion to forms used for storage in most tissues. The important metabolic sites that are sensitive to insulin include the liver, where glycogen (the main carbohydrate reserve, which is easily converted to glucose) is synthesized, stored, and broken down; skeletal muscle, where glucose oxidation produces energy; and adipose tissue, where glucose is converted to fatty acids, glycerol phosphate, and triglycerides.
Without insulin, glucose is not transported across cell membranes, which leads to a cascade of metabolic events. The body reacts by inducing gluconeogenesis (the liver converts glycogen to glucose). To produce energy, skeletal muscle converts its structural proteins to amino acids, which are carried to the liver, where they are converted to glucose. Resultant excess glucose, still not being used by cells, leads to hyperglycemia. Insulin deficiency increases fat catabolism: free fatty acids are broken down into keto acids to increase energy sources. Kidneys eliminate keto acids, which produces ketonuria and ketonemia. Keto acids also reduce blood pH, which can result in ketoacidoses, coma, and death. Diabetes is caused by a relative or absolute lack of insulin, with hyperglycemia being the hallmark medical finding. Once thought of as 1 disease, diabetes is now believed to be a chronic heterogeneous group of disorders that result from pathologic processes that depend on diabetes type.
**Microvascular and Macrovascular Complications**

**Diabetic retinopathy**
Diabetic retinopathy can be easily detected during a dilated eye exam and is the leading cause of blindness among adults in the United States. Visual loss can be prevented with early recognition and treatment of retinopathy.

**Nonproliferative retinopathy** (early stage)
- Microaneurysms
- Hemorrhages
- Cotton-wool spots
- Hard exudate
- Narrowed arterioles

**Proliferative retinopathy** (late stage)
- Massive hemorrhage
- Retinitis proliferans

**Diabetic nephropathy**
- Histologic view of diabetic glomerulosclerosis

**Cerebrovascular disease**
The high incidence of vascular complications among patients with diabetes is related not only to blood glucose elevations, but also to the frequent association of dyslipidemia, hypertension, a procoagulant state, and the tendency to form unstable plaques in the arterial wall.

- Ischemic stroke due to in situ thrombosis, usually triggered by plaque rupture in the carotid or cerebral artery.
- Myocardial infarction and related heart disease account for 70% of the mortality in people with diabetes.
- Atheromatous aorta and branches

**Figure 5-28 Type 1 Diabetes Mellitus**

In type 1 DM, the insulin-producing β cells of the pancreas are destroyed by either intrinsic genetic factors or extrinsic factors such as viruses or chemical toxins. In one theory that involves an autoimmune-mediated mechanism, predisposed patients react abnormally to environmental triggers by producing antibodies that are directed against β cells. Insulin secretion is impaired early in the disease and eventually stops. Type 1 DM usually develops abruptly during childhood or adolescence and usually presents with polydipsia, polyuria, and polyphagia. Ketoacidosis is more likely to occur in type 1 than in type 2 DM. Patients require lifelong treatment with exogenous insulin to control blood glucose levels and prevent short- and long-term macrovascular and microvascular complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. Oral hypoglycemic agents are ineffective in patients with type 1 DM because functioning β cells are required.
Central defects in type 2 DM are decreased insulin secretion and insulin resistance. Before diabetes is diagnosed, patients, often obese, have hyperinsulinemia caused by excess dietary carbohydrates. The pancreas malfunctions and fails to supply high insulin demands. This impaired secretion is complicated by insulin resistance; insulin cannot decrease plasma glucose levels through suppression of hepatic glucose production and stimulation of glucose use in skeletal muscle and adipose tissue. Resistance develops in several possible ways, eg, chronic hyperinsulinemia causes insulin receptor down-regulation, which leads to defects in insulin binding and postreceptor insulin signaling pathways. Unlike type 1 DM, type 2 DM has a more gradual onset, may not present with symptoms, and usually occurs in overweight patients older than 35 years. Oral hypoglycemic agents decrease plasma glucose levels, improve insulin resistance, and reduce long-term complications. Many patients need insulin therapy.
**Oral Antihyperlipidemic Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>Sulfonylureas (first generation)</td>
<td>Numerous interactions with drugs that alter hepatic metabolism or urinary excretion (e.g., chloramphenicol, cimetidine, warfarin, salicylates, certain sulfonamide antibiotics), especially with chlorpropamide and tolbutamide</td>
<td>Type 1 DM, pregnancy or breastfeeding, severe hepatic or renal dysfunctions, severe acute comorbidities or surgery</td>
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<tr>
<td>Acetohexamide</td>
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<td>Chlorpropamide</td>
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<td>Tolbutamide</td>
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<tr>
<td>Sulfonylureas (second generation)</td>
<td>Less likely to have drug interactions than first-generation agents</td>
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<td>Glimepiride</td>
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<tr>
<td>Glipizide</td>
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<td>Glyburide</td>
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<tr>
<td>α-Glucosidase inhibitors</td>
<td>Absorption possibly reduced by charcoal and digestive enzymes; possibly reduced digoxin, propranolol, and ranitidine levels</td>
<td>Malabsorption, inflammatory bowel disease, intestinal obstruction</td>
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<td>Acarbose</td>
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<td>Miglitol</td>
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<tr>
<td>Biguanide</td>
<td>Effect potentiated by alcohol and cimetidine; acute renal failure possibly caused by iodinated materials; metformin-induced lactic acidosis</td>
<td>Renal failure (creatinine clearance &gt;1.4 mg/dL in females, &gt;1.5 mg/dL in males), hepatic disease, congestive heart failure requiring drug treatment, history of lactic acidosis, alcoholism, imminent surgery, before and 48 hours after parenteral contrast studies</td>
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<tr>
<td>Metformin</td>
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<tr>
<td>Meglitinides</td>
<td>Effect of repaglinide possibly reduced by drugs that induce cytochrome P-450 enzyme system (antiepileptics, rifampin)</td>
<td>Type 1 DM</td>
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<td>Repaglinide</td>
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<tr>
<td>Nateglinide</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Metabolism of pioglitazone inhibited by drugs metabolized by cytochrome enzymes, such as ketoconazole; plasma concentrations of oral contraceptives reduced by pioglitazone</td>
<td>Type 1 DM, preexisting liver disease, severe congestive heart failure, premenopausal anovulatory women (TZDs may cause resumption of ovulation and unpredicted, possibly unwanted, pregnancy), drugs metabolized by cytochrome enzymes</td>
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<td>Pioglitazone</td>
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<td>Rosiglitazone</td>
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**Matching Pharmacology to Pathophysiology**

![Diagram showing the effects of insulin and medications on hyperglycemia](image)

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**Figure 5-30 Insulin Therapy**

Insulin is the sole therapy for type 1 DM. It is also used (combination therapy or monotherapy) in type 2 DM poorly controlled with diet and oral agents. Exogenous insulin stimulates carbohydrate metabolism and helps with transfer of glucose into cardiac and skeletal muscle and adipose tissue. Insulin also aids in conversion of glucose to glycogen, stimulates lipogenesis and protein synthesis, and reduces serum potassium and magnesium levels. Insulin, a protein, is degraded in the GI system if used orally, so it is given subcutaneously, or, in emergencies, intravenously. Absorption of an insulin product may vary in a patient from one injection to the next, absorption being affected by site of injection, temperature, physical activity, and dose. Insulin preparations differ in dose, onset, duration, and sources of origin, including biosynthetic and semisynthetic human (therapeutically equal), human insulin (least antigenic and most soluble), and beef and pork (replaced by human).
FIGURE 5-31 REACTIONS TO INSULIN: HYPOGLYCEMIA AND ADIPOSE TISSUE CHANGES

Major predisposing factors to hypoglycemia, the most common and serious adverse reaction to insulin, include inadequate food intake, poor timing of injections, exercise, and use of hypoglycemic drugs. Symptoms are autonomic (e.g., sweating, trembling, feeling of warmth) or neuroglycopenic (e.g., confusion, weakness, drowsiness). Hunger, tachycardia, blurred vision, and loss of consciousness also occur. Elderly patients with neuropathy, patients with long-standing diabetes (>10 years), and patients taking β-blockers can have blunted symptoms. Use of sugar packets, candy, or pure glucose products can help with hypoglycemia.

Unconscious patients must be injected with glucagon or IV glucose or dextrose. Insulin injection may also cause lipohypertrophy, which occurs in patients who use only 1 site rather than rotating sites. Rotating sites solves the problem. Lipodystrophy, an immunologic reaction to insulin, is treated by changing to human insulin and injecting it into the affected area.
**FIGURE 5-32 SULFONYLUREAS**

Sulfonylureas, the historical mainstay of therapy in type 2 DM, used as monotherapy or with insulin or other oral agents, act mainly by stimulating insulin secretion from pancreatic β cells, enhancing β-cell sensitivity to glucose, and reducing glucagon release. They work only if β cells are functioning. Older drugs (eg, chlorpropamide, tolbutamide) have been replaced by new agents (eg, glimepiride, glibizide, glyburide), with greater potency, fewer drug interactions, and better pharmacokinetic profiles. If glucose control fails with long-term sulfonylurea use, other agents may be added instead of increasing sulfonylurea doses. Sulfonylureas are best for patients diagnosed after the age of 40 years or when disease duration is less than 5 years, body weight is nearly ideal, and fasting glucose levels are less than 180 mg/dL. Main adverse effects are hypoglycemia and weight gain; others are GI-related effects, allergic reactions, hepatotoxicity, hypothyroidism, and disulfiram reaction (chlorpropamide).
Figure 5-33 Biguanides

Metformin, the only biguanide available in the United States, is used as initial monotherapy or with insulin or other oral drugs in patients with type 2 DM who have secondary failure to sulfonylurea monotherapy (initial response but then failed glucose control with long-term use). Metformin decreases blood glucose levels by reducing hepatic glucose production and glycogen metabolism and improving insulin resistance via enhancing insulin-mediated glucose uptake. It decreases triglyceride and total cholesterol levels, increases HDL levels, and causes weight loss and is ideal for overweight hyperlipidemic patients. Hypoglycemia occurs only when metformin is used with insulin or hypoglycemic drugs. Adverse effects are GI related and, of greatest concern, the rare lactic acidosis, caused by inhibited conversion of lactate to glucose and greater lactate production, which mostly affects patients with renal, hepatic, or cardiovascular disorders.
Meglitinides (repaglinide and nateglinide) are approved as monotherapy or in combination with metformin or TZDs in patients with type 2 DM. Similar to sulfonylureas, meglitinides cause an increase in insulin secretion from pancreatic β cells. Unlike sulfonylureas, meglitinides have a rapid onset and a shorter duration, which necessitates dosing within 30 minutes of each meal. These agents are especially useful for patients who have difficulty controlling postprandial hyperglycemia. The efficacy of meglitinides in producing reductions in glycosylated hemoglobin concentration (HbA₁c) and the fasting plasma glucose (FPG) level is comparable to that of sulfonylureas and metformin (reduces HbA₁c by 1.5-2% and FPG level by 50-70 mg/dL). Adverse effects include mild hypoglycemia (particularly if administration is not followed with food) and weight gain.
**Figure 5-35 α-Glucosidase Inhibitors**

α-Glucosidase inhibitors (acarbose, miglitol) can be used singly or with insulin or other oral drugs for type 2 DM. These drugs inhibit glucosidases in the small intestine brush border that break down (hydrolyze) complex polysaccharides and sucrose into absorbable monosaccharides. The rate of carbohydrate digestion and glucose absorption is thus delayed, which leads to lower postprandial glucose spikes (by 25-50 mg/dL). These drugs work best in patients with postprandial hyperglycemia and when taken with a meal containing complex carbohydrates. The drugs decrease FPG slightly (20-30 mg/dL) and HbA1c levels by 0.5% to 1.0%. Adverse effects are GI related (flatulence, diarrhea, abdominal pain), which result from fermentation of unabsorbed carbohydrates in the small intestine and are lessened by slow dose titration. Used with insulin or other oral drugs, they can cause hypoglycemia. Hepatic transaminase levels can increase (acarbose), so LFT results must be watched.
**Figure 5-36 Thiazolidinediones**

Thiazolidinediones (rosiglitazone and pioglitazone) are a relatively new class of antihyperglycemic agents that can be used as monotherapy or in combination with insulin or other oral agents in patients with type 2 DM. TZDs reduce hyperglycemia and hyperinsulinemia by decreasing insulin resistance (via enhancement of insulin-mediated glucose uptake) at peripheral sites and in the liver, which results in increased insulin-dependent glucose disposal and decreased hepatic glucose output. These effects are accomplished by selective binding at the peroxisome PPAR-γ, which is found in adipose tissue, skeletal muscle, and liver. Receptor activation modulates transcription of several insulin-responsive genes that control glucose and lipid metabolism.
Figure 5-37 Thiazolidinediones: Clinical Rationale and Adverse Effects

Thiazolidinedione pharmacology is based on suggestions that patients with type 2 DM already have too much insulin. The liver, however, is resistant to that insulin and therefore continues to produce large amounts of glucose. Instead of stimulating the pancreas to produce more insulin, sensitivity to existing insulin should be increased to slow hepatic glucose production. TZD effects on HbA1c and FPG fall between those of acarbose and the sulfonylureas and metformin. TZDs plus insulin enhance glycemic control and decrease insulin needs. TZDs also reduce triglyceride levels and increase HDL, but they also increase LDL levels. The first TZD (troglitazone) was withdrawn after causing hepatotoxicity. The 2 drugs now used have not had hepatotoxic effects, but LFTs should be checked before and during TZD therapy. TZDs also cause hematologic effects (reduced hemoglobin, hematocrit, neutrophils), hypoglycemia (when used with other drugs), and edema (thus should be used with care in congestive heart failure).
OVERVIEW

The gastrointestinal (GI) tract is an epithelium-lined muscular tube that runs from the mouth to the anus. The major functions of the GI system are food digestion, nutrient absorption, and delivery of nutrients to the blood for distribution. Other functions are excretion of waste and secretion of hormones into the blood for delivery to distal targets. The GI system has an important role in fluid and electrolyte balance. It is the normal route for water and salt intake and a potential source of fluid and electrolyte loss. During digestion, a large volume of digestive secretions is added to the ingested, chewed, and swallowed food. Nearly all of this combined mixture must be reabsorbed to avoid major disturbances in fluid-electrolyte and acid-base balance. The small intestine provides a large surface area for the absorption of nutrients and drugs. Substances are moved through the GI tract by peristalsis. Abnormally fast or slow peristalsis can disrupt absorption of nutrients, drugs, and water—the origin of most GI dysfunctions, including constipation, diarrhea, peptic ulcer disease, gastroesophageal reflux disease (GERD), and emesis.

Laxatives are used for constipation. Laxatives cause emptying of the colon and defecation by stimulating peristalsis or by adding more bulk or water to the feces. Opioids (diphenoxylate and loperamide) are the most effective drugs for controlling diarrhea. Diarrhea is also treated with antiinflammatory drugs such as the nonsteroidal antiinflammatory drugs (NSAIDs) aspirin and indomethacin. Bismuth compounds are used for simple diarrhea.

Peptic ulcer disease is caused by an erosion of the mucosal layer of the stomach or proximal small intestine (duodenum). Helicobacter pylori infection is the most common cause. GERD is a similar disorder that occurs in the esophagus and is treated with similar medications. Peptic ulcer disease is best treated by a combination of lifestyle changes and drugs. Histamine H₂-receptor antagonists are the first-line drugs for peptic ulcers. These blockers reduce stomach acidity without producing adverse effects. Proton pump inhibitors (PPIs) are effective at reducing gastric acid secretion by blocking H⁺,K⁺-ATPase, an enzyme expressed by stomach parietal cells. PPIs are therapeutically effective but usually must be discontinued because of an adverse effect profile. Antacids neutralize stomach acid and blunt reflux disease symptoms. They are the first-line drugs for GERD.

Several drugs are available to treat nausea, vomiting, and motion sickness. These agents include histamine antagonists, corticosteroids, phenothiazines, benzodiazepines, and serotonin receptor antagonists.
The nervous system exerts a profound influence on all digestive processes (motility, ion transport associated with secretion and absorption, and blood flow). Some of this control emanates from connections between the digestive system and the CNS, but just as important, the digestive system is endowed with its own, local nervous system, referred to as the enteric or intrinsic nervous system. Principal components of the enteric nervous system are 2 networks or plexuses of neurons, both of which are embedded in the wall of the digestive tract and extend from the esophagus to the anus. The myenteric (Auerbach) plexus is located between the longitudinal and circular layers of muscle in the tunica muscularis and controls primarily digestive tract motility. The submucosal (Meissner) plexus regulates GI blood flow and epithelial cell function by monitoring luminal contents.
The enteric plexuses contain 3 types of neurons, most of which are multipolar. Motor neurons control GI motility, secretion, and absorption. They act directly on smooth muscle, secretory cells (parietal, chief, mucous, pancreatic exocrine cells), and GI endocrine cells. Sensory neurons receive information from sensory receptors in the mucosa and muscle. They respond to mechanical, thermal, osmotic, and chemical stimuli. Chemoreceptors are sensitive to pH, glucose, and amino acids. Sensory receptors in muscle respond to stretch and tension. Interneurons integrate information from sensory neurons and transmit it to enteric motor neurons. Enteric neurons secrete ACh and norepinephrine. Neurons that secrete ACh are excitatory and stimulate smooth muscle contraction, increase intestinal secretions, release enteric hormones, and relax (dilate) blood vessels. Norepinephrine, released from extrinsic sympathetic neurons, is inhibitory and opposes biologic actions of ACh.
The digestive tube shows 2 basic motility patterns: propulsion, the movement of food along the tube so that food can be catabolized and absorbed, and peristalsis, the major type of propulsive motility, seen especially in the esophagus and small intestine. A ring of muscle contraction appears on the oral side of a food bolus and moves toward the anus, so the luminal contents are forced in that direction. As the ring moves, the muscle on the other side of the distended area relaxes for smooth passage of the bolus. Mixing
Function and Regulation of the GI System

### Factors Affecting Gastric Emptying

- **Duodenal chemoreceptors**
  - Acid
  - Fats
  - Amino acids/peptides

- **Gastrointestinal hormones**
  - Secretin
  - Cholecystokinin
  - Gastric inhibitory peptide (GIP)
  - Gastrin

Duodenal stimuli elicit hormonal inhibition of gastric emptying.

### Sequence of Gastric Motility

1. Stomach is filling. A mild peristaltic wave (A) has started in antrum and is passing toward pylorus. Gastric contents are churned and largely pushed back into body of stomach.

2. Wave (A) fading out as pylorus fails to open. A stronger wave (B) is originating at incisurae and is again squeezing gastric contents in both directions.

3. Pylorus opens as wave (B) approaches it. Duodenal bulb is filled, and some contents pass into second portion of duodenum. Wave (C) starting just above incisura.

4. Pylorus again closed. Wave (C) fails to evacuate contents. Wave (D) starts higher on body of stomach. Duodenal bulb may contract or may remain filled as peristaltic wave originating just beyond it empties second portion.

5. Peristaltic waves are now originating higher on body of stomach. Gastric contents are evacuated intermittently. Contents of duodenal bulb area pushed passively into second portion as more gastric contents emerge.

6. 3 to 4 hours later, stomach is almost empty. Small peristaltic wave empties duodenal bulb with some reflux into stomach. Reverse and antegrade peristalsis present in duodenum.

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**Figure 6-3 Gastrointestinal Motility (continued)**

ensures that ingested materials are exposed to digestive enzymes and properly absorbed. In the absence of mixing, food is not in contact with epithelial cells that absorb nutrients. Segmentation contractions are a common type of mixing motility seen especially in the small intestine; segmental rings of contraction break down and mix food. Alternating contraction and relaxation of longitudinal muscle in the gut wall also provides effective mixing of its contents.
Food in the intestinal lumen causes smooth muscle contraction above the bolus and relaxation below, so that a peristaltic wave moves food down the intestine from the mouth to the anus. The enteric nervous system controls peristalsis and can work separately from the CNS, but digestion needs enteric nervous system and CNS coordination. Parasympathetic and sympathetic neurons connect the CNS and digestive tract, which allows sensory information to be sent to the CNS, as well as CNS regulation of GI function and relay of non-GI system signals. Sympathetic stimulation inhibits GI secretion and motor activity and causes GI sphincter and blood vessel contraction. Parasympathetic stimulation increases GI secretion and motor activity and causes GI sphincter and blood vessel dilation. Important peristaltic reflexes are the gastrocolic, in which stomach distension causes colonic exodus, and the enterogastric, in which small intestine distension or irritation reduces stomach secretion and motor activity.
The endocrine system regulates GI function by secreting hormones that modify the physiology of target cells. Digestive function is affected by hormones produced in many endocrine glands, but the greatest control is exerted by hormones produced within the GI tract. The GI tract is the largest endocrine organ in the body, and the endocrine cells within it are referred to collectively as the enteric endocrine system. Three of the best-studied enteric hormones are gastrin, cholecystokinin (CCK), and secretin. Gastrin is secreted from the stomach and plays an important role in control of gastric acid secretion. CCK is a small intestinal hormone that stimulates secretion of pancreatic enzymes and bile. Secretin is a hormone secreted from small intestinal epithelial cells that stimulates secretion of bicarbonate-rich fluids from the pancreas and liver.

### Figure 6-5 Hormones of the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Neurones/Endocrine Cell Type and Location</th>
<th>Stimulus for Secretion</th>
<th>Primary Action</th>
<th>Other Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>G cell, stomach, duodenum</td>
<td>Vagus, distention, amino acids</td>
<td>Stimulate HCl secretion</td>
<td>Inhibit gastric emptying</td>
</tr>
<tr>
<td>Secretin</td>
<td>S cell, duodenum</td>
<td>Acid</td>
<td>Stimulate pancreatic ductal cell H₂O and HCO₃⁻ secretion</td>
<td>Inhibit gastric secretion, inhibit gastric motility, and stimulate bile duct secretion of H₂O and HCO₃⁻</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>I cell, duodenum, jejunum</td>
<td>Fat, vagus</td>
<td>Stimulate enzyme secretion by pancreatic acinar cells and contract the gallbladder</td>
<td>Inhibit gastric motility</td>
</tr>
<tr>
<td>GIP</td>
<td>K cell, duodenum, jejunum</td>
<td>Fat</td>
<td>Inhibit gastric secretion and motility</td>
<td>Stimulate insulin secretion</td>
</tr>
<tr>
<td>Motilin</td>
<td>M cell, duodenum, jejunum</td>
<td></td>
<td>Increase motility and initiate the MMC</td>
<td></td>
</tr>
</tbody>
</table>
Secretions of gastric acid (H⁺) by parietal cell mediated by neurocrine, paracrine, and endocrine mechanisms. Medical or surgical blockade of these mechanisms affords therapeutic options.

Parietal cell mechanisms of acid (H⁺) secretion involve series of chemical exchanges across basal membrane, with final active exchange of H⁺ for K⁺ mediated across apical (secretory) membrane by H⁺-K⁺-ATPase (proton pump).

**Figure 6-6 Parietal Cell Function Regulation**

The stomach's parietal cells secrete approximately 2 L of acid a day as hydrochloric acid. This acid eradicates bacteria, aids in digestion by solubilizing food, and maintains optimal pH (1.8-3.2) for the function of pepsin, a digestive enzyme. H⁺,K⁺-ATPase (the proton pump) is expressed on parietal cell apical membranes and uses energy from ATP hydrolysis to pump hydrogen ions into the lumen in exchange for potassium ions. Three regulatory molecules stimulate acid secretion—ACh, histamine, gastrin—and one inhibits acid secretion—somatostatin. ACh increases acid secretion by stimulating muscarinic (M₂) receptors. Histamine, a paracrine hormone released from enterochromaffinlike cells, stimulates acid secretion by activating H₂ receptors. Gastrin, a hormone released by G cells (endocrine cells in gastric epithelium), increases acid release by activating gastrin receptors. Somatostatin is also secreted by gastric endocrine cells and, with prostaglandins, opposes the stimulatory actions of gastrin.
Exocrine pancreas secretion is under neural and endocrine control. Pancreatic secretions, the major mechanism for neutralizing gastric acid in the small intestine, are stimulated by food entering the stomach and chyme entering the small intestine. The vagus nerve innervates the pancreas (and the stomach) and applies a low-level stimulus for secretion in anticipation of a meal. The most important stimuli for pancreatic secretion come from 3 enteric nervous system hormones. CCK is synthesized and secreted by duodenal endocrine cells in response to partly digested proteins and fats in the small intestine. CCK is released into blood and binds to receptors on pancreatic acinar cells, which induces digestive enzyme secretion. Secretin, secreted in response to acid in the duodenum, stimulates pancreatic secretion of water and bicarbonate. Gastrin, like CCK, is secreted by the stomach and stimulates acid secretion by parietal cells and digestive enzyme secretion by pancreatic acinar cells.
Defecation (passing of feces through the rectum and anus) occurs via relaxation of the involuntary and voluntary internal anal sphincter and heeding the rectosphincteric reflex; it is prevented by external anal sphincter contraction. The rectum filling with fecal material causes the urge to defecate. When the external anal sphincter relaxes, rectal smooth muscle contracts to force feces out. The presence of food in the stomach increases colon motility. A rapid parasympathetic response (stimulated GI motility by depolarizing smooth muscle cells) is initiated; CCK and gastrin mediate a slower hormonal response. Disorders of large intestine motility may be caused by emotional factors via the extrinsic autonomic nervous system; IBS, a disorder worsened by stress, causes constipation or diarrhea. Megacolon (Hirschsprung disease), the absence of the colon enteric nervous system, causes intestinal contents near the constriction to accumulate and severe constipation.
Proteolytic enzymes are packaged in vesicles in an inactive form and are thus protected against the harsh pH conditions of the GI tract. Pepsin is a stomach enzyme derived from pepsinogen that is active at low pH. Pepsin cleaves the peptide bond between acidic (aspartic or glutamic acid) and aromatic (phenylalanine, tyrosine) amino acids. This endonuclease catalyzes proteins into smaller peptides. Trypsin is a pancreatic enzyme derived from trypsinogen that is active at slightly basic pH. Trypsin hydrolyzes peptide bonds adjacent to the basic amino acids lysine and arginine, thus hydrolyzing proteins into smaller peptides. Other endopeptidases, such as chymotrypsin and enterokinase, digest proteins into multiple amino acid fragments. Pancreatic carboxypeptidase is an exopeptidase that hydrolyzes dipeptides at the carboxyl end. Small intestine aminopeptidase is an exopeptidase that hydrolyzes dipeptides from the amino end. Finally, dipeptidase liberates free amino acids.


**FIGURE 6-10 FAT DIGESTION**

Fat digestion and absorption depend on bile, which, secreted by the liver and released into the gut by the action of CCK on the gallbladder, acts as an emulsifier to break up fat globules to aid digestion. Pancreatic lipase is a water-soluble enzyme and thus acts only on fat globule surfaces (hydrolyzes neutral fats to give free fatty acids and 2-monoglycerides). The detergent action of bile salts, especially lecithin, is needed to disperse fat into small globules for efficient lipase action. Bile also forms micelles—aggregates of free fatty acids, monoglycerides, and bile—which help transport water-insoluble fatty acids. Micelles take fat digestion products away from the digestion site to be absorbed by enterocytes. These products thus do not inhibit lipases (negative feedback). Poor fat absorption causes excess fat in stools, or steatorrhea. Stools are bulky, pale, and odiferous.
Disorders of Colonic Motility

Diarrhea

Motility patterns in the colonic lumen include peristalsis, which propels luminal contents toward the rectum, and those that extend contact of the luminal contents with absorptive epithelial cells. Prolonging contact facilitates absorption of fluid from the laces. Processes that promote propulsive patterns produce diarrhea. *Diarrhea* is defined as loose, watery stools that occur at least 3 times per day. Bacterial infections, viral infections, adverse food reactions, parasites, and functional bowel disorders can lead to diarrhea. Because dehydration is caused by diarrhea, treatments include rehydration with electrolytes (e.g., broths, soup, potassium supplements) or slowing motility with loperamide, bismuth subsalicylate, or kaolin pectin suspension. Most types of diarrhea are caused by viruses, so antibiotics are usually ineffective. Raspberry or blueberry leaves are sometimes taken with tea to alleviate some symptoms.

Figure 6-11 Colonic Motility and Treatment of Diarrhea
Other antidiarrheal drugs include agents that inhibit motility and modify fluid and electrolyte transport, such as NSAIDs. Loperamide and diphenoxylate (meperidine derivatives) are 2 antimotility drugs that reduce peristalsis by activating presynaptic opioid receptors in the GI tract and decreasing acetylcholine release. Adverse effects include dizziness, drowsiness, and stomach cramping; the use of these drugs is contraindicated in children. NSAIDs such as indomethacin and aspirin are thought to relieve diarrhea by blocking COX-1 and inhibiting prostaglandin synthesis. The most common adverse effects of aspirin are bleeding, respiratory depression, hypersensitivity reactions, hepatitis (particularly children), and salicylate toxicity.
Constipation, one of the most common GI problems in the United States, refers to passage of small amounts of hard and dry stools. Bowel movements occur fewer than 3 times a week. Women (especially pregnant) and older adults (older than 65 years) report constipation most often. Under normal conditions, the colon absorbs water as food passes through it and waste products (stool) form. Stool becomes solid because most of the water is absorbed. The hard and dry stools occur when the colon absorbs too much water or the colon's muscle contractions are slow. Common symptoms are lethargy, feeling bloated, and painful bowel movements. Causes can be metabolic and endocrine; neurogenic (involving the CNS or PNS); and idiopathic. These causes include a lack of dietary fiber, inadequate hydration, lack of exercise, IBS, changes in life routines (pregnancy, travel), aging, laxative abuse, ignoring urges to have a bowel movement, stroke, colonic disease, and intestinal disease.
Treatments for constipation include aluminum- and calcium-containing antacids, calcium channel blockers (antihypertensives), iron supplements, diuretics, and antidepressants. Bulk-forming laxatives (fiber supplements) are considered the safest but can interfere with absorption of some drugs. They are taken with water and absorb water in the intestine and to make the stool softer. Stimulant laxatives cause rhythmic muscle contractions in the intestines. Because phenolphthalein, an ingredient in some stimulants, may increase the risk of cancer, the US FDA proposed a ban on over-the-counter products containing phenolphthalein. Thus, safer ingredients replaced phenolphthalein in most laxatives. Stool softeners provide moisture to the stool, prevent dehydration, and are used after childbirth and surgery. Lubricants (mineral oil) add oil to the stool, which allows the stool to move through the intestine more easily. Saline laxatives draw water into the colon for easier passage of stool.
Irritable Bowel Syndrome

Abdominal pain or discomfort associated with changes in stool frequency and/or form

Altered bowel wall sensitivity and motility result in irritable bowel symptom complex.

Enterochromaffin cell

Actions of gut wall 5-hydroxytryptamine (5-HT) may underlie abnormalities of motility and sensation.

Nerve ending

Rome II diagnostic criteria* for irritable bowel syndrome

12 weeks† or more in the past 12 months of abdominal discomfort or pain that has 2 of 3 features:
   a. Relieved with defecation
   b. Onset associated with change in frequency of stool
   c. Onset associated with change in form (appearance) of stool

* In the absence of structural or metabolic abnormalities to explain the symptoms
† The 12 weeks need not be consecutive

Symptoms not essential for the diagnosis, but if present increase the confidence in the diagnosis and help to identify subgroups of IBS

- Abnormal stool frequency (>3 daily or <3 weekly)
- Abnormal stool form (lumpy/hard or loose/watery stool) >1/4 of defecations
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation) >1/4 of defecations
- Passage of mucus >1/4 of defecations
- Bloating or feeling of abdominal distension >1/4 of days

Figure 6-15 Treatment of Irritable Bowel Syndrome

Irritable bowel syndrome, a functional disorder that mainly affects the bowel, causes cramping, bloating, gas, diarrhea, and constipation. Other names for IBS are spastic colon, mucous colitis, spastic colitis, and nervous stomach. IBS is caused by disturbed interaction of the intestines, brain, and ANS that alters bowel motility (motor function) or sensory function. Added dietary fiber may relieve constipation and diarrhea but can lead to worsened bloating and distension. Less flatulence may occur with polycarbophil agents than
psyllium ones. Peripheral narcotic opiate antagonists (trimebutine and fedotozine), serotonin antagonists (tegaserod), and muscarinic antagonists (zamifenacin) are being studied. Trimebutine, with equal affinity for μ, δ, and κ-opioid receptors, stimulates small intestine transit but inhibits colonic motility. Serotonin blockers inhibit intestinal motility; muscarinic blockers inhibit colonic motility and GI secretion. CCK and calcium channel antagonists may also be useful.
Protozoal GI Infection

Giardiasis is the most frequent cause of nonbacterial diarrhea in North America. Human giardiasis may involve diarrhea within 1 week after ingestion of the cyst, which is the environmental survival form and infective stage of the organism. Illness normally lasts for 1 to 2 weeks, but cases of chronic infections have lasted months to years. Chronic cases, both those with defined immune deficiencies and those without, are difficult to treat. The disease mechanism is unknown, with some investigators reporting that the organism produces a toxin but others not being able to confirm existence of the toxin. Metronidazole is normally quite effective in terminating infections. Antibiotics such as albendazole, metronidazole, and furazolidone are often prescribed to treat giardiasis; paromomycin may be considered for pregnant women.
**Figure 6-17 Helicobacter pylori Infection Overview**

*Helicobacter pylori*, a spiral bacterium found in the gastric mucous layer or adherent to the epithelial lining of the stomach, causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers. Approximately 66% of the world's population is infected with *H. pylori*. It causes chronic persistent and atrophic gastritis in adults and children. Before *H. pylori* was discovered in 1982, spicy food, acid, stress, and lifestyle were considered major causes of ulcers. Most patients had long-term pharmacotherapy with histamine antagonists (H₂ blockers) and PPIs. These drugs relieve ulcer-related symptoms and gastric mucosal inflammation but do not eradicate the infection. When acid suppression is removed, the majority of *H. pylori*-induced ulcers recur. Chronic infection with *H. pylori* weakens natural defenses of the stomach lining against acid. Agents that eradicate *H. pylori* (antimicrobials), neutralize stomach acid (antacids), and reduce stomach acid output (H₂ blockers, PPIs) are used.
Diagnosis and Management of *Helicobacter pylori*

Uninvestigated dyspepsia (UID)

- Upper abdominal discomfort without alarm signs (vomiting, weight loss, bleeding, anemia)

Test for *Helicobacter pylori*

- Positive test

Test for *Helicobacter pylori*

- Proton pump inhibitor
- 2 antibiotics
- 10 to 14 days

Persistent symptoms

Symptom relief

Other conditions that warrant *H pylori* testing

- Active or prior peptic ulcer
- Non-Hodgkin lymphoma or gastric adenocarcinoma
- Moderate to severe gastritis on endoscopy
- Family history of gastric carcinoma

Most *H pylori*-infected patients have asymptomatic chronic gastritis. Dyspepsia is hallmark of symptomatic infection.

Tests for *Helicobacter pylori*

- Urea breath test
- Endoscopy with biopsy
- Serologic testing (ELISA)

13C-labeled urea is ingested; if *H pylori* is present it provides “urease,” which splits off the labeled CO₂, which is passed into circulation and expired in breath (active infection).

For patients undergoing upper endoscopy, biopsy samples submitted for histology or rapid urea testing (RUT) histology is gold standard (active infection).

Endoscopy

Serology testing (ELISA) detects IgG antibodies and documents past or current infection, but not eradication.

**Figure 6-18  Treatment of *Helicobacter pylori* Infection**

Antibiotics can eliminate the infection in most patients, with resolution of mucosal inflammation and minimal ulcer recurrence. *H pylori* is difficult to eradicate from the stomach because the organism can develop antibiotic resistance. Antibiotics are usually coadministered with a PPI and/or bismuth-containing compounds, which have anti-*H pylori* effects. Therapy for *H pylori* infection consists of 2 weeks of 1 or 2 antibiotics, such as amoxicillin, tetracycline (not for children younger than 12 years), metronidazole, or clarithromycin, plus ranitidine bismuth citrate, bismuth subsalicylate, or a PPI. Acid suppression by an *H₂* antagonist or PPI in conjunction with antibiotics alleviates ulcer-related symptoms (e.g., abdominal pain, nausea), heals gastric mucosal inflammation, and enhances efficacy of antibiotics against *H pylori* at the gastric mucosal surface. Common combinations are a PPI, amoxicillin, and clarithromycin or a PPI, metronidazole, tetracycline, and bismuth subsalicylate.
Antacids, PPIs, H₂ blockers, muscarinic antagonists (M₁ blockers), and misoprostol (prostaglandin E₂ derivative) are commonly used. PPIs (e.g., omeprazole) bind irreversibly to and inactivate the H⁺,K⁺-ATPase pump, which blocks acid secretion until more pumps are synthesized. Antacids neutralize 90% of gastric acid at a pH of 3.3. Histamine stimulates acid secretion by activating H₂ receptors, so drugs that block H₂ receptors (e.g., cimetidine, ranitidine) reduce acid levels. Common side effects are allergic reactions, interference with phase 1 oxidation (hepatic cytochrome P-450 system), and impotence (especially with cimetidine). Misoprostol stimulates mucus secretion, which protects GI endothelial cells from high acid levels. The cytoprotective sucralfate (sucrose-sulfate-aluminum hydroxide) stimulates bicarbonate, mucus, and prostaglandin secretion. ACh activates M₁ receptors to stimulate acid release; M₁ blockers (e.g., hyoscyamine) block this action and reduce GI acid levels.
Complications of Peptic Reflux (Esophagitis and Stricture)

In GERD, stomach acids move back into the esophagus, an action called reflux. The esophagus moves swallowed food into the stomach via peristalsis. Reflux occurs when these muscles fail to prevent acid from moving backward. Starch, fat, and protein in food are broken down by hydrochloric acid and enzymes (pepsin). The mucous lining of the stomach protects it from acid and enzymes, but the esophageal lining offers only weak resistance to these substances. GERD symptoms are usually short-lived and infrequent, but GERD is chronic in approximately 20% of cases. Esophagitis occurs when acid causes irritation or inflammation; extensive esophageal damage and injury lead to erosive esophagitis. GERD symptoms can occur with no signs of esophageal inflammation or injury (nonerosive esophageal reflux disease, or NERD), but patients have some GERD symptoms (burning sensations behind the breastbone). Nerves near the endothelial lining are exposed to acid, and pain results.
Proton pump inhibitors reduce acid reflux by blocking the expulsion of hydrogen ions by proton pumps. The standard agent used has been omeprazole. Newer oral PPIs include lanoprazole, esomeprazole, and rabeprazole, but they do not cure the condition. Even when drugs relieve symptoms completely, the condition usually recurs within months after the drugs are discontinued. Chronic cases require treatment for life. Celecoxib, rofecoxib, and valdecoxib, the COX-2 inhibitors, reduce inflammation and pain in a manner similar to that of aspirin and ibuprofen. Unlike aspirin, however, these COX-2 drugs block the activity of COX-2, which alters the activity of COX-1. This action is important because COX-1 is constitutive (unvarying gene expression regardless of molecular conditions), whereas COX-2 is inducible (variable and dependent on molecular conditions such as inflammation or infection). It is hoped that these COX-2 blockers will cause fewer peptic ulcers and bleeding compared with aspirin.
Acute Pancreatitis

Early stage, edema, congestion

Advanced hemorrhagic pancreatitis, blood blebs, fat necrosis

Necrotic abscess, gangrene

Acute necrosis of pancreas with inflammation

**Figure 6-22 Treatment of Pancreatitis**

Pancreatitis is acute or chronic inflammation of the pancreas, which secretes digestive enzymes into the small intestine (for fat, protein, and carbohydrate digestion) and insulin and glucagon into the blood (for glucose regulation). Acute pancreatitis is sudden and brief and caused by gallstones or excessive alcohol consumption. Dyspnea and hypoxia are common. Treatment of acute pancreatitis includes use of IV fluids, oxygen, antibiotics (eg, imipenem-cilastatin), or surgery. Chronic pancreatitis, which may develop if
Chronic (Relapsing) Pancreatitis

Moderate involvement of head and body; dilatation of duct

Extensive involvement of entire pancreas; calculi; duct dilatation; biliary obstruction

Fibrosis with multiple cyst formation

**FIGURE 6-22 TREATMENT OF PANCREATITIS (continued)**

Pancreatic injury continues, is caused by digestive enzymes’ attacking and destroying pancreatic tissue. Prolonged alcohol abuse is a common cause, but the chronic form may occur after only 1 acute attack, especially if a patient has damaged pancreatic ducts, cystic fibrosis, hypercalcemia, or hyperlipidemia. Chronic pancreatitis therapy includes use of antiinflammatory agents, a high-carbohydrate diet, a low-fat diet, and protease pancreatic enzyme supplements.
Gallstones develop in the gallbladder from crystals of cholesterol or bilirubin. Stones can be too small to be seen with the eye (biliary sludge) or can be the size of golf balls. There may be 1 or hundreds of stones. The presence of gallstones is called cholelithiasis. Obstruction by gallstones of the cystic duct (that leads from the gallbladder to the common bile duct) causes pain (biliary colic), infection, and inflammation (cholecystitis). Gallstone disease affects 10% to 15% of the US population, but only 1% to 3% report symptoms in a given year. Women, particularly during pregnancy, are at increased risk because estrogen stimulates the liver to remove more cholesterol from blood and divert it into bile. Avoidance of fatty meals or nonsurgical approaches are used only in special situations (when a serious medical condition prevents surgery and for cholesterol stones). Stones usually recur after nonsurgical intervention.
Pathogenesis of Gallstones

Solubility of cholesterol in bile depends on incorporation of cholesterol in bile acid–lecithin micelles and lecithin vesicles. When bile becomes saturated with cholesterol, vesicles fuse to form liposomes, or liquid crystals, from which crystals of cholesterol monohydrate nucleate.

**Stage 1**
- Normal cholesterol
- Normal bile acids
- Normal lecithin

**Stage 2**
- Normal cholesterol
- Reduced bile acids
- Normal lecithin

**Stage 3**
- Elevated cholesterol
- Reduced bile acids
- Normal lecithin

**Stage 4**
- Elevated cholesterol
- Reduced bile acids
- Reduced lecithin

**Conditions that increase biliary cholesterol relative to bile acids and lecithin favor saturation of bile and formation of gallstones.**

**Gallstone formation**

**Predisposing Factors**

**Cholesterol stones**
- Female
- Multiparity
- Genetics
- Antilipemic drugs
- Type IV hyperlipemia
- Oral contraceptives
- Crohn disease of ileum
- American Indian
- Secondary hemolytic anemia

**Pigment stones**
- Cirrhosis of liver
- Congenital biliary tract anomalies
- Total parenteral nutrition
- Primary hemolytic anemia

**Nucleation promoters**
- Mucous glycoproteins
- Heat-labile proteins

**Nucleation inhibitors**
- Apolipoprotein
- Lecithin vesicles

**Gastrointestinal System**

**Figure 6-24 Gallstone Pathogenesis and Treatment**

Using drugs synthesized from bile acid to dissolve gallstones is known as oral dissolution therapy. Ursodiol and chenodiol work best for small cholesterol stones. Months of treatment may be necessary before all the stones dissolve. Both drugs cause mild diarrhea, and chenodiol may increase blood cholesterol levels and increase the activity of transaminase, a hepatic enzyme. Contact dissolution therapy is an experimental procedure that involves injecting a drug directly into the gallbladder to dissolve stones. The drug methyl-tert-butyl ether can dissolve some stones in 1 to 3 days, but it must be used carefully because it is a flammable and toxic anesthetic. Extracorporeal shock wave lithotripsy (ESWL) is the use of shock waves to disintegrate stones into tiny pieces that can pass through bile ducts without causing blockage. Attacks of biliary colic (intense pain) are common after treatment, and the success rate of ESWL is unknown.
Figure 6-25 Liver Function

The liver creates, regulates, stores, and secretes substances used by the GI system, bile being the major digestive chemical synthesized. During a meal, bile is secreted by liver cells and moves through the hepatic duct system into the small intestine, where it is used to break down fat molecules. Between meals, the gallbladder stores bile. Bile serves as a waste disposal system for toxins removed from blood by the liver. The liver plays a major role in regulation of blood glucose. The liver also synthesizes, dissolves, and stores amino acids, protein, and fat, and it stores several important vitamins (B₁₂ and A). The liver disposes of cellular waste and decomposes toxic substances such as alcohol, with disposal occurring via the bile. Because the liver clears toxins, hepatocytes are organized for optimal contact with sinusoids (leading to and from blood vessels) and bile ducts. The liver is unique in that it can regenerate, but this capacity can be exceeded by extensive damage.
Specific hepatic cells produce bilirubin (unconjugated or indirect), a degradation product of hemoglobin. Hepatocytes sequester bilirubin, conjugate it with glucuronic acid, and excrete it into bile. Intestinal bacteria convert conjugated (direct) bilirubin into urobilinogen, which is returned to the liver and bile or excreted by kidneys. Bilirubin assay is used to determine liver (jaundice) or gallbladder dysfunction. Jaundice occurs, as a result of liver disease or bile duct blockage, when red blood cells are broken down too fast for the liver to process. Syndromes related to bilirubin include Crigler-Najjar type II, which causes increased indirect bilirubin levels. These patients live into old age and are not at risk for kernicterus (brain damage). Patients with Gilbert syndrome, a benign disorder with no increase in mortality or morbidity, usually have no complications from hyperbilirubinemia. Phenobarbital is used for high bilirubin levels and is thought to act by enzyme induction.
In cirrhosis, widespread nodules in the liver combined with fibrosis distort normal liver architecture, which interferes with blood flow through the organ. Cirrhosis can also lead to inability of the liver to perform biochemical functions. The most common cause is alcoholic liver disease. Others are chronic viral hepatitis B, C, and D; chronic autoimmune hepatitis; inherited metabolic diseases (hemochromatosis, Wilson disease); bile duct diseases; chronic congestive heart failure; parasitic infections (schistosomiasis); and long-term exposure to toxins or drugs. Cirrhosis is irreversible, but treatment of underlying liver disease may slow its progression. Cessation of alcohol intake stops progress of alcoholic cirrhosis. Stopping a hepatotoxic drug or removal of an environmental toxin also halts disease progression. Interferon is used to treat viral hepatitis B and C; prednisone and azathioprine are used to treat autoimmune hepatitis. Drugs such as ursodiol may help in primary biliary cirrhosis.
Ascites, the abnormal accumulation of fluid within the abdominal cavity, has a wide range of causes (cancer and kidney, heart, and pancreatic disease) but most often develops as a result of liver disease. The underlying disorder requires treatment (eg, bed rest to improve kidney function and decreased sodium and fluid intake to reduce blood volume). Diuretics used include potassium-sparing agents such as spironolactone, amiloride, and triamterene. Spironolactone blocks aldosterone receptors in collecting ducts of
FIGURE 6-28 ASCITES (continued)

Kidneys, thus stopping aldosterone-evoked sodium reabsorption and potassium loss. Triamterene and amiloride indirectly antagonize actions of aldosterone by blocking sodium channels and preventing sodium reabsorption. Stronger diuretics such as loop diuretics (eg, bumetanide, furosemide, torsemide) and thiazides (eg, hydrochlorothiazide) may be used if potassium-sparing agents are ineffective but can cause hypokalemia, hypovolemia (and shock), and hyperuricemia (and gout).
Emesis is expulsion of undigested food through the mouth. Nausea, the state preceding vomiting, is the sensation of needing to vomit. Emesis is caused by allergy, food, anticancer drugs (eg, cisplatin), hepatitis, stress, and pregnancy. Central neural vomiting regulation is located in the medulla. The chemoreceptor trigger zone (CTZ), in the area postrema on the floor of ventricle IV, is quite sensitive to chemicals. The blood-brain barrier is poorly developed in the CTZ (accessible to emetic agents in circulation). The vomiting
center (VC) integrates the emetic response and is located in the
dorsolateral border of the medullary reticular formation (includes
the nucleus tractus solitarius, parvicellular reticular formation, and
visceral and somatic motor nuclei). The VC gets excitatory inputs
from nerve endings of vagal sensory fibers in the GI tract, vestibular
nuclei, higher centers in the cortex (for vomiting induced by
disgust), the CTZ, and intracranial pressure receptors.
Vomiting induced by the emetic syrup of ipecac is occasionally recommended for pediatric ingestions, being managed at home, in consultation with the poison center. It no longer has a role in the hospital management of poisonings.

Receptors, Transmitters, and Drugs Involved in Mediating Vomiting

<table>
<thead>
<tr>
<th>Structures</th>
<th>Receptors</th>
<th>Agonists</th>
<th>Antagonists</th>
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<tbody>
<tr>
<td>Area postrema</td>
<td>$D_2$</td>
<td>Apomorphine</td>
<td>Antidopaminergic drugs</td>
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<tr>
<td></td>
<td></td>
<td>l-Dopa</td>
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<tr>
<td>CTZ</td>
<td>M, $H_1$</td>
<td>Cholinomimetics</td>
<td>Dimenhydrinate</td>
</tr>
<tr>
<td>Vestibular nuclei</td>
<td></td>
<td>Histamine</td>
<td>Atropine</td>
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<tr>
<td>Nucleus tractus solitarius</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting center</td>
<td>M</td>
<td>Cholinomimetics (eg, physostigmine)</td>
<td>Atropine</td>
</tr>
<tr>
<td>Vagal sensory nerve endings</td>
<td>5-HT$_3$</td>
<td>Serotonin</td>
<td>Ondansetron, Granisetron</td>
</tr>
</tbody>
</table>

**Figure 6-30 Antiemetics**

There are several classes of antiemetic drugs. $H_1$ antagonists (eg, dimenhydrinate, clizines, diphenhydramine, hydroxyzine) block $H_1$ receptors in the midbrain to relieve histamine-induced emesis. Most $H_1$ blockers have additional anticholinergic action, and adverse effects include drowsiness and loss of coordination. The newer histamine blockers are not useful because they cannot penetrate the blood-brain barrier. Dopamine antagonists (eg, metoclopramide, domperidone, chlorpromazine, droperidol) are usually used as antipsychotic drugs but can suppress emesis by blocking $D_2$ receptors in the area postrema and CTZ. Benzodiazepines (eg, diazepam, lorazepam) are useful for anticipatory nausea and vomiting before cancer therapy. They are also used for vestibular disorders (vertigo, dizziness, nystagmus). Muscarinic receptor antagonists have also been used (scopolamine is not now available). These drugs relieve emesis by blocking $M_1$ receptors in vestibular nuclei.
CHAPTER 7

DRUGS USED IN DISORDERS OF THE RESPIRATORY SYSTEM

OVERVIEW

Respiration comprises the sequence of events that result in exchange of oxygen and carbon dioxide between the atmosphere and the body's cells. The major structural components of the respiratory system are the nasal cavity, larynx, pharynx, trachea, and lungs. The lungs contain the bronchi, which branch into smaller passages called bronchioles and end as pulmonary alveoli. The respiratory system serves 4 major functions: (1) gas exchange (oxygen and carbon dioxide); (2) sound production, or vocalization, caused by passage of air over the vocal cords; (3) coughing; and (4) abdominal compression during urination, defecation, and parturition (childbirth).

Cellular respiration requires inspiration of oxygen and elimination (via expiration) of excess carbon dioxide, the poisonous waste product of this process. Gas exchange supports cellular respiration by constantly supplying oxygen and removing carbon dioxide. Inspiration occurs when contraction of respiratory muscles produces an expansion of lung volume, decrease in alveolar pressure, and influx of air (oxygen) into lungs. Expiration compresses the lungs and increases alveolar pressure, thus pushing carbon dioxide–rich gas out of the lungs. Every 3 to 5 seconds, nerve impulses stimulate the breathing process, or ventilation, which moves air through a series of passages into and out of the lungs, after which an exchange of gases occurs between the lungs and the blood (called external respiration). Blood transports the gases to and from cells in tissues. Exchange of gases between the blood and cells is called internal respiration. Finally, cells use oxygen for specific functions: cellular metabolism, or cellular respiration.

The process of cellular respiration is compromised by diseases of the respiratory system. Common respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD, which includes emphysema and chronic bronchitis), acute bronchitis, dyspnea (difficult breathing), and pneumonia. Drugs for treating the respiratory system are used primarily to open bronchial tubes, either by reversing effects of histamines (which are released by the body when exposed to substances that cause allergic reactions) or by relaxing muscle bundles surrounding bronchial tubes.

Asthma, which involves constriction of pulmonary passages and secretion of excess mucus, is characterized by dyspnea, coughing, and wheezing, and can be precipitated by triggers such as allergens, cold air, viral infections, bacterial infections, and exercise. Anti-IgE antibodies, mast cell degranulation blockers, smooth muscle relaxants, and anti-inflammatory agents are major drug classes used for asthma.

Emphysema results from the breakdown of alveolar walls, which leads to reduced alveolar surface area and impaired cellular respiration and gas exchange. Acute bronchitis results from inflammation of bronchial passages and has causes similar to those of asthma. Chronic bronchitis is characterized by persistent production of excess mucus in bronchial tubes. Cough, shortness of breath, and lung damage are typical of chronic bronchitis. Medications for COPD include short-acting b2 agonists and bronchodilators.

Pneumonia is an acute lung inflammation that results in collapse of lung tissue and can be treated with antibiotics only when the cause is bacterial.
Respiration means ventilation, or breathing. The 2 phases of breathing are inspiration (inhalation) and expiration (exhalation). Primary functions of the respiratory system are to provide oxygen to tissues and to expel carbon dioxide from the body. Respiration is classified into 3 functional categories: external respiration, exchange of gas between the atmosphere and blood; internal respiration, exchange of gas between the blood and cells; and cellular respiration, the process whereby cells use oxygen and convert energy into useful forms. The major waste product of cellular respiration, carbon dioxide, diffuses from cells into blood, in which it is transported to the lungs and expelled during expiration. Secondary functions of the respiratory system are sound production, coughing, sneezing, and abdominal compression during urination, defecation, and parturition. Pharmacologic intervention becomes necessary when the respiratory system functions improperly.
The most common respiratory disorders are asthma, cough, COPD (emphysema; chronic bronchitis), and pneumonia. Less common disorders are hyperventilation (excessive inspiration and expiration); apnea (temporary breathing cessation that may follow hyperventilation); and rhinitis (nasal mucosa inflammation). Drugs used for these conditions are normally given by inhalation (metered-dose or nebulized inhaler) or by oral means. Inhalation is preferred because of direct drug delivery to lungs, avoidance of first-pass metabolism by the liver and intestine, and minimization of adverse effects. Certain drugs used to treat asthma (e.g., theophylline, albuterol, terbutaline) can be given orally. Parenteral dosing (intravascular, subcutaneous, or intramuscular) may be needed, especially when rapid onset of action is critical or drug absorption from the GI tract is poor; it controls the dose delivered, but adverse effects can result.
The term allergy, from the Greek allos (altered state) and ergon (reactivity), was first used to describe patients who had reactions caused by the effect of external factors, or allergens, on the body's immune system. It is often defined as hypersensitive reactions of the immune system to substances (allergens) that are usually innocuous in most people, such as food, animal dander, pollen, bee stings, mold, ragweed, and drugs. The allergic person's immune system recognizes something as foreign and mounts a specific reaction to identify the allergen and destroy it via inflammation. Thus, a sensitivity to a material that causes a symptom is allergic only if it has an identifiable mechanism. This distinction between allergic and nonallergic disorders is important because it determines evaluation and treatment. Treatment of an allergy as if it were nonallergic will fail and vice versa. In asthma, allergens increase sensitivity of bronchial smooth muscle, thereby creating an allergic state.
Humans have a special immune system to combat infectious and toxic agents (e.g., bacteria and viruses). Major cells involved in defense against foreign substances are leukocytes, or white blood cells. Like all blood cells, they are synthesized in bone marrow. Leukocytes can be classified into 2 basic classes: granular, which store mediators in granules, and mononuclear or agranular, which have no granules. Three types of granular leukocytes exist: neutrophils, eosinophils, and basophils. Eosinophils, which phagocytize antigen-antibody complexes (antigen-IgE complexes that initiate an asthmatic reaction), and basophils, which release heparin (clotting), serotonin (clotting), and histamine (immune reaction), play primary roles in asthma. Agranular cells are monocytes, which phagocytize foreign particles, and lymphocytes, which play a critical role in the delayed asthmatic response. T cells (a subtype of lymphocytes) synthesize cytokines; B cells (another subtype) synthesize IgE antibodies.
**Figure 7-5 Allergic Rhinitis**

Allergic rhinitis (hay fever), an inflammation or irritation of the mucous membranes lining the nose, is initiated when allergens cause the body to defend itself by producing antibodies. The allergen-antibody combination prompts histamine release and the allergic response. Symptoms are sneezing, stuffy or runny nose, itchy eyes, noisy breathing, chronic fatigue, poor appetite, and nausea. The seasonal disorder is caused by pollen and normally wanes during winter; the perennial disorder occurs year-round and is caused by indoor allergens (e.g., animal dander, mold spores, dust mites). Treatments are antihistamines (treatment of choice; blocks histamine action but can cause drowsiness), decongestants (relieve nasal stuffiness but can increase histamine release and worsen congestion), corticosteroids (desensitize cellular response to histamine and minimize the allergic reaction), and cromolyn sodium (inhibits histamine release, which reduces or stops the allergic response).
FIGURE 7-6 INTRODUCTION TO ASTHMA

Bronchial asthma, known simply as asthma, is a chronic lung disease characterized by inflammation and obstruction of lower airways. Asthma affects approximately 5% of the US population, or 10 million people. The most common symptoms are acute constriction of bronchial smooth muscle, cough, chest tightness, wheezing, and rapid breathing. Asthma typically occurs in 2 stages: an initial phase followed by a second, delayed phase that occurs 6 to 12 hours later. Unlike diseases such as cystic fibrosis or chronic bronchitis, asthma is not a progressive disorder leading to COPD. Rather, it is a recurrent illness with periods of remission and exacerbation. However, a small percentage of patients with asthma present symptoms continuously. Precipitating factors include infections, allergens, irritant inhalants, stress, and other triggers. Deaths caused by asthma are infrequent.
Extrinsic Allergic Asthma: Clinical Features

- Young patient: child or teenager
- History of eczema in childhood
- "Allergic shiner" may be present
- Favorable response to hyposensitization
- IgE associated
- Attacks acute but usually self-limiting; prognosis favorable; condition often outgrown but may become chronic; death rare

Features common to both extrinsic allergic and intrinsic asthma:
- Respiratory distress, dyspnea, wheezing, flushing, cyanosis, cough, flaring of alae, use of accessory respiratory muscles, apprehension, tachycardia, perspiration, hyperresonance, distant breath sounds and rhonchi, eosinophilia

Figure 7-7 ExtraIntrinsic and Intrinsic Asthma

Pharmacotherapy of asthma depends on understanding the disease pathogenesis. In the immunologic, or antigen challenge, model, IgE antibodies produced by airway mucosa mast cells mediate asthma. B lymphocytes synthesize IgE antibodies after exposure to an antigen. IgE antibodies attach to mast cells and, with reexposure to antigen, form antigen-antibody complexes. The complexes trigger synthesis and release of mediators, such as histamine, leukotrienes (LTC₄ and LTD₄), and prostaglandins, from mast cells.
Intrinsic Asthma: Clinical Features

Adult patient: age 35 or over

- Family history usually negative
- Attacks related to infections, exercise, other stimuli
- Skin tests usually negative

No history of eczema in childhood

- Unfavorable response to hyposensitization
- Not IgE associated

Attacks more fulminant; prognosis poorer; condition may become chronic; death may occur

Features common to both extrinsic allergic and intrinsic asthma:
- Respiratory distress, dyspnea, wheezing, flushing, cyanosis, cough, flaring of alae, use of accessory respiratory muscles, apprehension, tachycardia, perspiration, hyperresonance, distant breath sounds and rhonchi, eosinophilia

Figure 7-7  EXTRINSIC AND INTRINSIC ASTHMA (continued)

Bronchoconstriction and vascular leakage result. Other substances (e.g., cytokines) mediate the late response (IgE release). Corticosteroids reduce bronchial responses by inhibiting cytokine production. In some asthmatic patients who are not hypersensitive to antigens, infections and nonantigenic stimuli can evoke symptoms. Intrinsic asthma develops later in life, has unclear causes, is associated with a worse prognosis, and is less responsive to treatment than extrinsic asthma.
When exposure to allergens cannot be avoided, drug therapy is needed, the major goals being to reverse asthmatic symptoms and prevent recurrent episodes by disrupting actions of endogenous agents that worsen bronchospasm and inflammation. Major classes of drugs for asthma are anti-IgE antibodies, blockers of mast cell degranulation, smooth muscle relaxants, and antiinflammatory agents. Bronchodilators were the first and most effective treatment, but a better approach is prophylactic use of antiinflammatory agents to control bronchial inflammation. With these agents, patients with asthma are rarely hospitalized, seriously ill, or in need of emergency treatment. Patients can control their disease, and this therapy is much less expensive than previous emergency management. Now, antiinflammatory agents are the first-line therapy for patients who have more than occasional symptoms. Bronchodilators are still used but only when antiinflammatory therapy is inadequate, and then in smaller amounts.
FIGURE 7-9 ANTI-IGE ANTIBODIES

One of the more novel therapies is use of anti-IGE antibodies. In theory, drugs acting as anti-IGE antibodies would prevent IgE binding to mast cell surfaces. This action would reduce formation of activated antigen-IGE complexes and suppress release of mediators that induce immediate bronchoconstriction in the early phase. That is, mediators such as histamine, prostaglandins, and leukotrienes would be unable to cause sneezing, wheezing, itching, and coughing. The most notable anti-IGE antibody, Rhumab-E25, is a recombinant humanized monoclonal antibody to IgE. By binding to circulating IgE in the blood, Rhumab-E25 blocks release of inflammatory mediators by keeping IgE from binding to mast cells. This antibody, administered by parenteral injection, is currently in phase III clinical trials for seasonal allergic rhinitis and allergic asthma.
Cromolyn and nedocromil block mast cell degranulation by suppressing release of mediators of immediate bronchoconstriction (early response) and reducing eosinophil recruitment causing airway inflammation. Neither drug directly alters smooth muscle tone or reverses bronchospasm. Both drugs, usually inhaled as aerosols, can be used for intrinsic (antigen-induced) or extrinsic (non–antigen-induced) asthma. Nedocromil enhances corticosteroid effects and is more potent than cromolyn in patients with extrinsic asthma (especially exercise induced); even when given after re-exposure to antigen, it blocks delayed inflammation. Both drugs are poorly absorbed, so adverse effects (e.g., chest tightness, cough) are restricted to deposition site. Cromolyn is preferred for young patients. Both drugs alter Cl⁻ channel function, which (1) on airway neurons underlies cough inhibition, (2) on mast cells delays antigen-evoked bronchoconstriction, and (3) on eosinophils prevents inflammatory responses to antigens.
Asthma

Hand nebulizer

Bulb squeezed synchronously with deep inhalation and breath held briefly to permit settling of medication mist on mucosa

![Diagram showing the mechanism of bronchodilation and the effects of Theophylline and Muscarinic antagonists.]

Intermittent positive pressure breathing (IPPB)

Nebulizer for bronchodilator medication

**Figure 7-11 Bronchodilators**

Drugs that expand pulmonary airways (bronchi)—bronchodilators—block the early response by inhibiting immediate bronchconstriction. Some agents, especially theophylline and β₂-adrenergic agonists, inhibit late response inflammation. These drugs are usually used when a persistent cough and bronchial constriction are present. In addition to relaxing smooth muscles and reducing airway reactivity, bronchodilators reduce coughing, wheezing, and shortness of breath. Agents are usually given via inhalation, but some can be given orally or parenterally (intravenous, intramuscular, or subcutaneous route). Most drugs have a rapid onset of action (within minutes), but the effect usually wanes in 5 to 7 hours. Some agents, especially theophylline, inhibit the delayed response to antigen. The most common bronchodilators are methylxanthines (e.g., theophylline, caffeine), β-adrenergic agonists (e.g., isoproterenol, albuterol, epinephrine), and cholinergic antagonists (e.g., atropine, tiotropium).
The methylxanthines theophylline, caffeine, and theobromine, found in cola, tea, and coffee, are bronchodilators that reduce bronchial smooth muscle activity, most likely by increasing intracellular cAMP levels. Signal molecules (e.g., transmitters, drugs) activate GPCRs on airway smooth muscle cells and increase the conversion rate of ATP to cAMP. Increased cAMP levels relax bronchial muscle and reduce airway reactivity. Phosphodiesterase stops cAMP effects and reduces cAMP levels by catalyzing hydrolysis of cAMP to AMP. Methylxanthines may prevent cAMP hydrolysis. Or, theophylline may block cell membrane receptor effects of adenosine, which may induce bronchoconstriction and inflammation. These drugs may also be antiinflammatory. Theophylline, the most widely prescribed and of low cost, comes as short-acting tablets and syrups, sustained-release capsules and tablets, and intravenous doses. The synthetic dyphylline may help patients who are unable to use theophylline.
Methylxanthines: Adverse Effects

Methylxanthine doses must be closely watched. Low doses have little effect if any, whereas high doses can affect the central nervous, cardiovascular, skeletal muscle, GI, and renal systems. Theophylline is most selective at smooth muscle; caffeine induces the most marked CNS effects. Even at low to moderate doses, these drugs enhance cortical arousal and alertness and defer fatigue. In hypersensitive patients, insomnia and nervousness may occur. Methylxanthines reduce blood viscosity, increase blood flow, increase cardiac output, and induce tachycardia in healthy subjects. In sensitive persons, cardiac arrhythmias are common. These drugs strengthen contractions of isolated skeletal muscles in vitro and improve contractility and reverse fatigue of the diaphragm in patients with COPD, which accounts for their usefulness in COPD. Although methylxanthines enhance gastric acid and digestive enzyme secretion in the GI tract and induce a slight diuresis, these effects are minor.
**Figure 7-14 β-Adrenergic Agonists**

Another class of drugs that enhance sympathetic discharge, β-adrenergic agonists, is used to relieve a sudden asthma attack or block exercise-induced asthma. These drugs relax bronchial smooth muscle, inhibit mediator release, increase transport of mucus, and alter composition of mucus by stimulating β adrenoceptors. Bronchodilation is mediated by β₂ adrenoceptors that are located on smooth muscle cells in human airways. Nonselective β-adrenoceptor agonists (e.g., epinephrine, ephedrine, isoproterenol) stimulate all β adrenoceptors (β₁ and β₂ classes). These nonselective actions often produce adverse effects, particularly in the CNS and cardiovascular system. Selective drugs that activate only β₂ receptors (e.g., albuterol, terbutaline, salmeterol) are the most commonly prescribed sympathomimetic agents.
**Figure 7-15 Nonselective β-Adrenergic Agonists**

Agents that activate both β₁ and β₂ adrenoceptors have long been used to treat asthma. These drugs are potent, rapidly acting bronchodilators, but their stimulation of the cardiac system is a serious drawback. The major agents are epinephrine, ephedrine, and isoproterenol. Epinephrine is either inhaled or given subcutaneously and is the active agent in many over-the-counter preparations. Maximal bronchodilation is achieved 15 minutes after injection and lasts approximately 90 minutes. Because this drug stimulates cardiac output, increases heart rate, and exacerbates angina, physicians rarely prescribe it. Ephedrine, used in China more than 2000 years ago, has the longest history of use of any antiasthmatic. It has a longer duration of action, lower potency, and greater oral activity than epinephrine. However, it has marked adverse effects, particularly in the CNS, and is rarely administered. Isoproterenol is characterized by a rapid onset of action, with peak bronchodilation occurring within 15 minutes of injection.

**Management of Acute Asthmatic Attack**

1. Give aqueous epinephrine 1:1000 subcutaneously. If initial response is inadequate, repeat at 30 to 60 minute intervals as needed; oxygen as indicated.

2. If response to epinephrine is inadequate or if patient becomes refractory, give aminophylline intravenously very slowly; administer oxygen.

3. If necessary, corticosteroids, which act more slowly, also can be given.
Selective $\beta_2$-adrenergic agonists are the most widely prescribed sympathomimetic drugs because of their $\beta_2$ selectivity, oral activity, and rapid onset and long duration of action (4 hours). The major drugs—metaproterenol, terbutaline, albuterol, salmeterol, and formoterol—have minimal $\beta_1$-mediated effects on the nervous and cardiac systems. The inhalation route allows the greatest local effects with the fewest adverse effects. Inhaled agents cause bronchodilation that equals that of isoproterenol and persists for 4 hours. Terbutaline, metaproterenol, and albuterol can be given orally as tablets. Terbutaline, the only drug that can be used subcutaneously, is given for severe asthma attacks or if insensitivity to inhaled agents exists. Two new drugs, salmeterol and formoterol, have a long duration of action and high lipid solubility. Both drugs at high concentrations move slowly into airway smooth muscle, so effects can last up to 12 hours. Both also enhance antiasthmatic actions of corticosteroids.
Acetylcholine mediates its physiologic effects via 2 types of receptors: muscarinic and cholinergic. Muscarinic receptors are GPCRs that are densely expressed in the airways. When stimulated, muscarinic receptors cause muscle contraction, which leads to narrowing of the airways and bronchoconstriction. Muscarinic antagonists, or anticholinergics, prevent acetylcholine from producing smooth muscle contractions and excess mucus in the bronchi. Ipratropium bromide and atropine are most commonly used. Anticholinergics are less effective than $\beta_2$-adrenergic activators. However, these drugs enhance bronchodilation induced by $\beta_2$-adrenergic agonists, so patients often take both anticholinergics and $\beta_2$ agonists. Dry mouth, bitter taste, scratchy throat, and headache are the major adverse effects.
Corticosteroids are antiinflammatory drugs similar to natural corticosteroid hormones produced by the adrenal cortex. Treatment with these agents improves symptoms of asthma, allergic rhinitis, eczema, and rheumatoid arthritis. Corticosteroids inhibit late phase allergic reactions (including late asthmatic response to antigen challenge) by various mechanisms, eg, reduced (1) number of mast cells lining the surfaces of airway mucosal cells; (2) chemotaxis and activation of eosinophils; and (3) cytokine production by eosinophils, monocytes, mast cells, and lymphocytes. Corticosteroids taken regularly reduce bronchial reactivity, enhance airway quality, and decrease the severity and frequency of asthma attacks. However, corticosteroids do not directly relax smooth muscle. These drugs would be the only ones needed to treat asthma if their adverse effects were not so pronounced. Commonly used agents are prednisone, methylprednisolone, beclomethasone, flunisolide, budesonide, and mometasone.
Corticosteroids have marked adverse effects on nonrespiratory systems, so inhalation (maintenance therapy in asthma, via inhaler) or the intranasal (in allergy, as nasal spray) route is preferred. Intranasal corticosteroids relieve stuffy nose, nasal irritation, and other discomforts. Corticosteroids inhaled by mouth effectively prevent asthma attacks. Spacers (chambers) can be attached to metered-dose inhalers to reduce the velocity and particle size of the drug; the amount of drug reaching the lungs is maximized, and the quantity of drug deposited in the mouth is minimized. Spacers are crucial for therapy with corticosteroids, which have many adverse effects. Regular doses of aerosol agents are smaller than doses used in pill form. The smaller, regular doses reduce side effect risk and may eliminate a need for aerosol steroids. Oral prednisone or IV methylprednisone is used only when patients are insensitive to the inhaled drugs or need urgent treatment for severe asthma attacks.
Corticosteroids

Brain
- Increased appetite
- Mood alterations
- Insomnia
- Headache

Lungs
- Reduced bronchial reactivity
- Reduced asthma attack frequency
- Reduced severity of asthmatic symptoms
- Decreased inflammation
- No direct muscle relaxation

Heart
- Increased hypertension

Liver and gastrointestinal tract

Diabetes

Bone
- Osteoporosis

Kidney
- Increased salt retention

**Figure 7-20 Corticosteroids: Adverse Effects**

Taking corticosteroids orally (prednisone) and intravenously (methylprednisolone) can cause unwanted side effects. Short-term use (days) of prednisone can lead to increased appetite, weight gain, diarrhea, headache, mood changes, and insomnia, and possibly hyperglycemia and hypertension. Cessation of short-term corticosteroid use or taking smaller doses of these agents usually minimizes or eliminates the effects. Adverse effects that accompany long-term (months to years) oral and IV therapy are suppressed immune system, increased cholesterol levels, and rapid weight gain. Long-term use may also promote osteoporosis, cataracts, and thinning of the skin. Efforts to develop safer corticosteroids with antiinflammatory properties but lacking adverse effects are ongoing. Lipophilic steroids, such as beclomethasone, flunisolide, budesonide, and mometasone, have a strong safety profile and are almost devoid of the orally precipitated systemic effects.
**FIGURE 7-21 LEUKOTRIENES**

Leukotrienes are arachidonic acid derivatives that are involved in inflammatory processes including asthma and anaphylaxis. The enzyme 5-lipoxygenase catalyzes synthesis of arachidonic acid into unstable intermediates, which are converted into leukotrienes. A number of airway cells (including mast cells, macrophages, eosinophils, and basophils) synthesize, store, and secrete several subtypes of proinflammatory leukotrienes. Leukotriene B₄ (LTB₄) attracts additional leukocytes, and LTC₄ and LTD₄ increase bronchial reactivity, bronchoconstriction, and secretion of mucus. Evidence that inhaled leukotrienes increase bronchial reactivity and that antigen challenge in sensitized airways augments leukotriene synthesis supports a role for these mediators in asthma and a rationale for development of drugs that block leukotriene or 5-lipoxygenase action.
**Figure 7-22 Leukotriene Antagonists**

Efforts to develop drugs that disrupt proinflammatory actions of leukotrienes produced 2 types of drugs: 5-lipoxygenase inhibitors and leukotriene antagonists. Zileuton reduces the leukotriene synthesis rate by blocking 5-lipoxygenase. Zafirlukast and montelukast, LTD₄ antagonists, block leukotriene receptors and prevent these mediators from causing an asthmatic response. When taken regularly, these drugs work as well as inhaled corticosteroids in reducing the frequency of asthma attacks. However, leukotriene antagonists are less successful for relieving symptoms, reducing bronchial reactivity, and improving airway quality. These drugs are effective and safe when taken orally, an advantage compared with inhaled corticosteroids. The strong safety profile and excellent oral activity account for the popularity of leukotriene antagonists for children. Leukotriene antagonists also reduce responses in aspirin-induced asthma, a disorder affecting nearly 10% of patients with asthma.
**Cough**

Cough—forceful release of air from lungs—is a sudden, often involuntary reflex and a major defense mechanism. Airway irritation activates the reflex, which forcefully removes irritants, by stimulating the airways, which then activates afferent nerves going from respiratory passages through the vagus nerve to the medulla. Activated cough receptors in the medulla drive a reflex that initiates inspiration (2.5 L of air); increases contraction of diaphragmatic, abdominal, and intercostal (rib) muscles; increases lung pressure; and emits air and irritants (at 100 mph). Coughs triggered by drainage of mucus from nasal passages into airways are treated with cough suppressants (antitussives). Infection-related coughs (eg, in bronchitis) last for approximately 2 weeks. Persistent, chronic coughs (eg, in smokers) must be evaluated. Coughs occurring with blood, chest pain, shortness of breath, weight loss, or dyspnea may indicate serious disease. Coughs in infants may indicate a serious lung disorder.

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**Etiology of Chronic Cough With a Normal Chest Radiograph**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnasal drip</td>
<td>28-41%</td>
</tr>
<tr>
<td>Asthma</td>
<td>24-33%</td>
</tr>
<tr>
<td>GERD</td>
<td>10-21%</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Postinfectious (often, viral URI) bronchial hyperresponsiveness</td>
<td>10%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>4%</td>
</tr>
<tr>
<td>ACE inhibitors, tracheomalacia, eosinophilic bronchitis, psychogenic, etc</td>
<td>5%</td>
</tr>
</tbody>
</table>

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**Causes of Chronic Cough With Abnormal Chest Radiograph**

- Pulmonary tuberculosis
- Cystic fibrosis and bronchiectasis
- COPD (pulmonary emphysema)
- Left-sided congestive heart failure and pulmonary hypertension
- Ectatic mucus-filled spaces
- Dilated air sacks
- Carcinoma of lung
- L. ventricular hypertrophy and dilation

---

**Figure 7-23 Cough**
**RESPIRATORY SYSTEM**

**Cough**

**Key**
- Blue: Parasympathetic efferents
- Red: Sympathetic efferents
- Black: Afferents

**Opioid agonists**

**Figure 7-24 Cough Suppressants (Antitussive Agents)**

Cough suppressants are opioids that reduce the sensitivity of central cough receptors to peripherally activated afferent fibers. Receptor desensitization disrupts the reflex and minimizes coughing. Opioids include opiates (morphine and drugs derived from the opium poppy plant, such as hydromorphone, hydrocodone, and codeine) and synthetic drugs that mimic effects of morphine. Opioids desensitize central cough receptors, reduce airway mucus secretion, and alter mucus composition. These drugs also produce many adverse effects, including analgesia, addiction, sedation, euphoria, respiratory depression, nausea, vomiting, and constipation. The doses of opioids needed to suppress cough are lower than doses that evoke most of the undesirable effects, particularly analgesia and addiction. Dextromethorphan, a morphine derivative and glutamate antagonist, suppresses the cough center and has fewer adverse effects than other opioids, which accounts for its popularity in over-the-counter preparations.
Chronic obstructive pulmonary disease, the term used to describe airflow obstruction, encompasses emphysema and chronic bronchitis. Long-term smoking is the most frequent cause of COPD and accounts for approximately 90% of all cases. Heredity, second-hand smoke, exposure to air pollution, and history of childhood respiratory infections are also major risk factors. COPD symptoms are chronic cough, chest tightness, shortness of breath, and increased production of mucus. Emphysema causes irreversible lung damage by weakening and destroying air sacs within the lungs, which reduces lung elasticity and causes airway collapse and obstruction. Chronic bronchitis is an inflammatory disease that begins in smaller lung airways and advances gradually to larger airways. Increased mucus in the airways and more frequent bacterial infections in the bronchial result, which, in turn, impedes airflow. Ipratropium, theophylline, and albuterol are among drugs used for treatment.
Emphysema is a condition in which structures in alveoli are overinflated. The lungs lose elasticity and cannot fully expand and contract. Patients can inhale, but exhalation is difficult and inefficient. Emphysema in children is usually caused by congenital abnormalities of the lung and α1-antitrypsin deficiency. Although emphysema ranks ninth among chronic conditions that reduce activity, the seriousness of the disease varies. Some persons never reach a stage of incapacity and live with relatively little inconvenience. In others, the disease worsens until breathing becomes impossible. Shortness of breath, chronic cough, cyanosis (bluish coloration of skin caused by lack of oxygen), and exertion-induced wheezing are the most common symptoms. Dizziness, anxiety, stress, impotence, fatigue, impaired ability to concentrate, excessive daytime sleepiness, and insomnia may also occur.
**FIGURE 7-27 EMPHYSEMA: CAUSES**

The primary cause of emphysema is cigarette smoking. Tobacco smoke and other pollutants promote release of chemicals within alveoli that damage the walls of air sacs. The alveoli play a critical role in respiration because they facilitate exchange of oxygen from the air for carbon dioxide in the blood. Cases diffuse easily through the thin and fragile alveolar walls. Damage to air sac walls is irreversible and results in permanent holes in tissues of the lower lungs. The lungs can thus transfer less oxygen to the bloodstream, which causes shortness of breath. Lungs also lose elasticity, and the patient exhales with great difficulty. Emphysema does not develop suddenly; it occurs after years of exposure to cigarette smoke, air pollution, and irritating fumes.
Inherited emphysema involves deficiency of α₁-antitrypsin, a major blood protein of many genetic variations, only a few of which cause lung disease. This protein is produced by hepatic cells and protects lungs by blocking effects of enzymes called elastases. Elastases, carried in leukocytes, protect lungs by killing inhaled bacteria and removing tiny particles. α₁-Antitrypsin blocks elastase action after protective enzymatic work ends. Elastases destroy air sacs of lungs in people who lack α₁-antitrypsin. Intravenous α₁-proteinase inhibitor, a novel therapy for this deficiency, replaces α₁-antitrypsin in the blood. Symptoms of inherited emphysema are also managed by exercise, avoiding infection, oxygen therapy, and pulmonary rehabilitation. Smoking accelerates progression of the disease and shortens lifespan, so avoiding cigarettes and second-hand smoke is critical. Lung transplantation and lung reduction surgery are options for patients with serious effects of α₁-antitrypsin deficiency.
**Figure 7-29 Chronic Bronchitis**

Bronchi are air passages that connect the trachea, or windpipe, with alveoli. Bronchitis is inflammation of the bronchi causing excessive production of mucus and swelling of bronchial walls. Many people with a severe cold experience a brief attack of acute bronchitis, which is usually accompanied by fever, cough, wheezing, and spitting. The term chronic bronchitis is applied when these symptoms persist for months. Also, in chronic bronchitis, the episodes recur and generally last longer each time. Obstruction to airflow in air passages caused by swelling of the bronchial wall and the presence of mucus that cannot be cleared eventually produces shortness of breath after mild exertion. Chest infections are more prevalent in patients with chronic bronchitis.
A. Avoidance of respiratory irritants

- Stop smoking
- Avoidance of air pollution (environmental or occupational) and of temperature extremes
- Use of air filters, purifiers, or conditioners

B. Exercise

- Continuation of usual activities up to limits of capability
- Additional mild exercise if capable
- Specific breathing exercises

C. Precautions against infection

- Avoidance of crowds and persons with respiratory infections; use of influenza and pneumococcal vaccine important
- Prompt treatment of respiratory infections with antibiotics, bed rest, and other indicated measures

D. Adequate hydration

- At least 3 L/24 h

E. Adequate nutrition

- Frequent small meals, bedtime snacks, etc.

F. Practice of pursed-lip breathing

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**Figure 7-30 COPD: General Treatment Measures**

Various treatments are available for people with severe COPD (ie, chronic bronchitis and emphysema). Traditional management has involved medicines, inhalers, cessation of smoking, regular exercise, and oxygen therapy. Exercise is particularly crucial and should be continued to the point of exertion and shortness of breath. Breathing exercises, along with regular physical activity, are also used to strengthen respiratory muscles. Medicines may provide some relief but rarely have a major impact on physical limitations brought on by COPD. Such drugs include antibiotics for bacterial infections, oral medications, bronchodilators, and other inhaled medications. Oxygen supplementation from portable containers, lung reduction surgery to remove damaged lung tissue, and lung transplantation are used in extreme cases of COPD.
Specific medications prescribed for people with COPD are short-acting β₂ agonists (eg, albuterol), anticholinergic bronchodilators (eg, ipratropium), and long-acting bronchodilators (eg, salmeterol), which all help to open narrowed airways. Corticosteroids that are inhaled or taken orally minimize inflammation. The role of the anti-inflammatory medications is not well defined, and, although clinical trials are ongoing, these agents are not approved in the United States for treatment of COPD. Oxygen is given in cases of acute COPD (severe hypoxemia). Antibiotics are often given at the first sign of respiratory infection to prevent further damage of diseased lungs. Finally, expectorants, which help to loosen and expel mucus from the airways, can facilitate respiration. Adverse effects of bronchodilators and corticosteroids can include arrhythmias, cough, steroid myopathy, osteopenia, and cataracts.
Restrictive lung disease reduces the amount of inhaled air because of decreased elasticity or amount of lung tissue. Reduced lung volume results from altered lung parenchyma or disease of the pleura, chest wall, or neuromuscular apparatus. Lower total lung capacity, vital capacity, or resting lung volume often occurs. These disorders are classified on the basis of anatomical structure; (1) Intrinsic lung diseases, or diseases of lung parenchyma, cause inflammation or scarring of lung tissue or result in filling of airspaces with debris (pneumonitis). These diseases are idiopathic fibrotic, connective tissue, drug-induced lung, and primary lung diseases (eg, sarcoidosis). (2) Extrinsic, or extraparenchymal, diseases affect chest wall, pleura, and respiratory muscles (respiratory pump components), with resultant lung restriction, impaired ventilatory function, and respiratory failure. Corticosteroids, immunosuppressants, and cytotoxic agents are major drugs for restrictive lung disease.
**Pneumococcal Pneumonia**

A. Lobar pneumonia; r. upper lobe. Mixed red and gray hepatization (transition stage); pleural fibrinous exudate

B. R. upper lobe and segment of r. lower lobe pneumonia

C. Purulent sputum with pneumococci (Gram stain)

D. Colonies of pneumococci growing on agar plate

E. Pathologic changes in zones of the pneumonic lesion

- **Outer edema zone**
  - Alveoli filled with edema fluid containing pneumococci

- **Zone of early consolidation**
  - Polymorphonuclear and some red cell exudation

- **Zone of resolution**
  - Alveolar macrophages replace leukocytes

F. Complications of pneumococcal pneumonia

- Septic arthritis
- Intravascular coagulopathy (in asplenic patient)
- Purulent pericarditis
- Endocarditis
- Empyema
- Sterile pleural effusion
- G. Quellung reaction. Swelling of bacterial capsule when exposed to antibody

**Figure 7-33 Pneumonia**

Pneumonia is inflammation of the lung, with consolidation of the diseased part and alveolar air spaces filled with exudate, inflammatory cells, and fibrin. Most cases result from infection caused by various microorganisms, including viruses, bacteria (eg, *Streptococcus pneumoniae*), and parasites. Pneumonia often begins after an upper respiratory tract infection, with infections of the nose and throat being the most common culprits. Symptoms vary and depend on the patient’s age and the cause of the
## Infectious Agents Causing Pneumonia

<table>
<thead>
<tr>
<th>Class</th>
<th>Etiologic Agent</th>
<th>Type of Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Bacterial pneumonias</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Legionnaires disease</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td>Aspiration (anaerobic) pneumonia</td>
</tr>
<tr>
<td></td>
<td><em>Yersinia pestis</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Legionnaires bacillus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Peptostreptococcus, Peptococcus</em></td>
<td></td>
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<tr>
<td></td>
<td><em>Bacteroides</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Fusobacterium</em></td>
<td></td>
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<tr>
<td></td>
<td><em>Veillonella</em></td>
<td></td>
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<tr>
<td>Actinomycetes</td>
<td><em>Actinomyces israelii</em></td>
<td>Pulmonary actinomycosis</td>
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<tr>
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<td><em>Nocardia asteroides</em></td>
<td>Pulmonary nocardiosis</td>
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<tr>
<td>Fungi</td>
<td><em>Coccidioides immitis</em></td>
<td>Coccidioidomycosis</td>
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<td></td>
<td><em>Histoplasma capsulatum</em></td>
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<td>Aspergillos</td>
</tr>
<tr>
<td></td>
<td><em>Phycomycetes</em></td>
<td>Mucormycosis</td>
</tr>
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<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
</tr>
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<td>Psittacosis</td>
</tr>
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<td></td>
<td>Ornithiosis</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Mycoplasmal pneumonia</td>
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<td>Viruses</td>
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<td>Viral pneumonia</td>
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<tr>
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<td><em>syncytial virus, etc</em></td>
<td></td>
</tr>
<tr>
<td>Protozoa</td>
<td><em>Pneumocystis carinii</em></td>
<td><em>Pneumocystis pneumonia</em> (plasma cell*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pneumonia)</td>
</tr>
</tbody>
</table>

### Figure 7-33 Pneumonia (continued)

Infection. The symptoms, which begin after 2 or 3 days of a cold or sore throat, include fever, chills, cough, rapid ventilation, wheezing, emesis, chest pain, abdominal pain, decreased activity, and loss of appetite. In extreme cases, lips and fingernails may appear bluish or gray, particularly in children. Treatment aims to cure a bacterial infection with antibiotics, which do not attack viruses. It may be hard to distinguish between viral and bacterial pneumonia, so antibiotics may be given.
Viral pneumonia is an inflammation of the lungs caused by infection with a virus such as influenza or parainfluenza virus, adenovirus, rhinovirus, herpes simplex virus, respiratory syncytial virus, Hantavirus, or cytomegalovirus. Vaccines against influenza virus and respiratory syncytial virus are available for high-risk patients. Antibiotics are ineffective for treating viral pneumonia, but some more serious forms can be treated with antiviral medications (e.g.,
Influenza pneumonia on left and several days later on right in a patient with mitral stenosis.

Cross section of lung; marked congestion of bronchial mucosa; parenchyma hemorrhagic and edematous with patches of consolidation and emphysema.

Alveolar septa thickened by edema and cellular infiltrate; capillaries engorged; alveoli filled with fibrin-containing desquamated epithelial cells, leukocytes, and macrophages.

Section of lung showing hyaline membranes and necrosis of alveolar walls.

Figure 7-34 Viral Pneumonia (continued)

Ribavirin. Other supportive care for viral pneumonia includes use of humidified air, increased fluids, and oxygen. Most episodes of viral pneumonia improve without treatment within 1 to 3 weeks, but some last longer and cause more serious symptoms that require hospital stays. Serious infections can cause respiratory failure, liver failure, and heart failure.
**FIGURE 7-35 BACTERIAL PNEUMONIA**

Bacterial pneumonia, an infection that causes lung irritation, swelling, and congestion, occurs most often in winter. It usually follows a cold and starts suddenly with fever and chills. Painful breathing and a cough with bloody or yellow sputum are common; other signs are rapid breathing, tiredness, abdominal pain, and blue lips. Antibiotics and a humidifier (to loosen sputum and facilitate expectoration) are common remedies. Most cases of infectious pneumonia are caused by bacteria, and nearly 70% of these cases are due to *S. pneumoniae*. These bacteria cause disease when they move to the lower respiratory tract in susceptible individuals. Pneumococci are spread by droplets or direct contact with an infected person. The incubation period is 1 to 3 days. Therapy with penicillin or erythromycin makes the patient noninfective and usually leads to rapid recovery. Vaccines for pneumococcal pneumonia are available for patients at highest risk of fatal infection (eg, those older than 65 years).
CHAPTER 8
DRUGS USED IN DISORDERS OF THE REPRODUCTIVE SYSTEM

OVERVIEW
Sex hormones include androgens, progestins, and estrogens. They are produced by the gonads and the adrenal glands and are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics during puberty. These hormones are used therapeutically as contraceptives, as therapy for postmenopausal complications and breast cancer, and as replacement therapy in hypogonadism.

Combination oral contraceptives (COCs) are effective in blocking ovulation in approximately 98% of patients and come in many different formulations. Ethinyl estradiol and mestranol are the commonly used estrogens; desogestrel and norgestimate are commonly used progestins. Also used for contraception are progestin-only formulations to inhibit or delay ovulation and emergency preparations such as mifepristone (RU-486), given along with misoprostol, for medical termination of intrauterine pregnancy. Although COCs do have adverse effects, they are associated with benefits unrelated to contraception, such as a reduced risk of ovarian cysts, and can also ameliorate other menstrual and reproductive system abnormalities, acne, and hirsutism. Their ability to induce neoplasms is controversial.

The doses of estrogen used in hormone replacement therapy (HRT) for treatment of postmenopausal symptoms including vasomotor manifestations, genitourinary atrophy, and osteoporosis are substantially less than those used in oral contraceptives (OCs). The risks and benefits of estrogen in postmenopausal women with regard to cardioprotection, neuroprotection, and carcinogenicity have been a subject of much debate and are the focus of considerable research efforts.

Certain hormone-like drugs whose estrogenic activities are tissue selective (the selective estrogen receptor modulators, or SERMs) have different therapeutic uses, including prevention and treatment of breast cancer (tamoxifen) and osteoporosis (raloxifene).

Infertility associated with anovulatory menstrual cycles can be treated by use of antiestrogens such as clomiphene.

In female patients with failure of ovarian development, therapy with estrogen, usually in combination with progestin, replicates most of the events of puberty. Testosterone replacement therapy is used for male patients with hypogonadism.
Sex hormones include progestins, estrogens, and androgens. They are produced by the gonads and adrenal glands and are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics. As one example of these functional gonadal relations, the menstrual cycle is controlled by a neuroendocrine cascade involving the hypothalamus, pituitary, and ovaries. For control of this cycle, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which triggers the anterior pituitary to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), with effects on the ovaries. Androgens are steroids with anabolic and masculinizing effects in both males and females. Testosterone, the main androgen in humans, is synthesized and secreted primarily by testicular Leydig cells, as well as by ovaries in women and by adrenal glands. Testosterone secretion is also controlled by the hypothalamus-pituitary cascade.
Estrogen is synthesized in several forms, estradiol being the most potent and estrone and estriol having one tenth its potency. Many organs and processes in women are under the influence of estrogen, but the menstrual cycle shows its greatest effects. For control of this cycle, the hypothalamus periodically releases GnRH, which triggers the anterior pituitary to release the gonadotropins LH and FSH. LH and FSH, which are responsible for growth and maturation of ovarian follicles, also control ovarian production of estrogen and progestrone, which exert feedback regulation on the pituitary and hypothalamus and signal them when to start and stop releasing GnRH, FSH, and LH. In males, the hypothalamus and anterior pituitary also effect release of FSH (starts spermatogenesis) and LH (triggers steroidogenesis in Leydig cells). The testosterone resulting from steroidogenesis inhibits hormone production via negative feedback on the pituitary and hypothalamus, and release of GnRH, FSH, and LH ends.
**Neuroendocrine Regulation of Menstrual Cycle**

**Hypothalamic regulation of pituitary gonadotrophin production and release**

- Pulsed release of GnRH by hypothalamus (1 pulse/1-2 hr) permits anterior pituitary production and release of FSH and LH (normal).
- Continuous, excessive, absent, or more frequent GnRH release inhibits FSH and LH production and release (down-regulation).
- Decreased pulsed release of GnRH decreases LH secretion but increases FSH secretion (slow-pulsing model).

**Ovarian feedback modulation of pituitary gonadotrophin production and release**

- Presence of pulsed GnRH and low estrogen and progesterone levels result in increased levels of pulsed LH and FSH (negative feedback).
- Presence of pulsed GnRH, rapidly increasing levels of estrogen, and small amounts of progesterone result in high pulsed LH and moderately increased pulsed FSH levels (positive feedback).
- Presence of pulsed GnRH and high levels of estrogen and progesterone result in decreased LH and FSH levels (negative feedback).

**Correlation of serum gonadotrophic and ovarian hormone levels and feedback mechanisms**

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**Figure 8-3 Events of the Normal Menstrual Cycle**

In the early (follicular) phase, the hypothalamus releases GnRH, which triggers the anterior pituitary to release LH and FSH. These gonadotropins cause the graafian follicle to mature and secrete estrogen. Estrogen inhibits the pituitary; it reduces the gland’s release of LH and FSH (negative feedback loop). In midcycle, however, estrogen triggers a surge in gonadotropin release from the pituitary (a brief positive feedback effect), which stimulates follicular rupture and ovulation. The ruptured follicle becomes the corpus luteum, which produces progesterone and estrogen under the influence of LH during the second half of the cycle (luteal phase). Progesterone promotes development of a secretory endometrium that can accommodate embryo implantation. Conception causes progesterone secretion to continue, with the endometrium maintained as suitable for pregnancy. Without conception, the corpus luteum stops progesterone release and ceases to function, hormone levels decrease, and menstruation begins.
Combination oral contraceptives contain both estrogen and progestin and prevent pregnancy through several mechanisms. They inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of FSH and LH secretion by the anterior pituitary. Estrogen suppresses FSH release from the pituitary during the follicular phase of the menstrual cycle and inhibits the midcycle surge of gonadotropins. Progestin inhibits the estrogen-induced LH surge. COCs also produce alterations in the genital tract. Progestin is likely responsible for changing the cervical mucus and rendering it unfavorable for sperm penetration even if ovulation occurs. COCs induce an environment in the endometrium that is unfavorable for implantation. COCs may also alter the tubal transport of the sperm, egg, and fertilized ovum through the fallopian tubes.
Figure 8-5 Major Adverse Effects of Combination Oral Contraceptives

Major effects, related to excess or lack of estrogen or progestin, include breast fullness, depression, dizziness, edema, edema, and vomiting. Serum lipoprotein profiles can change; estrogen increases HDL levels and decreases LDL levels; progestins (especially norgestrel) cause the unwanted opposite effect. COCs are associated with gallbladder disease, cholestasis, and abnormal glucose tolerance and are not used if cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, abnormal genital bleeding, chronic diabetes, or liver disease exists. Benefits include reduced risk of ovarian cysts, benign breast disease, and ectopic pregnancy and improved premenstrual symptoms, dysmenorrhea, endometriosis, acne, and hirsutism. COCs reduce endometrial and ovarian tumor incidence; their cause of other neoplasms is controversial. Other drugs—antibiotics (eg, tetracycline), rifampin, rifabutin, anticonvulsants—may decrease the efficacy of COCs.
**Figure 8-6 Estrogen and Coagulation**

Estrogens may affect fibrinolytic pathways and cause a small increase in coagulation factors VII and XII and a decrease in anticoagulation factors protein C, protein S, plasminogen-activator inhibitor protein I, and antithrombin III. By causing this imbalance between coagulation and anticoagulation, estrogens may produce serious associated complications, including thromboembolism, thrombophlebitis, myocardial infarction, and cerebral and coronary thrombosis. These complications are more likely to occur in women who smoke and are older than 35 years.
Progestin only contraceptives

Progestin thickens cervical mucus, which decreases sperm penetration and alters the endometrium, thus preventing implantation. Progestin-only formulations are available as pills ("minipills"), depot injections, and implants. Pills contain norethindrone or norgestrel, taken daily on a continuous schedule; they are less effective than COCs because they block ovulation in only 60% to 80% of cycles. Depot injections of medroxyprogesterone acetate (MPA) impair implantation and produce plasma drug levels that are high enough to prevent ovulation in virtually all patients by slowing GnRH release, which thus prevents the LH surge required for ovulation. Progestin implants (subdermal capsules containing levonorgestrel) offer contraception for approximately 5 years. They are nearly as effective as sterilization, with completely reversible effects if the implants are surgically removed. Drug-related effects are weight gain, breast tenderness, headaches, and frequent occurrence of irregular menstrual bleeding.
Postcoital, or emergency, contraceptives consist of high-dose estrogen (ethinyl estradiol), administered within 72 hours of coitus and continued twice daily for 5 days. Alternatively, 2 doses of ethinyl estradiol plus norgestrel can be used within 72 hours of coitus, followed by another 2 doses 12 hours later. The hormones may inhibit or delay ovulation if taken during the first half of the cycle. They may also alter endometrial receptivity for implantation, interfere with the functions of the corpus luteum that maintains pregnancy, decrease sperm penetration, affect fertilization, and alter the transport of sperm, egg, or embryo. Emergency contraception does not interrupt an established pregnancy, which officially begins with implantation. Emergency contraceptives are associated with a high incidence of nausea and vomiting because of the high doses of hormones used.
A progestin antagonist with partial agonist activity, mifepristone (RU-486) is used for medical termination of intrauterine pregnancy through 49 days of pregnancy. Taken early in pregnancy, mifepristone interferes with progesterone, causing a decline in human chorionic gonadotropin and subsequent abortion of the fetus. Mifepristone is also known to sensitize the endometrium to prostaglandins, which terminate gestation by inducing uterine contractions. Therefore, it is rational to use mifepristone with the prostaglandin misoprostol, especially because mifepristone alone is more likely to cause an incomplete abortion. The regimen consists of a single dose of mifepristone, followed by a single dose of misoprostol 2 days later. Expected major adverse effects are cramping and bleeding, which are similar to symptoms of a spontaneous abortion. Incomplete abortion is also possible.
**Endometriosis**

Endometriosis is characterized by the presence of endometrial tissue on ovaries, fallopian tubes, and peritoneum or on more remote extrauterine sites such as the bowel, rectum, kidneys, and lungs. The most frequent symptoms of genital tract endometriosis include dyspareunia, dysmenorrhea, low back pain, menstrual irregularities, and infertility. The pathogenesis of endometriosis is multifactorial, but essentially it involves retrograde menstruation, in which endometrial cells implant in the pelvis and create “endometrial islands” that bleed and cause local inflammation in response to cyclic hormonal stimulation. Endometriosis is likely to remain problematic as long as menstruation continues. Therefore, the mainstay of medical therapy involves interrupting or decreasing menstruation.

**Figure 8-10**

A. **Normal findings** (indigo carmine visible at end of tube)

B. **Endometriosis** (involving ovary and distorting fallopian tube)
Danazol is a synthetic androgen that suppresses ovarian estrogen production by inhibiting the midcycle surge of LH and FSH from the pituitary. The resultant relatively hypoestrogenic state leads to atrophy of ectopic endometrial lesions and pain relief. Danazol is started when the patient is menstruating and is continued for 6 to 9 months, depending on disease severity. During therapy, the patient is usually amenorrheic, but ovulation may still occur. Patients should use nonhormonal contraception, because use of danazol during pregnancy should be avoided. Regular ovulatory cycles are resumed within 4 weeks after ending danazol therapy. Adverse effects are characteristic of estrogen deficiency and include headache, flushing, sweating, and atrophic vaginitis. Androgenic side effects include acne, edema, hirsutism, deepening of the voice, and weight gain. Although danazol has been highly effective in relieving the symptoms of endometriosis, newer, better-tolerated treatments have reduced its use.
Figure 8-12 Gonadotropin-Releasing Hormone Agonists, Combination Oral Contraceptives, and Progestin

Gonadotropin-releasing hormone agonists (e.g., leuprolide, goserelin) create a temporary medical oophorectomy by causing paradoxical effects on the pituitary: initial stimulation of LH and FSH release, and then inhibition of hormone release. These effects result in reduced sex hormone levels and regression of endometriosis-related lesions. Long-acting formulations are usually given every 28 days for approximately 6 months. GnRH agonists are contraindicated in pregnancy and have hypoestrogenic side effects, eg, mild bone loss (which reverses after the drug is stopped). Because of concerns about osteopenia, add-back low-dose estrogen therapy has been used. COCs and progestins also suppress LH and FSH, so they render endometrial tissue thin and compact, thus alleviating endometriosis. COCs can be taken continuously or cyclically. Therapy can be stopped after 6 to 12 months or continued indefinitely. Progestins may have greater adverse effects than COCs; a depot form may delay return to fertility.
**Figure 8-13** **ESTROGEN DECLINE**

In the premenopausal period, ovarian secretion of estradiol, the most potent form of estrogen, is the major source of estrogen production. In menopause, production of estradiol diminishes as the ovaries cease to function. In the postmenopausal period (1 year after amenorrhea), gonadotropin levels increase and ovarian hormone levels decrease secondary to ovarian failure. Peripheral conversion of adrenal androstenedione to estrone (one tenth the potency of estradiol) becomes the principal source of estrogen. Consequences of this estrogen deficiency include vasomotor symptoms, genitourinary atrophy, and osteoporosis.
The chief vasomotor symptoms reported by women are described as hot flashes, which occur over the anterior part of the body, especially the face, neck, and chest. Usually lasting a few minutes but varying in frequency and severity, these symptoms are caused by a decrease in the tone of arterioles. This compromised state results in increased blood flow to the skin and a subsequent increase in skin temperature. Hot flashes seem to be synchronous with the increased hypothalamic release of GnRH that occurs in response to estrogen deficiency. GnRH neurons are coincidentally close to the hypothalamic centers that regulate temperature. Estrogen replacement therapy reestablishes feedback control of hypothalamic secretion of GnRH, leading to a decreased incidence of hot flashes.
Postmenopausal estrogen deficiency leads to several changes in the vagina, including thinning of the epithelium, a decreased blood supply, dryness, and a change from acidic to a neutral or alkaline pH that predisposes to infection. Chief symptoms include vaginal discharge secondary to infection and painful intercourse from dryness, as well as dysuria and urinary incontinence from bladder atrophy. Estrogen increases the vascularity and epithelial proliferation of the vagina, which allows greater lubrication, increased protection from vaginitis, and reduced vaginal trauma from intercourse. Estrogen also reverses atrophy of the bladder.
Lower estrogen levels enhance calcium efflux from bone mineral stores and increases serum Ca\(^{2+}\) levels. These effects suppress parathyroid hormone secretion, which reduces vitamin D3 synthesis, thus decreasing intestinal calcium absorption. Estrogen deficiency and advanced age also reduce secretion of the hormone calcitonin, which inhibits bone resorption. Bones thin and weaken, with increased risk of fractures, especially compression fractures of vertebrae (and thus height loss) and minimal-trauma hip and wrist fractures. Preventive and therapeutic measures include use of estrogen, calcium, vitamin D, calcitonin, fluoride, bisphosphonates, and drugs such as raloxifene. Therapeutic estrogen primarily decreases bone resorption, which reduces bone loss (does not restore bone mass); decreases calcium excretion, producing a premenopausal calcium balance; increases vitamin D3 synthesis; increases serum calcitonin levels; and (given with calcium) decreases hip fracture occurrence.
Unopposed estrogen is associated with a large increase in the incidence of endometrial carcinoma, which is thought to be due to the hormone's continuous stimulation of endometrial hyperplasia. In patients with an intact uterus, progestin is added to estrogen therapy because it reduces endometrial hyperplasia by increasing local conversion of estradiol to the less potent estrone, converting the endometrium from a proliferative to a secretory state, or both. Progestin also reduces the risk of estrogen-induced irregular bleeding. Patients who have undergone a hysterectomy can use unopposed estrogen therapy; progestin is unnecessary, especially because it may unfavorably alter the HDL/LDL ratio.
Figure 8-18 Route of Hormone Administration

A major pharmacologic consideration in HRT is the route of administration. Oral dosage forms of estrogen go through portal circulation and thus expose the liver to high hormone concentrations. Also, oral administration is associated with a more rapid conversion of estradiol to estriol. Transdermal estradiol overcomes these problems and still relieves vasomotor and genitourinary symptoms and protects against bone loss. Vaginally applied estrogen cream can be used to treat genitourinary symptoms, but the response may be lost after 14 days because of tissue cornification or downregulation of estrogen receptors. Stopping treatment for 7 to 14 days and then restarting can overcome this effect. Conjugated estrogen vaginal cream and its equivalents have 4 times the activity of oral estrogens on local tissues. Because estrogen in the cream may enter the systemic circulation, warnings related to its use are essentially the same as those for systemic preparations.
Figure 8-19 General Adverse Effects

The doses of estrogen used in HRT are substantially less than those used in OCs, so adverse effects of HRT tend to be less severe than those of OCs. Estrogen may cause nausea, vomiting, edema, headache, hypertension, and breast tenderness. Estrogen is also a major cause of postmenopausal uterine bleeding, which is more likely to occur during the withdrawal period if estrogen is given cyclically with progestin. Progestin is likely responsible for edema and depression. Androgen-like progestins can increase the LDL/HDL ratio and cause thrombophlebitis, hirsutism, weight gain, and acne.
Risks and benefits of estrogen with regard to cardioprotection, neuroprotection, and carcinogenicity in postmenopausal women have been a subject of much debate. Estrogen had been believed to be cardioprotective, possibly through favorable changes in lipid metabolism and direct vasodilatory effects. However, a landmark trial (Women’s Health Initiative) found estrogen-progestin HRT to be associated with an increased risk of stroke, venous thromboembolism, coronary heart disease, nonfatal myocardial infarction, and death from heart disease. Also, estrogen alone or with progestin did not affect the progression of atherosclerotic lesions in older postmenopausal women with at least 1 coronary artery lesion. Estrogen increased the risk of Alzheimer disease, a finding that contradicts earlier data indicating a possible association between estrogen and neuroprotection.
Figure 8-21 Cancer Risks

Estrogen was shown in the Women’s Health Initiative trial and another large study to increase the risk of breast cancer. The latter trial evaluated HRT in more than 1 million British women and found that those who received HRT (especially both estrogen and progestin) had an increased risk of development of and death resulting from breast cancer. The risk of development of cancer increased with duration of HRT use, but it also declined after discontinuation of HRT. The trial indicated that estrogen-progestin reduced the risk of colorectal cancer and confirmed beneficial effects on reduction of hip and vertebral fractures. However, these benefits do not seem to outweigh the risks. As a result, in 2003, the US FDA urged clinicians to limit the use of HRT to a few months for temporary relief of postmenopausal symptoms.
Selective estrogen receptor modulators (SERMs), hormonelike drugs with tissue-selective estrogenic activities, act as competitive antagonists or weak agonists: estrogenic in bone but no effect or antagonistic in breast and endometrium. Tamoxifen, first classed as antiestrogenic, is used to prevent and treat hormone-responsive breast cancer (inhibits cell proliferation and reduces tumors, as a result of estrogen receptor antagonism). It has estrogenic actions in the uterus (stimulates endometrial proliferation and thickening, which increases carcinoma risk) and in the skeletal and cardiovascular systems (reduces bone loss; improves lipid profiles). Hot flashes, menstrual abnormalities, thrombosis, and pulmonary embolism are adverse effects. Raloxifene is used to prevent and treat osteoporosis; it has estrogen agonist action in bone and on lipid metabolism and antagonist action in breast and uterus; it is antiproliferative for estrogen-positive breast cancer cells. Adverse effects are hot flashes, leg cramps, and venous thromboembolism.
Antiestrogens are distinguished from SERMs in that they act as pure antagonists in all tissues. The antiestrogen clomiphene binds competitively to estrogen receptors and decreases the sites available to endogenous estrogen, including hypothalamic and pituitary estrogen receptors. This inhibition leads to a disruption in the negative feedback of estrogens on the hypothalamus and pituitary, a subsequent increase in secretion of GnRH and gonadotropins, and ultimately stimulation of ovulation. The agent is used to treat infertility associated with anovulatory menstrual cycles, but it is effective only in women with a functional hypothalamus and adequate endogenous estrogen production. Adverse effects are dose related and include ovarian enlargement, vasomotor symptoms, and visual disturbances.
In several conditions in females, such as Turner syndrome (ovarian dysgenesis and dwarfism), the ovaries do not develop (or have no primordial follicles and may be represented only by a fibrous streak), and puberty does not occur. Other characteristics include short stature, primary amenorrhea, sexual infantilism, high gonadotropin levels, and multiple congenital abnormalities. Conception is impossible. In males, dysfunction of Leydig cells or failure of the hypothalamic-pituitary system can lead to inadequate secretion of androgens, for which testosterone replacement therapy is used. If testosterone deficiency occurs before puberty, it results in failure to complete puberty. After completion of puberty, testosterone deficiency can lead to loss of libido and energy, decreased muscle mass and strength, decreased hematocrit and hemoglobin, and decreased bone mineral density.
Figure 8-25 Hypogonadism Treatment and Adverse Effects

For females, appropriate therapy with estrogen, usually with progestin, replicates most events of puberty. Genital structures grow to normal size, breasts develop, axillary and pubic hair grows, and the body achieves a normal feminine contour. Estrogen may increase growth, but if used too soon, it can accelerate epiphyseal fusion and cause a short final height (treated with androgens and growth hormone). For male testosterone deficiency, an oral drug is ineffective because of liver metabolism. Intramuscular (cyponate or enanthate) or transdermal testosterone overcomes first-pass metabolism to reach normal serum concentrations. In prepubertal children, testosterone causes acne, hirsutism, gynecomastia, and sexual aggression as well as growth disturbances. Excess androgen in men can cause priapism, impotence, reduced spermatogenesis, and gynecomastia. Androgens can also cause edema and an increased LDL/HDL ratio, which may be harmful to those with hyperlipidemia or CHF.
OVERVIEW

For many drugs, the kidney is the major organ of elimination. In the healthy human, the kidney receives between 20% and 25% of the blood pumped by each beat of the heart. The kidney’s primary function is 2-fold: to eliminate unwanted substances (e.g., toxic substances, drugs, and their metabolites) and to retain (reabsorb, recycle) wanted materials (e.g., water and electrolytes). The amount of drug and metabolites eliminated (cleared) from the body depends on several factors, including the glomerular filtration rate (GFR), the urine flow rate, and the pH. The rate of renal elimination is the net result of glomerular filtration, secretion, and reabsorption.

The functional microscopic unit of the kidney is the nephron, a tube that is open at one end and closed at the other end by a semipermeable membrane. The nephron has 5 distinct anatomical and functional units: glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct. Large drug molecules (>5-6 kd) and drug molecules that are bound to plasma proteins do not pass into the nephron of a healthy kidney. Most of the water and other substances that enter the nephron are reabsorbed into the surrounding tissue and blood supply. The small residual amount is excreted as the urine.

The flow and contents of the urine are determined by 3 processes, most of which are coupled: filtration through the glomerulus, reabsorption of water and other substances from the tubule, and secretion of substances into the tubule. Many processes involve active transport, passive transport, or osmotic gradients. Most of the water and solutes (e.g., sodium, glucose, bicarbonate, amino acids) are reabsorbed during passage through the proximal convoluted tubule, and further concentration occurs in the countercurrent system of the loop of Henle. The thick ascending limb and the distal convoluted tubule are involved in Na⁺-K⁺ and H⁺ exchange under tight homeostatic control and hormonal influence, including adrenal steroid hormones such as aldosterone. The collecting duct is the primary site of action of antidiuretic hormone (ADH).

Drugs that target the renal system, primarily diuretic agents, have been a major advance in treatment of hypertension, heart failure, and other disorders. Each class of diuretics affects different processes located at different sites along nephrons. Therefore, each class has its own set of associated therapeutic advantages or drawbacks. Each also has characteristic effects on electrolyte balance, which is an important consideration for long-term use. Many effects can be anticipated on the basis of a drug’s mechanism of diuretic action and can be ameliorated by dietary or drug regimens. Combinations of diuretics may offer a remedy for resistance to a single agent.

A decline in renal function, whether caused by advanced age or disease, has a significant effect on clearance of drugs that are eliminated predominantly via the kidney. Dosages must be adjusted in these situations.
The kidneys are a pair of specialized, retroperitoneal organs located at the level between the lower thoracic and upper lumbar vertebrae. Each kidney is reddish brown and has a characteristic shape: a convex lateral edge and concave medial border with a marked depression or notch termed the hilus. Each adult kidney is approximately 11 cm long, 2.5 cm thick, and 5 cm wide and weighs 120 to 170 g. Kidneys contribute to several important processes, including regulation of fluid volume; regulation of electrolyte balance; excretion of metabolic wastes; and elimination of toxic compounds, drugs, and their metabolites. It also acts as an endocrine organ. Each kidney is divided into a cortex and a medulla, both parts containing nephrons (approximately 1.25 million per kidney). The fluid that exits a nephron flows out the papilla of a pyramid (8-15 per medulla), enters a minor calyx, joins effluent of other minor calyces in the major calyx, and is eliminated as urine through the ureter.
Each kidney contains approximately 1 to 3 million tubular nephrons (Greek nephros, meaning kidney). A nephron originates in the glomerular apparatus. The part adjoining this corpuscle is termed the proximal convoluted tubule because of its tortuous course that remains close to its point of origin. The tubule then straightens in the direction of the center of the kidney and forms the Henle loop, by making a hairpin turn and returning to the vascular pole of its parent renal corpuscle. The loop extends to the distal convoluted tubule and then to the collecting tubule. Collecting tubules unite to form larger collecting ducts. Most nephrons originate in the kidney cortex, are short, and extend only to the outer medullary zone. Other nephrons originate close to the medullary level (juxtamedullary glomeruli) and extend deep into the medulla, almost as far as the papilla. Each part of the nephron acts in physiologic processes that affect or are affected by metabolism of drug molecules (or their metabolites).
Figure 9-3 Blood Vessels Surrounding Nephrons

Critical to multiple kidney functions is close association of nephrons with blood vessels, in that water and other substances pass from nephron to blood and vice versa. Kidneys have a great influence on volume and composition of plasma and urine, so the architecture of renal vasculature reflects functions other than tissue oxygenation. In the outer renal cortex, each afferent arteriole enters a glomerulus, divides, forms a capillary network, becomes an efferent arteriole, and exits the glomerulus. Neurotransmitters, drugs, and environmental factors that relax the afferent arteriole or constrict the efferent arteriole increase the GFR; those that constrict the afferent arteriole or relax the efferent arteriole reduce the GFR. Blood vessels surround and outnumber tubular segments of each nephron and form a peritubular network of capillaries that allows exchange of water, electrolytes, and other substances. This exchange is the target for actions of many drugs, especially diuretics.
Figure 9-4 The Glomerulus

The glomerulus is an important interface between afferent arteriolar blood flow and the nephron. The glomerulus filters plasma, and the fluid, minus cells, enters the nephron as an ultrafiltrate. The glomerulus is also a barrier to molecules larger than approximately 5 kDa (e.g., plasma proteins). Thus, plasma proteins and drug molecules bound to them do not pass into nephrons of a healthy kidney; only smaller free drug or metabolite molecules do so. However, damaged glomeruli allow passage of plasma proteins, and the presence of these proteins in the urine indicates a renal disorder. In renal disease, drugs enter the nephron and are excreted at a rate greater than normal, which is noted as a shorter plasma half-life of drugs (or metabolites). Hormones and hormonemimetic drugs that alter the GFR include angiotensin II (constricts afferent arterioles and thereby reduces the GFR) and atrial natriuretic peptide and prostaglandin E₂ (dilate afferent arterioles and thus increase it).
The GFR is an important characteristic of kidney functioning and an important variable in elimination of drugs and their metabolites. In general, the greater the GFR is, the greater the rate of elimination is. The GFR can be measured noninvasively by determining the rate at which a substance is removed from plasma (or appears in urine), which requires the use of a substance that is freely filtered by the glomerulus and is neither reabsorbed nor secreted within the nephron. These criteria are fulfilled by the 5-kd fructose polysaccharide inulin. For the assay, after a uniform blood level of inulin is established, measurement of the concentration of inulin in plasma ($P_{in}$), the concentration of inulin in urine ($U_{in}$), and urine flow rate ($V$) yields the GFR from the equation: $\text{GFR} = \frac{V \times U_{in}}{P_{in}}$. The GFR of a healthy adult kidney is approximately 120 mL/min. Decreased clearance, which is common in the elderly, usually results in slower drug elimination and requires an appropriate dosage adjustment.
**Figure 9-6 Tubular Segments**

The structure and function of tubular segments are important for understanding drug effects on the kidney. The proximal portion and thick segment of the descending limb have a similar structure (slight variation in cell size and shape). Tight junctions between cells prevent escape of material in the tubular lumen. Proximal segment cells act to reabsorb water and other substances. The proximal segment's brush border is replaced in the thin tubular segment by fewer short microvilli. Permeability to water and position of descending and ascending limbs of the Henle loop create a countercurrent multiplier for urine concentration. The distal segment of the nephron consists of the thick ascending limb of the Henle loop and the distal convoluted tubule. The ultrastructure and large surface area of the distal segment serve the energy requirements of active Na+ transport from luminal fluid, formation of ammonia, and urine acidification. Drug action in each segment alters kidney function in specific ways.
Figure 9-7 Ion and Water Reabsorption

More than 99% of glomerular ultrafiltrate is reabsorbed from the tubular lumen. The kidney is thus more an organ of retention than of elimination. The driving factor for water and Na⁺ reabsorption in the nephron is active Na⁺ transport. Drugs affecting Na⁺ transport can alter urine flow and composition. Na⁺ reabsorption occurs against concentration and electrical potential gradients (the lumen is electrically negative compared with peritubular fluid) and is an active process requiring energy (supplied by ATP). The active uptake mechanism (pump) for Na⁺ involves a cotransporter that exchanges Na⁺ for K⁺, an important factor for drugs that affect Na⁺ transport. Cl⁻ and other ions move by cotransport with Na⁺ or other ions or by passive diffusion. The osmotic gradient (established by ion transport) drives water out of the lumen. Hormones and drugs that decrease ion transport or the osmotic gradient reduce ion and water reabsorption and thus increase urine flow (diuresis) and ion content.

<table>
<thead>
<tr>
<th>Filtered Load Reabsorbed (%)</th>
<th>Factors That Stimulate Reabsorption</th>
<th>Factors That Inhibit Reabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>67</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>25</td>
<td>Sympathetic nerves</td>
</tr>
<tr>
<td>Distal tubule</td>
<td>-4</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>-3</td>
<td>Aldosterone</td>
</tr>
</tbody>
</table>
A notable ion with regard to drug metabolism is bicarbonate, or $\text{HCO}_3^-$. $\text{HCO}_3^-$ and $\text{Cl}^-$ are the most relevant ions for the class of diuretic drugs known as carbonic anhydrase inhibitors. $\text{HCO}_3^-$ is freely filtered through the glomerulus and enters the nephron. Almost all of it is reabsorbed along the tubule—most of it (80%–85%) in the proximal convoluted tubule—in a process that involves $\text{H}^+$ secretion, and thus reabsorption of $\text{HCO}_3^-$ is inhibited by carbonic anhydrase inhibitors. Although usually all the filtered $\text{HCO}_3^-$ is reabsorbed and none is excreted in the urine, a number of factors influence $\text{H}^+$ secretion by the nephron, and a small amount of $\text{HCO}_3^-$ can be lost in the urine. The kidneys generate new $\text{HCO}_3^-$ to replenish this loss. Acetazolamide is a diuretic that affects $\text{HCO}_3^-$ exchange, predominantly at the proximal convoluted tubule (see Figure 9-14).
The kidneys are the primary route of excretion of $K^+$ from the body. Although a large fraction of the filtered $K^+$ is reabsorbed along the proximal convoluted tubule and the loop of Henle, the amount of $K^+$ excretion in the urine is determined mainly by the highly variable secretory activity of the distal convoluted tubule. Several diuretics and other drugs cause excess urinary $K^+$ loss as a side effect by increasing the distal tubular flow rate and $Na^+$ delivery (eg, ethacrynic acid and furosemide), by alkalining the distal tubular fluid (eg, carbonic anhydrase inhibitors such as acetazolamide), or by blocking tubular $K^+$ reabsorption (eg, ouabain). Some diuretics, known as potassium-sparing diuretics, do not cause $K^+$ loss (see Figure 9-16).
ADH is produced in supraoptic and paraventricular nuclei of hypothalamus and descends along nerve fibers to neurohypophysis, where it is stored for subsequent release.

Blood osmolality and volume are modified by fluid intake (oral or parenteral); water and electrolyte exchange with tissues, normal or pathologic (edema); loss via gut (vomiting, diarrhea); loss into body cavities (ascites, effusion); or loss externally (hemorrhage, sweat).

**ADH release increased by:**
- High blood osmolality affecting hypothalamic osmoreceptors
- Low blood volume affecting thoracic and carotid volume receptors
- Pain, emotion, trauma
- Some barbiturates
- Nicotine
- Morphine
- Ether

**ADH release inhibited by:**
- Low blood osmolality
- High blood volume
- Ethanol

In presence of ADH, blood flow to renal medulla is diminished, thus augmenting hypertonicity of medullary interstitium by minimizing depletion of solutes via bloodstream.

ADH causes walls of collecting ducts to become more permeable to water and thus permits osmolar equilibrium and absorption of water into the hypertonic interstitium; a small volume of highly concentrated urine is excreted.

**Figure 9-10 Antidiuretic Hormone**

Antidiuretic hormone, also known as arginine vasopressin in humans, is a 1-kd nonapeptide that is synthesized in the hypothalamus and released into the blood from the posterior pituitary gland. It is structurally similar to oxytocin but is a more potent (>100 times) antidiuretic. ADH alters the morphology of cells of the collecting duct and increases their permeability. Water passes from the collecting duct lumen into the renal interstitium, so an osmotic equilibrium between interstitium and fluid in the duct occurs. In the presence of ADH, the amount of water that can be reabsorbed from collecting ducts is limited only by the amount flowing through them. Various stimuli induce ADH release (and thus production of a small volume of concentrated urine): plasma osmolality, pain, emotion, trauma, and drugs (eg, nicotine, morphine, ether, some barbiturates). ADH is inhibited by ethanol.
In addition to ADH, a second volume-regulating system—the renin-angiotensin-aldosterone system— Involves the kidney. The kidneys synthesize and secrete renin, a proteolytic enzyme of approximately 40 kDa, in response to decreased blood pressure, fluid volume, and Na⁺ and increased H⁺. Renin secretion results in conversion of angiotensinogen (a blood-borne α globulin produced by the liver) to the decapeptide angiotensin I. Angiotensin I is converted (primarily in lungs) to angiotensin II, which is a potent vasoconstrictor and a stimulator of aldosterone release from the adrenal gland. Angiotensin II and aldosterone stimulate NaCl and water reabsorption by the proximal convoluted tubule and the collecting duct, respectively. The enzyme that catalyzes conversion of angiotensin I to angiotensin II, termed angiotensin-converting enzyme (ACE), is the target of the ACE inhibitor class of antihypertensive drugs.

**Figure 9-11 Renin-Angiotensin-Aldosterone System**

![Mechanisms of Renin Release](image)

- **Baroreceptor mechanism:** Increased pressure in afferent arteriole inhibits renin release from JG cells (red arrows); decreased pressure promotes renin release (green arrows).
- **Sympathetic nerve mechanism:** β₁-Adrenergic nerves stimulate renin release (green arrows).
- **Macula densa mechanism:** Increased NaCl in distal nephron inhibits renin release (red arrows); decreased load promotes renin release.
Figure 9-12 General Considerations: Volume Homeostasis

The kidneys are part of an integrated homeostatic mechanism for maintaining the volume of the extracellular fluid. Other organs involved in this mechanism include the heart (e.g., cardiac output and heart rate), the CNS (e.g., sympathetic tone and ADH release), the lungs (e.g., conversion of angiotensin I to angiotensin II), and the adrenal gland (e.g., release of aldosterone). Several feedback control mechanisms operate among the components of this control mechanism, which ensure responses to volume expansion.
**Figure 9-12 General Considerations: Volume Homeostasis (continued)**

(increased extracellular fluid) and volume contraction (decreased extracellular fluid). The design of drugs that selectively target the components of this system has led to major advances in therapy for cardiovascular diseases such as hypertension and heart failure (discussed in chapter 4).
Figure 9-13 Mercurial Diuretics

Organomercurial agents inhibit active Cl⁻ transport, especially in the ascending limb of the Henle loop. In acidic conditions, Hg²⁺ dissociates, binds to, and inhibits sulfhydryl enzymes. Na⁺ reabsorption is thus decreased; more Na⁺ and Cl⁻ are excreted. Because more Na⁺ is delivered to the distal nephron during diuresis, K⁺ and H⁺ excretion (sum of urinary NH₄⁺ + titratable acid - urinary HCO₃⁻) may increase. In alkaline conditions, Hg²⁺ does not dissociate, and patients become refractory to mercurials.

Acidiifying agents (e.g., NH₃Cl) can be used to counteract this effect. Mercurial diuretics (e.g., mercaptomerin) are poorly absorbed when taken orally, so an intramuscular route is required. Because of this difficulty and their toxicity (e.g., systemic poisoning, cardiac toxicity, hypersensitivity, worsening of renal insufficiency), mercurials are largely obsolete. They are sometimes used for CHF, cirrhosis, and portal obstruction because they do not deplete K⁺.
Diuretic drugs such as acetazolamide, brinzolamide, dichlorphenamide, and dorzolamide inhibit carbonic anhydrase, particularly at the proximal convoluted tubule. Carbonic anhydrase catalyzes dehydration of carbonic acid ($H_2CO_3$). As a result, $H^+$ needed for $Na^+\cdot H^+$ exchange is reduced, $HCO_3^-$ and $Na^+$ reabsorption in proximal tubules is suppressed, and diuresis is promoted. Because of the decreased reabsorption of $Na^+$, $Na^+\cdot K^+$ exchange increases in the distal convoluted tubules. Increased amounts of $Na^+$, $K^+$, and $HCO_3^-$ are excreted in the urine, and $Cl^-$ is retained. Acidosis that may result eventually leads to a refractory response to the diuretic. Carbonic anhydrase inhibitors are relatively weak diuretics. They are also used for glaucoma (to reduce formation of aqueous humor), petit mal epilepsy (mechanism unclear), and salicylate or $HCO_3^-$ poisoning (to alkalinize urine). These agents can cause CNS effects, hypokalemia, and hyperglycemia.
**Figure 9-15 Thiazide Diuretics**

Thiazide (benzothiadiazide) diuretics—bendroflumethiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide—inhibit Cl⁻ reabsorption, especially in the distal portion of the ascending limb of the Henle loop and the proximal portion of the distal convoluted tubule. Excretion of Na⁺, K⁺, Cl⁻, and HCO₃⁻ is increased; refractoriness does not develop to the diuretic effect. Thiazide diuretics are often used to treat chronic edema and essential hypertension and, less often, nephrosis, some forms of diabetes insipidus, and hypercalciumia. Common adverse effects are hypokalemia (K⁺ supplements are recommended), which may lead to alkalosis, and hyperglycemia. Extra caution is needed when these agents are used with digoxin for CHF because of greater digitalis toxicity in conditions of low K⁺. Because thiazides are excreted via glomerular filtration and tubular secretion, they compete with uric acid for tubular secretion.
Figure 9-16 Potassium-Sparing Agents

Two major categories of K⁺-sparring diuretic drugs are Na⁺ channel antagonists (e.g., amiloride, triamterene) and aldosterone receptor antagonists (e.g., spironolactone). The former inhibit active Na⁺ reuptake. Enhanced Na⁺ and Cl⁻ excretion disrupts Na⁺ transport and reduces K⁺ secretion. These drugs moderately increase Na⁺, Cl⁻, and HCO₃⁻ excretion; when they are used with other diuretics, Na⁺ excretion increases and K⁺ is retained. Reversible azotemia can occur. Triamterene can increase serum uric acid levels, so caution is needed for its use in patients with gout. Spironolactone reduces aldosterone-mediated Na⁺-K⁺ exchange at the distal convoluted tubule, which increases Na⁺ loss while reducing K⁺ excretion. Adverse effects of both types of drugs include hyperkalemia (especially when impaired renal function exists). Combination therapy with K⁺-sparring drugs is not usually advised, but they are often used with diuretics (e.g., thiazides) that increase K⁺ excretion.
FIGURE 9-17 LOOP (HIGH-CEILING) DIURETICS

This class of diuretic drugs (eg, bumetanide, ethacrynic acid, furosemide, torsemide) acts mainly on the thick ascending limb of the Henle loop. Because they elicit the greatest diuresis possible, they are also termed high-ceiling diuretics. They act at the luminal nephron surface and inhibit electrolyte reabsorption, with resultant greater Na⁺, Cl⁻, K⁺, Mg²⁺, and Ca²⁺ excretion. Inhibition of NaCl reabsorption in the Henle loop decreases the strength of the countercurrent concentrating mechanism and causes greatly increased urine output. Bumetanide, furosemide, and torsemide are weak inhibitors of carbonic anhydrase; ethacrynic acid, which is not a sulfonamide, does not inhibit this enzyme. The drugs increase Cl⁻ more than Na⁺ excretion, which can lead to hypochloremic alkalosis. Refractoriness does not occur. Loop diuretics are used for acute pulmonary edema, edema associated with CHF, cirrhosis, and renal disease. Fluid and electrolyte imbalances are the most common adverse effects.
**Figure 9-18 Osmotic Agents**

Osmotic diuretics (e.g., mannitol, glycerol) enter the nephron through the glomerulus but are poorly reabsorbed along the nephron because of their relatively large molecular size. The presence of unabsorbed molecules in the tubule lumen creates a concentration (osmotic) gradient across the tubular membrane. In the proximal convoluted tubule, reabsorption of Na⁺ and water decreases, which produces diuresis without marked changes in Na⁺ or Cl⁻ excretion. Mannitol, the agent used most often, is a hexacarbon sugar alcohol that is given intravenously; it is not metabolized. Osmotic diuretics are used to treat cerebral edema and glaucoma (by reducing cerebrospinal or intraocular fluid pressure), oliguria and anuria, and certain phases of acute renal failure (as prophylaxis). Because osmotic diuretics increase blood volume, adverse effects include decompensation in patients with CHF. Hyperosmolarity or hyponatremia can occur during therapy of renal failure or cirrhosis.
## Figure 9-19  Summary of Therapeutics

Each class of diuretic drug affects various transport processes that are located along different segments of the tubular nephron. Because the drugs tend to have relatively selective actions on specific transport processes and predominant actions on specific segments, they produce characteristic effects on electrolyte and acid-base balances in patients. It is therefore possible to provide
<table>
<thead>
<tr>
<th>Relative Potency</th>
<th>Effect on K⁺</th>
<th>Effect on Acid Secretion</th>
<th>Effect on Renal Hemodynamics</th>
<th>Particularly Useful for:</th>
<th>Side Effects of Diuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>Partial inhibition of distal K⁺ secretion but hypokalemia may occur</td>
<td>H⁺ secretion increased</td>
<td>No effect on RPF or GFR</td>
<td>Patients with dilutional hyponatremia; moderate to extensive edema</td>
<td>Hypokalemia and hypochloremic alkalosis; nephrotoxicity in patients with renal disease; hypersensitivity reactions</td>
</tr>
<tr>
<td>++</td>
<td>K⁺ secretion increased</td>
<td>H⁺ excretion diminished (bicarbonate diuresis)</td>
<td>Little effect on RPF or GFR</td>
<td>Patients with metabolic alkalosis; cor pulmonale</td>
<td>Hyperchloremic acidosis; hypokalemia</td>
</tr>
<tr>
<td>+++</td>
<td>K⁺ secretion increased</td>
<td>Little effect on net acid-base</td>
<td>May depress RPF or GFR</td>
<td>Mild to moderate edema</td>
<td>Hypokalemia; hypochloremia and metabolic alkalosis; diurnal hypotension, prerenal azotemia; hyperuricemia</td>
</tr>
<tr>
<td>+</td>
<td>Amloride/ Triamterene: Depress K⁺ excretion Spironolactone: Retards K⁺ secretion stimulated by aldosterone</td>
<td>Amloride/ Triamterene: Inhibit distal H⁺ excretion Spironolactone: Retards aldosterone-stimulated H⁺ excretion</td>
<td>Amloride/ Triamterene: May depress GFR Spironolactone: No effect on RPF</td>
<td>Patients with hyperaldosteronism (cirrhosis with ascites, nephrosis, severe cardiac failure)</td>
<td>Hyperkalemia; metabolic acidosis; azotemia</td>
</tr>
<tr>
<td>+++++</td>
<td>K⁺ secretion increased</td>
<td>H⁺ excretion accelerated</td>
<td>Little effect at low doses; large doses may increase RPF and GFR</td>
<td>Patients with pulmonary edema; edema complicated by azotemia, electrolyte or acid-base disorders</td>
<td>Hypokalemia, hypochloremia; metabolic alkalosis; may lead to extracellular fluid depletion; ototoxicity in patients with renal disease; hyperuricemia</td>
</tr>
<tr>
<td>Variable; related to dose</td>
<td>K⁺ secretion slightly increased</td>
<td>H⁺ excretion little affected (some increase in HCO₃⁻ excretion)</td>
<td>RPF and GFR increased</td>
<td>Prerenal azotemia; cerebral edema; poisonings</td>
<td>May produce pulmonary edema in cardiac patients; cellular dehydration; extracellular fluid depletion; hyponatremia if urinary losses are insufficiently replaced</td>
</tr>
</tbody>
</table>

**Figure 9-19 Summary of Therapeutics (continued)**

the general mechanistic and adverse effect characteristics of each class of drug. Consideration of the characteristics of each class may facilitate the choice of diuretic or combination of diuretics.
**Figure 9-20 Urinary Incontinence**

Urinary retention is normally under autonomic or voluntary control. Incontinence (an increased stimulus to void, a decreased ability to prevent voiding, or both) results when these pathways are interrupted or are overactivated or underactivated, or when smooth muscle of the bladder contracts weakly, incoordinate, or inappropriately. Although incontinence is not life threatening, it has significant medical and social consequences. It is often cited as a primary reason for inability of families to care for elders at home.

Drugs for treatment are far from ideal but include those that reduce bladder contraction, such as cholinergic antagonists (eg, oxybutynin, propantheline, tolterodine); those that increase bladder outlet function, such as 3adrenoceptor agonists (eg, phenylpropanolamine, pseudoephedrine); and those for which the mechanism is not fully understood, such as tricyclic antidepressants (possibly related to anticholinergic actions) and estrogens (in postmenopausal women).
Figure 9-21 Urinary Tract Calculi (Kidney Stones)

Urinary calculi are hardened crystals composed of a nucleus (often urate) and surrounding layers of precipitated minerals, such as calcium and magnesium salts, and other components of the urine (including metabolites of drugs excreted in the urine). These stones are usually found in the kidney, but they also occur in the ureter and the bladder (in the latter, the stones are usually passed from the kidney). They occur in all age groups but primarily in persons aged between 20 and 55 years. Treatment (surgical or pharmacologic) depends on the cause, size, and location of the stone. Two common types for which drugs are used are due to hypercalciuria and hyperuricuria. Drugs for hypercalciuria include sodium cellulose phosphate (inhibits calcium reabsorption) and thiazides (mild diuresis stimulates convoluted tubule reabsorption of calcium). Drugs for hyperuricuria include allopurinol (decreases urate formation) and alkali (increases urinary citrate, which inhibits stone formation).
**Figure 9-22 Effect of Renal Insufficiency on Drug Action**

Many drugs and drug metabolites are excreted via the kidneys, so changes (e.g., advanced age, disease) that alter renal function affect the elimination (half-life) of many agents. Blood levels of a drug or its metabolites are greater when decreased renal clearance exists than during normal renal clearance. This change is clinically relevant for drugs eliminated primarily by kidneys and becomes more critical for drugs with a small therapeutic index. Sometimes the effect of renal insufficiency on a drug metabolite (e.g., norepinephrine) is more important than that on the drug itself (e.g., meperidine). Renal function usually declines with age, so elderly patients are often given reduced doses of drugs eliminated mainly via the kidneys. Examples of altered drug action in renal insufficiency are enhanced hyperkalemia with K+-sparing diuretics or NSAIDs; delayed or decreased diuretic effectiveness; and greater risk of NSAID-induced GI bleeding.
**Currently Known Dialyzable Substances**

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Tricyclic secondary amines</th>
<th>Tricyclic tertiary amines</th>
<th>Polymyxin</th>
<th>Quinine</th>
<th>Streptomycin</th>
<th>Sulfonamides</th>
<th>Tetracycline</th>
<th>Vancomycin</th>
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<tr>
<td>Acetophenetidin</td>
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<tr>
<td>Acetylsalicylic acid*</td>
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<td>Dextropropoxyphene</td>
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<td></td>
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<tr>
<td>Methylsalicylate*</td>
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<tr>
<td>Paracetamol</td>
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<td></td>
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<tr>
<td>Ampicillin</td>
<td>Bacitracin</td>
<td>Carbenicillin</td>
<td>Cephalosporins</td>
<td>Chloramphenicol</td>
<td>Cycloserine</td>
<td>Isoniazid</td>
<td>Kanamycin</td>
<td>Neomycin</td>
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<td><em>Antidepressants</em></td>
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<tr>
<td>Amphetamine</td>
<td>Isocarboxazid</td>
<td>Methamphetamine</td>
<td>Monoamine oxidase inhibitors</td>
<td>Pargyline</td>
<td>Phenelzine</td>
<td>Tranzylypromine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyxin</td>
<td>Quinine</td>
<td>Streptomycin</td>
<td>Sulfonamides</td>
<td>Tetracycline</td>
<td>Vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depressants, Sedatives, and Tranquillizers</strong></td>
<td></td>
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<tr>
<td>Chloral hydrate</td>
<td>Diphenhydramine</td>
<td>Diphenhydantoin</td>
<td>Ethchlorvynol*</td>
<td>Ethinamate</td>
<td>Gallamine tiethiodide</td>
<td>Glutethimide*</td>
<td>Heroin</td>
<td>Methobromate</td>
</tr>
</tbody>
</table>

*Kinetics of dialysis thoroughly studied and/or clinical experience extensive.


For complete details and supporting data, the reader is advised to consult the original reference.

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**Figure 9-23 Effect of Hemodialysis on Drug Action**

Hemodialysis is used as maintenance therapy for patients with renal failure and to clear toxic substances from the blood of patients who ingested poisons or overdoses of drugs. The fundamental physiologic principle in dialysis is that of a solute moving across a semipermeable membrane in a direction and at a rate consistent with concentration and osmotic gradients. This principle is the basis for operation of artificial or mechanical kidneys. If a patient receives therapy with a drug that can be dialyzed (ie, pass through the membrane), the amount lost during dialysis must be considered, and supplementary doses may be needed to replace the lost drug.
OVERVIEW

The goal of the drugs discussed in this chapter is total destruction of a disease-causing organism (bacteria, fungus, or virus). Because antimicrobials are by design cytotoxic, the distinguishing feature of each agent is relative selectivity for particular pathogens rather than the host. The greater the selectivity for the pathogen is, the fewer the adverse effects of the drug are. A major concern for this therapeutic class is the emergence of resistance of pathogens to drugs.

Antimicrobials selectively kill or inhibit replication of a pathogen by interfering with a phase of cell physiology that is required by the pathogen. Antibiotics are typically classified and subclassified according to mechanism of action, chemical structure, and spectrum of activity against particular organisms. Narrow-spectrum antibiotics act on a single group or a limited number of groups of organisms, whereas broad-spectrum agents are effective against a wide variety of microbes. Tetracyclines have the broadest antibacterial spectrum of any class of antibiotics. They bind reversibly to the 30S and 50S subunits of the bacterial ribosome, thereby inhibiting protein synthesis. Aminoglycosides and macrolides inhibit bacterial protein synthesis by binding directly and irreversibly to 30S and 50S subunits, respectively, of the bacterial ribosome. β-Lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams, and vancomycin) act by interfering with bacterial wall synthesis, which causes rapid cell lysis. However, β-lactam antibiotics are subject to inactivation by β-lactamase-producing organisms, so many of these agents are used in combination with β-lactamase inhibitors. Carbapenems are the broadest spectrum β-lactam antibiotics. Quinolones are broad-spectrum bactericidal antibiotics that inhibit intracellular DNA topoisomerase II (DNA gyrase) or topoisomerase IV, which are essential for duplication, transcription, and repair of bacterial DNA.

Fungi have more rigid cell walls than bacteria and are resistant to antibiotics. Drugs used to treat systemic fungal infections include amphotericin B, the azole antifungals, caspofungin, and voriconazole. All of these drugs interfere with critical components of the normal physiology of fungi.

Human immunodeficiency virus infection is a particularly difficult viral infection to treat because of the ability of the virus to rapidly mutate to drug-resistant forms. HIV attacks and binds to the CD4 receptor on specific cells of the immune system. Over time, HIV causes host cell lysis and prevents production of new CD4+ cells. Nucleoside reverse transcriptase inhibitors (NRTIs) suppress viral replication by inhibiting the enzyme responsible for conversion of viral RNA into DNA. Protease inhibitors (PIs) inhibit the enzyme required for the proteolysis of viral polypeptide precursors into individual functional proteins—a conversion essential for HIV to be infectious. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) prevent viral replication through noncompetitive inhibition of the reverse transcriptase enzyme. These and other drugs are often used in multidrug cocktails to enhance their effectiveness and minimize resistance.
Figure 10-1 Classification of Antibiotics

The clinical utility of antimicrobials is based on their ability to selectively kill or inhibit replication of invading organisms without causing significant harm to host cells. Designed to interfere with a phase of cell physiology that is unique to the pathogen, antimicrobials essentially make use of inherent structural differences among human, bacterial, viral, and fungal cells. Antibiotics are typically classified according to mechanism of action, chemical structure, and spectrum of activity against particular organisms. Drug classes include cell wall synthesis inhibitors (β-lactam drugs such as penicillins, cephalosporins, carbapenems, monobactams); protein synthesis inhibitors (e.g., tetracyclines, aminoglycosides, macrolides); DNA gyrase inhibitors (fluoroquinolones); RNA polymerase inhibitor (rifampin); and folate synthesis inhibitors (e.g., sulfonamides).
When characterizing the mechanism of action of an antibiotic, it is important to establish whether the agent is bacteriostatic or bactericidal. Bacteriostatic antibiotics arrest microbial growth and replication, which limits the spread of infection while the host’s immune system naturally eliminates the pathogens. If therapy ends before the immune system completely eliminates the organisms, a second cycle of infection may begin. Bactericidal agents kill bacteria, which leads directly to a reduced total number of viable pathogens in the host. Bactericidal agents are preferred for patients with neutropenia because these individuals have compromised immune systems and may not be able to eliminate remaining pathogens. Life-threatening infections such as endocarditis and meningitis should also be treated with bactericidal agents.
| Organisms                      | Penicillin G | Penicillin V | Methicillin | Nafcillin/Oxacillin | Cloxacillin/Oxacillin | Amox/Clav | Ampy/Sub | Ampy/Tazo | Piperacillin | Tazocillin | Ertapenem | Imipenem | Meropenem | Aztreonam | Piperacillin/Tazobactam | Ceftriaxone | Cefotaxime | Cefepime | Ceftepime | Cefpirome | Cefuroxime | Cefazolin | Cefaclor | Cefuroxime | Amoxicillin Monobactam | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxime | Cefuroxine in UTI, not in systemic infection. With permission from Gilbert DN et al., eds. The Sanford Guide to Antimicrobial Therapy. 32nd ed. Hyde Park, VT: Antimicrobial Therapy, Inc. 2002.

**Figure 10.3 Spectrum of Activity**

An antibiotic's spectrum of activity refers to the range of pathogenic organisms affected by that drug. Antibiotics with a narrow spectrum of activity act on a single organism or a few groups of organisms; broad-spectrum agents such as fluoroquinolones are effective against a wide variety of microbes. Extended-spectrum antibiotics such as ampicillin-sulbactam have an intermediate range of activity and target gram-positive organisms and some gram-negative species. Because broad- and extended-spectrum antibiotics eliminate a wide variety of microbial species, these agents can alter the nonpathogenic bacterial flora that normally colonizes the host and result in superinfection by organisms (e.g., Candida, Clostridium difficile) whose growth would otherwise be suppressed.
Bacteria such as Staphylococcus strains are resistant if their growth is not halted by the maximal level of an antibiotic that is tolerated by the host. Organisms develop into more virulent strains through mechanisms such as spontaneous DNA mutations. Main mechanisms of resistance are lower permeability of the antibiotic through the cell wall (eg, ampicillin), presence of antibiotic-inactivating enzymes (eg, β lactamases), and lack of drug-binding sites (eg, penicillin). Various factors contribute to the emergence of resistant strains, one of which is overprescribing of antibiotics in the community setting. Diagnostic uncertainty may be responsible: rapid diagnostic testing is available for only a few infections, so community physicians often distinguish between viral and bacterial infections on the basis of symptoms alone. For an uncertain diagnosis, physicians tend to use antibiotics. Other factors include inappropriate or indiscriminate drug use and patients' not completing courses of treatment.
**Figure 10-5 Examples of Resistance**

Increasing bacterial resistance to antibiotics in the outpatient setting now seems to affect hospitals. Second- or third-generation cephalosporins, with or without a macrolide, are often given to patients who stay in the hospital for multidrug-resistant pneumococcal infections. However, overprescribing of these cephalosporins in communities has left hospitals with few options for patients who are already using these agents and present with such resistant infections. Penicillin-resistant *Streptococcus pneumoniae* strains are increasingly found (now in 20% of all pneumococcal infections), with growing numbers of strains resistant to multiple drug classes, including macrolides and β-lactam antibiotics. Vancomycin is the fallback for therapy in such cases, but the utility of this drug may be limited because other bacteria such as *Enterococcus* and *Staphylococcus aureus* now have resistant strains. *Mycobacterium tuberculosis* strains can now evade many drugs, so this disease has become difficult to treat.
**Figure 10-6  Natural Penicillins: Penicillin G and Penicillin V**

Originally obtained from fermentation of the mold Penicillium chrysogenum, penicillins are the oldest and still the most widely used of all antibiotics. These agents exert bactericidal activity by interfering with the last step of bacterial cell wall synthesis, which causes rapid cell lysis. Therefore, penicillins are ineffective against organisms that lack a cell wall, such as mycobacteria, protozoa, fungi, and viruses. Natural penicillins target gram-positive and gram-negative cocci, gram-positive bacilli, oral anaerobes, and spirochetes. These drugs have been the cornerstone of therapy for a diverse group of infections including pneumococcal pneumonia, syphilis, meningitis, tetanus, and gonorrhea. Penicillin G and penicillin V have similar spectra of activity, with the latter agent being more acid stable and thus better absorbed by the oral route, whereas penicillin G is administered via injection.
Aminopenicillins are similar to natural penicillins in spectrum of activity but are also active against many gram-negative organisms (eg, *Helicobacter pylori*) and against *Listeria*. These drugs are used for septicemia; gynecologic, skin, and soft tissue infections; and urinary, respiratory, and GI tract infections. Because these drugs have become inactivated by β-lactamase–producing bacteria (eg, *Escherichia coli* and *Haemophilus influenzae*), their use has declined. However, the CDC still indicates amoxicillin as the drug of choice for uncomplicated acute otitis media, despite the presence of drug-resistant *S pneumoniae* (DRSP) and *H influenzae*. The CDC urged use of a high-dose regimen to give amoxicillin a better chance to eliminate DRSP for very young patients with recent exposure to antimicrobials. If amoxicillin fails, antibiotics with activity against DRSP (eg, cefuroxime) or β-lactamase–producing strains (ie, amoxicillin-clavulanate) should be tried.
Prevention of Burn Wound Infections, Which Can Be Caused by *P. aeruginosa*

Application of topical chemotherapy twice a day to minimize bacterial proliferation

Daily cleansing of burned area with surgical detergent disinfectant

Schematic section shows bacterial penetration of burn wound.

**Figure 10-8 Antipseudomonal Penicillins: Carbenicillin, Piperacillin, and Ticarcillin**

Antipseudomonal penicillins (carbenicillin, piperacillin, and ticarcillin) display improved activity against gram-negative organisms and are usually used in combination with aminoglycosides in patients with febrile neutropenia and in those with hard to treat nosocomial infections caused by strains of *Enterobacter, Klebsiella, Citrobacter, Serratia, Bacteroides fragilis,* and *Pseudomonas aeruginosa*. The antibacterial effects of all β-lactam antibiotics are synergistic with aminoglycosides because the former inhibit cell wall synthesis, which enhances diffusion of the latter into the bacterium. These drugs should never be placed into the same IV bag because positively charged aminoglycosides can form a precipitate with negatively charged penicillins. Like other penicillins, antipseudomonal agents can be inactivated by β-lactamase and are therefore commonly used together with β-lactamase inhibitors (see Figure 10-9).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible Organisms</th>
<th>Indications</th>
</tr>
</thead>
</table>
Otis media  
Sinusitis  
Skin and skin structure infections |
| Ampicillin-sulbactam        | β Lactamase-producing organisms such as *H influenzae*, *E coli*, and *Klebsiella*, *Acinetobacter*, *Enterobacter*, *S aureus*, *Bacteroides* species (anaerobes) | Gynecologic infections  
Intra-abdominal infections  
Skin and skin structure infections |
Gynecologic infections  
Intra-abdominal infections  
Lower respiratory tract infections  
Sepsis  
Skin and skin structure infections  
Urinary tract infections |
| Piperacillin-tazobactam     | Piperacillin-resistant β lactamase-producing organisms                                  | Appendicitis  
Pelvic inflammatory disease  
Peritonitis  
Pneumonia (community acquired and nosocomial)  
Postpartum endometritis  
Skin and skin structure infections including diabetic foot infections |

**Figure 10-9 β-Lactamase Inhibitors**

The structures of penicillins and other β-lactam antibiotics have in common a β-lactam ring that is essential to stability and antibacterial activity. After years of exposure to β-lactam antibiotics, a large number of bacterial organisms have developed resistance to the drugs by producing β-lactamase, an enzyme that hydrolyzes the β-lactam ring and inactivates the antibiotics. β-Lactamase inhibitors—clavulanate, sulbactam, and tazobactam—were developed to address this problem. With no antibacterial activity of their own, these inhibitors are used only in combination with β-lactam antibiotics, which creates a product that has extended activity against β-lactamase-producing strains.
**Figure 10-10 β-Lactamase–Resistant Penicillins: Cloxacillin, Dicloxacillin, Oxacillin, and Nafcillin**

β-Lactamase-resistant penicillins are semisynthetic penicillins that have the same coverage as natural penicillins but are designed to remain stable in the presence of β-lactamase–producing staphylococcal organisms. Cloxacillin is used for treatment of septic arthritis; dicloxacillin is used for treatment of skin and soft tissue infections; oxacillin is used for treatment of sepsis, toxic shock syndrome, and infections of wounds and vascular catheters; and nafcillin is used for treatment of endocarditis, osteomyelitis, skin and soft tissue infections, and encephalitis. Unfortunately, many strains of *S. aureus* have developed the ability to inactivate meticillin, leading to the increase of meticillin-resistant *S. aureus* (MRSA). This pathogen is considered a serious source of nosocomial infections and produces diseases that are usually treated with vancomycin.
Figure 10-11 Adverse Effects of Penicillins

Although considered the safest of all antibiotics, penicillins can still cause significant adverse effects, with hypersensitivity reactions being most notable. Approximately 5% of patients experience some kind of reaction, which is actually an immune response to the penicillin metabolite penicilloic acid and can range from a maculopapular rash to angioedema and the more significant anaphylaxis. Cross-allergic reactions occur among all β-lactam antibiotics. Other reactions that pertain to specific agents are given in the table.
**Figure 10-12 Cephalosporins**

Chemically and pharmacologically similar to penicillins, cephalosporins inhibit cell wall synthesis and cause rapid cell lysis. These antibiotics are classified into first, second, third, and fourth generations on the basis of spectrum of activity and susceptibility to β-lactamases. Agents in the first generation tend to have excellent gram-positive coverage but minimal gram-negative coverage, whereas agents in the higher generations tend to possess the reverse spectrum of activity. Also like penicillins, all cephalosporins can produce hypersensitivity reactions, ranging from a mild rash and fever to fatal anaphylaxis. Patients who are allergic to penicillins should avoid these agents because of cross-sensitivity of 5% to 15% between the 2 classes. Other adverse effects include GI disturbances and hematologic reactions including positive Coombs test results, thrombocytopenia, transient neutropenia, and reversible leukopenia.

<table>
<thead>
<tr>
<th>Drug Class and Selected Drugs</th>
<th>Coverage</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td>+++/-</td>
<td>Gram positive: β-lactamase-producing <em>S. aureus</em> and <em>Staphylococcus epidermidis</em>, <em>S. pneumoniae</em>, <em>Streptococcus agalactiae</em>, <em>Streptococcus pyogenes</em>; gram negative: <em>Klebsiella pneumoniae</em>, <em>E. coli</em>, <em>P. mirabilis</em>, <em>Shigella</em></td>
</tr>
<tr>
<td>• Cefazolin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cephalaxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefadroxil</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td>+/-</td>
<td><em>M. catarrhalis, H. influenzae, Enterobacter</em>, <em>Citrobacter</em>, <em>Providencia</em>, <em>Acinetobacter</em>, <em>Serratia</em>, <em>Neisseria</em></td>
</tr>
<tr>
<td>• Cefotetan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefoxitin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefprozil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefuroxime</td>
<td>Have weaker gram-positive coverage than first-generation agents, but display activity against more gram-negative pathogens than those agents</td>
<td></td>
</tr>
<tr>
<td>• Cefamandole</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Third generation</strong></td>
<td>-/-</td>
<td>-/-</td>
</tr>
<tr>
<td>• Ceftrime</td>
<td>Have minimal gram-positive coverage compared with agents from the first two generations, but excel in activity against gram-negative organisms, especially ones that produce β-lactamase</td>
<td></td>
</tr>
<tr>
<td>• Cefotaxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefazidime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefoxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Moxalactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefoperazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cefotaxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fourth generation</strong></td>
<td>+++/-</td>
<td>-/-</td>
</tr>
<tr>
<td>• Cefepime</td>
<td>Is effective against broad spectrum of gram-positive and gram-negative organisms</td>
<td></td>
</tr>
</tbody>
</table>
Lung Abscesses

Sagittal section of lung with abscess (cavity in superior segment of lower lobe containing fluid and surrounded by fibrous tissue and pneumatic patches); also pleural thickening over abscess

Multiple lung abscesses following septic embolization

Abscesses

FIGURE 10-13 CARBAPENEMS: IMIPENEM-CILASTATIN, ERTAPENEM, AND MEROPENEM

Carbapenems are the broadest spectrum β-lactam antibiotics. They derive potent activity from resistance to bacterial β-lactamases, affinity for penicillin-binding protein 2, and lack of permeability barrier. They act against aerobic (gram-positive and -negative) and anaerobic bacteria, including *P. aeruginosa*, *B. fragilis*, and *Serratia*, *Enterobacter*, *Acinetobacter*, and *Enterococcus* species. Alone or with an aminoglycoside, they are used for severe mixed infections (pulmonary, intraabdominal, soft tissue) caused by multidrug-resistant bacteria. Meropenem is beneficial in febrile neutropenia, urinary tract infections (UTIs), and meningitis. All drugs can have injection site reactions and should be avoided in penicillin-allergic patients. Imipenem-cilastatin (and ertapenem) can cause abnormal liver function test results, thrombophlebitis, and seizures. Imipenem is used with cilastatin to avoid nephrotoxicity. Meropenem can cause agranulocytosis, neutropenia, Stevens-Johnson syndrome, and angioedema.
Factors in Etiology of Cystitis

In female
- Descending infection via ureter (tuberculosis)
- Invasion from surrounding organs (diverticulitis etc)
- Trauma, surgical or accidental
- May be no apparent etiologic factor: diabetes, cachexia predispose to infection
- Calculus or foreign body
- Neoplasm
- Residual urine
  - Outlet obstruction (prostatic hypertrophy, stricture, cong. valve, etc)
  - Urinary retention (cystocele, diverticulum, neurogenic disorder)
- Ascending urethritis
- Catheter
- Vaginal infection

In male

Aztreonam is a monobactam antibiotic that inhibits bacterial cell wall synthesis and is resistant to most β-lactamases. The agent displays activity only against gram-negative organisms, including *P. aeruginosa, E. coli, Serratia marcescens, Klebsiella pneumoniae, Proteus mirabilis, H. influenzae, and Enterobacter and Citrobacter* species. Aztreonam is used for treatment of septicemia, lower respiratory tract infections (including pneumonia and bronchitis), and urinary tract, skin and skin structure, intraabdominal, and gynecologic infections. For treatment of mixed infections, aztreonam is combined with other antibiotics to ensure coverage of gram-positive and anaerobic bacteria. Adverse effects include frequent increases in liver function test results, nausea, vomiting, rashes, and phlebitis. The drug may be safe for use in patients who are allergic to cephalosporins and penicillins.
**FIGURE 10-15 VANCOMYCIN**

Vancomycin, a glycopeptide, inhibits bacterial cell wall synthesis by binding to cell wall phospholipids and inhibiting polymerase and transpeptidation, which leads to cell wall lysis. Because its site of action is different from that of other β-lactam antibiotics, no cross-resistance occurs. The drug of last resort, vancomycin targets methicillin-resistant staphylococci, *Staphylococcus epidermidis*, *Streptococcus viridans* or *Streptococcus bovis* (alone or with an aminoglycoside), and *Enterococcus faecalis* (with an aminoglycoside). The drug should be used only for serious infections caused by β-lactam-resistant gram-positive bacteria, infections caused by gram-positive bacteria in patients with serious allergy to β-lactam antibiotics, antibiotic-associated pseudomembranous colitis that is unresponsive to metronidazole, enterococcal endocarditis, and as prophylaxis for endocarditis after implantation of prosthetic materials or devices at institutions with a high rate of MRSA-related infection.
After long-standing efficacy against deadly gram-positive pathogens, resistance of *Enterococcus* and *Staphylococcus* species to vancomycin has begun, such as the case of an *S. aureus* isolate from a patient with renal disease that showed intermediate levels of resistance. The patient had undergone long-term peritoneal dialysis and multiple courses of vancomycin for recurring MRSA-associated peritonitis. Patients with renal failure who receive peritoneal dialysis are sometimes given once-weekly vancomycin, which is removed to some extent during each dialysis session. Thus, drug concentrations decrease, and the patient has low drug levels for the latter part of the week. During this time, the organism can mutate and develop resistance. Adverse effects of IV vancomycin include infusion-related events ("red man syndrome"); decreased blood pressure, wheezing, urticaria, pruritus, upper body flushing, pain, muscle spasms), thrombophlebitis, hypersensitivity, fever, neutropenia, ototoxicity, and nephrotoxicity.
Figure 10-17 Tetracyclines

Tetracyclines bind reversibly to the 30S and 50S subunits of the bacterial ribosome and inhibit protein synthesis, with the broadest spectrum of any antibiotic class: they are bacteriostatic for most gram-positive organisms, many gram-negative organisms, and certain anaerobic bacteria. They are drugs of choice for many animal-borne infections (eg, Lyme disease), sexually transmitted diseases (eg, gonorrhea), and other infections (eg, with Mycoplasma pneumoniae). Tetracycline is used for prostatitis, travelers’ diarrhea, acne, Chlamydia infections, and H pylori infections; doxycycline is used for prophylaxis and treatment of multidrug-resistant malaria. The most common adverse effects target the GI tract; more serious effects include pseudotumor cerebri, superinfections, and hepatotoxicity. These agents should be avoided in children, because of effects on teeth, and in renal disease (except doxycycline); they can render oral contraceptives less effective.
Acute Pyelonephritis: Pathology

Surface aspect of kidney: multiple minute abscesses (surface may appear relatively normal in some cases)

Cut section: radiating yellowish-gray streaks in pyramids and abscesses in cortex; moderate hydronephrosis with infection; blunting of calyces (ascending infection)

Acute pyelonephritis with exudate chiefly of polymorphonuclear leukocytes in interstitium and collecting tubules

**FIGURE 10-18 AMINOGLYCOSIDES**

Aminoglycosides are bactericidal agents that bind directly and irreversibly to 30S ribosomal subunits and inhibit bacterial protein synthesis. They target many aerobic gram-negative and some gram-positive organisms but not anaerobes. Monotherapy is limited to infections caused by gram-negative bacilli (e.g., septicemia, intraabdominal infections, serious UTIs). The drugs are usually used with other antibiotics for enhanced diffusion. Once-daily higher dosing allows less frequent drug level monitoring. These drugs tend to cause ototoxicity, which is reversible only if noted early and if the drug is stopped. Increased risk for hearing loss can occur when other ototoxic drugs are given. Nephrotoxicity leads to often reversible tubular necrosis. Neuromuscular blockade, causing skeletal weakness and respiratory distress, often occurs after high doses given by an intraperitoneal or an intrapleural route. Safer drugs (e.g., third-generation cephalosporins, impenem-cilastatin) have somewhat replaced aminoglycosides.
Legionnaires Disease
(Pneumonia Due to Legionnaires Bacillus)

A. Small, blunt, pleomorphic intracellular and extracellular bacilli in lung of patient with Legionnaires disease as shown by Dieterle silver impregnation stain, ×1500 (after Chandler et al.)

B. Chest x-ray film on fifth day of illness of 58-year-old man with serologically confirmed Legionnaires disease. L. lower lobe consolidation the only involvement. Clinical improvement within 2 to 3 days of initiation of treatment with erythromycin. Radiologic changes did not completely disappear for 2 months.

C. Legionnaires bacilli identified by specific fluorescent antibody stain

D. Histologic section of lung (H and E stain) from fatal case of Legionnaires disease; extensive intraalveolar exudate present, containing many large macrophages

**Figure 10-19** **MACROLIDES: ERYTHROMYCIN, AZITHROMYCIN, AND CLARITHROMYCIN**

The bacteriostatic macrolides, which bind to the 50S subunit of the bacterial ribosome and inhibit protein synthesis, are effective for sexually transmitted diseases and community-acquired pneumonia. Erythromycin is active against *Chlamydia*, *Treponema pallidum*, *M. pneumoniae*, *Ureaplasma*, *Corynebacterium diphtheriae*, and *Legionella*; clarithromycin has greater activity against *Chlamydia*, *Legionella*, and *Ureaplasma* plus coverage for *Haemophilus influenzae*. Erythromycin's spectrum of activity parallels that of penicillin, so it is often used if penicillin allergy exists. Azithromycin is less effective than erythromycin for *Streptococcus* and *Staphylococcus* but better for respiratory infections caused by *H. influenza*, *Moraxella catarrhalis*, and *M. pneumoniae*. Azithromycin is preferred for *Mycobacterium avium-intracellulare* complex. The most common adverse effect is epigastric pain. Erythromycin can cause cholestatic jaundice and thrombophlebitis; it should be avoided in hepatic dysfunction.
Although chemically distinct, clindamycin is similar to erythromycin in mechanism of action and spectrum of activity. It is used mainly for infections caused by anaerobic bacteria such as *B. fragilis*, which is responsible for abdominal infections related to trauma. It is also used for aspiration pneumonia and infections caused by streptococci and methicillin-sensitive *S. aureus* in patients who are allergic to penicillin. Its most serious adverse effect is pseudomembranous colitis, a possibly fatal superinfection (**C. difficile** overgrowth in the bowel). This complication, which is more likely to occur with clindamycin than with other antibiotics, may present with watery diarrhea, abdominal pain, fever, and leukocytosis. Symptoms begin 3 to 10 days after starting the drug or soon after stopping it. Oral metronidazole and vancomycin effectively eradicate the superinfection, but the latter is usually used only if the former fails. Other adverse effects include nausea, rash, and impaired liver function.
Figure 10-21 Quinolones

Quinolones (eg, ciprofloxacin), broad-spectrum bactericidal antibiotics that inhibit DNA gyrase or topoisomerase IV (essential for duplication, transcription, and repair of bacterial DNA), target various aerobic gram-positive (eg, methicillin-resistant and β-lactamase-producing Staphylococcus species, S pneumoniae) and gram-negative (eg, H influenzae, M catarrhalis, P aeruginosa, Legionella, Chlamydia) organisms. They are used for resistant respiratory infections; chlamydial infections; UTIs; and infections of the GI tract, joints, bones, skin, and skin structures. The most common adverse effects are nausea, headache, phototoxicity, and dizziness; more serious are CNS effects (psychosis, agitation, tremors), hepatotoxicity, interstitial nephritis, tendonitis or joint rupture, and prolonged QTc interval (and thus arrhythmias). Patients with neurologic disorders (eg, seizure), those taking certain antiarrhythmics, and those with a prolonged QTc interval should avoid quinolones.
Empiric Therapy for Patients With Community-Acquired Pneumonia*

<table>
<thead>
<tr>
<th>Outpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General preferred (not in particular order)</td>
</tr>
<tr>
<td>— Doxycycline</td>
</tr>
<tr>
<td>— A macrolide: erythromycin, azithromycin, clarithromycin</td>
</tr>
<tr>
<td>— A fluoroquinolone: levofloxacin, moxifloxacin, gatifloxacin</td>
</tr>
<tr>
<td>Selection should be influenced by regional antibiotic susceptibility patterns for <em>S. pneumoniae</em> and the presence of other risk factors for drug-resistant <em>S. pneumoniae</em>.</td>
</tr>
<tr>
<td>Penicillin-resistant pneumococci may be resistant to macrolides and/or doxycycline.</td>
</tr>
<tr>
<td>For older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients.</td>
</tr>
<tr>
<td>Hospitalized patients (general medical ward)</td>
</tr>
<tr>
<td>Generally preferred are an extended-spectrum cephalosporin combined with a macrolide or a β-lactam/β-lactamase inhibitor combined with a macrolide, or a fluoroquinolone (alone).</td>
</tr>
<tr>
<td>Extended-spectrum cephalosporins: ceftiraxone, cefotaxime, cefepime</td>
</tr>
<tr>
<td>Macrolides: erythromycin, azithromycin</td>
</tr>
<tr>
<td>β-Lactam/β-lactamase inhibitor combination: piperacillin/tazobactam, ampicillin/subbactam</td>
</tr>
<tr>
<td>Fluoroquinolone: levofloxacin, gatifloxacin, moxifloxacin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalized patients (intensive care unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally preferred are an extended-spectrum cephalosporin or β-lactam/β-lactamase inhibitor plus either fluoroquinolone or macrolide.</td>
</tr>
<tr>
<td>Alternatives or modifying factors</td>
</tr>
<tr>
<td>Structural lung disease: antipseudomonal agents (piperacillin, piperacillin-tazobactam, imipenem or merapenem, or cefepime) plus a fluoroquinolone (including high-dose ciprofloxacin)</td>
</tr>
<tr>
<td>β-Lactam allergy: fluoroquinolone ± clindamycin</td>
</tr>
<tr>
<td>Suspected aspiration: fluoroquinolone with or without clindamycin, metronidazole, or a β-lactam/β-lactamase inhibitor</td>
</tr>
</tbody>
</table>

*Dose may need to be adjusted for weight, or renal or hepatic failure.*


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**Figure 10-22 New-Generation Quinolones**

Compared with older quinolones, the newer drugs (e.g., levofloxacin,sparfloxacin,grepafloxacin,gatifloxacin,moxifloxacin) possess enhanced activity against gram-positive organisms, including *S. pneumoniae* strains that are resistant to other antibiotics. These agents are thus often used to treat multidrug-resistant community-acquired pneumonia. As with all antibiotics, the new drugs are used excessively and inappropriately in the community setting, which leads to bacterial resistance to the antibiotics. Ciprofloxacin
**Figure 10-22 New-Generation Quinolones (continued)**

is a good example of the future for these newer drugs: although this older quinolone was once 95% effective against *P. aeruginosa*, today it affects only 70% of those isolates. Older quinolones were also once active against MRSA, but today, the activity of ciprofloxacin against *S. aureus* is variable. Although new quinolones are quite effective against pneumococci, increased minimal inhibitory concentrations for ofloxacin against *S. pneumoniae* strains have been reported.
### Treatment of Septicemia

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Possible Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient admission</td>
<td>Third-generation cephalosporin (eg, ceftriaxone, cefotaxime) or piperacillin/tazobactam, or imipenem (or meropenem) each with an aminoglycoside</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>Piperacillin/tazobactam or imipenem (or meropenem) each with an aminoglycoside</td>
</tr>
<tr>
<td>Possible MRSA</td>
<td>Add vancomycin</td>
</tr>
<tr>
<td>Hospitalized patient*</td>
<td>Inipenem (or meropenem) or piperacillin/tazobactam (at doses to cover <em>Pseudomonas aeruginosa</em>) plus aminoglycoside; ceftazidime, cefepime, and ciprofloxacin are alternatives; use <strong>quinupristin/dalfopristin</strong> for <em>Enterococcus faecium</em> infection</td>
</tr>
<tr>
<td>Neutropenic patient</td>
<td>Inipenem (or meropenem), cefepime, ceftazidime alone or with an aminoglycoside; piperacillin/tazobactam (at doses to cover <em>Pseudomonas aeruginosa</em>) is an alternative; vancomycin if fevers persist or likelihood of MRSA is high</td>
</tr>
<tr>
<td>Possible tick exposure</td>
<td>Add doxycycline</td>
</tr>
</tbody>
</table>

*Local epidemiology of nosocomial infection and antibiotic resistance patterns should be used to guide therapy.*

---

**Figure 10-23 Quinupristin/Dalfopristin**

Perhaps destined to replace vancomycin as the drug of last resort for certain pathogens, quinupristin/dalfopristin is an injectable streptogramin product in which 2 compounds act synergistically to inactivate bacteria via effects on protein synthesis in the bacterial ribosome: dalfopristin inhibits the early phase of synthesis, and quinupristin inhibits the late phase. This drug is used for life-threatening bloodstream infections caused by vancomycin-resistant *Enterococcus faecium* and skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*. Identifying *Enterococcus* species (faecium and faecalis) by blood culture is critical to avoid misuse of this drug (it is active against only the former). The most common adverse effects are pain at the infusion site, arthralgia, and myalgia. Drug interactions may occur, with agents metabolized by the cytochrome P-450 3A4 system (eg, cyclosporine, nifedipine) and with drugs prolonging the QTc interval.
Another antibiotic for otherwise untreatable infections, linezolid is an oxazolidinone derivative that binds to ribosomal subunits and interferes with bacterial protein synthesis. The drug is intended for treatment of multidrug-resistant gram-positive cocci, particularly as an alternative in infections caused by vancomycin-resistant Enterococcus, multidrug-resistant S. pneumoniae (including vancomycin-ceftriaxone resistant), and MRSA or methicillin-resistant S. epidermidis. The antibiotic is bacteriostatic against Enterococcus and staphylococci and bactericidal against most streptococcal strains. The most common adverse effects are nausea, diarrhea, and headache. Linezolid may cause myelosuppression, which could predispose patients to anemia, leukopenia, pancytopenia, and thrombocytopenia. The drug inhibits monoamine oxidase, so consumption of foods with high tyramine content or concomitant use of adrenergic or serotoninergic drugs should be avoided.
Sulfonamides inhibit synthesis of folic acid and thus synthesis of purines and pyrimidines, so bacteria fail to grow and divide. These bacteriostatic agents are used for trachoma (caused by *Chlamydia*), UTIs caused by *E. coli*, and nocardiosis. Trimethoprim, a dihydrofolate reductase inhibitor, is often used with sulfamethoxazole (as co-trimoxazole) for synergy and a broader spectrum of activity. Co-trimoxazole is used for *Pneumocystis jiroveci* pneumonia (a common opportunistic infection in patients with AIDS), chronic UTIs, GI infections (shigellosis and nontyphoid salmonella), and acute gonococcal urethritis. Adverse effects of sulfonamide include crystalluria (minimized by hydration and alkalinization of urine), hypersensitivity reactions (rash, angioedema, and Stevens-Johnson syndrome), and kernicterus in newborns. Adverse effects of trimethoprim (megaloblastic anemia, leukopenia, granulocytopenia) are related to folate deficiency.
**FIGURE 10-26 NATURE OF FUNGAL INFECTIONS AND THERAPY**

Compared with bacteria, fungi have more rigid cell walls and a cell membrane containing ergosterol, they often cause chronic infections, and they are resistant to all antibiotics. Fungal infections, or mycoses, can be superficial, subcutaneous, or systemic. The occurrence of systemic mycoses—the most difficult to treat and usually life threatening—is increasing because there are more immunocompromised patients, such as those with HIV infection, those with cancer, and those who have undergone organ transplantation. In the hospital, complicated surgical procedures, use of implanted devices, and administration of broad-spectrum antibiotics have dramatically increased the incidence of nosocomial fungal infections. The most notable opportunistic fungal pathogens include *Candida albicans* and non-albicans *Candida*, *Aspergillus*, *Cryptococcus*, and *Zygomycetes* species. Agents used to treat systemic fungal infections include amphotericin B, azole derivatives, caspofungin, and voriconazole.
**Figure 10-27 Amphotericin B**

Amphotericin B, a polyene antifungal agent, binds to ergosterol in fungal plasma membranes, interferes with membrane function, and causes cell death. The drug is active against most species including Cryptococcus neoformans, C. albicans, Sporotrichum, Blastomycetes dermatitidis, Histoplasma capsulatum, Coccioidiodes immitis, and Aspergillus fumigatus. The drug is usually reserved for life-threatening infections (e.g., cryptococcal meningitis, histoplasmosis, disseminated candidiasis, coccidioidomycosis, North American blastomycosis, aspergillosis, sporotrichosis). Drug resistance is rare but does occur. Major adverse effects of amphotericin are the reason for its nickname “ampho-terrible.” A major adverse effect is renal impairment (reduced by previous sodium loading). Other effects are fever and chills, hypotension, anemia, thrombophlebitis, and neurotoxicity. Lipid-based formulations limit exposure of human cells to the drug and are thus less toxic but are costly and not interchangeable.
Aspergillosis

Azole antifungals prevent ergosterol synthesis in fungal cell membranes. Fluconazole is active against C. albicans, many non-albicans Candida species, and C. neoformans but not Candida krusei or Aspergillus species. Itraconazole has excellent anti-Candida activity; is more effective than fluconazole against H. capsulatum, Sporothrix schenckii, and B. dermatitidis; and is fungistatic against Aspergillus. Voriconazole has great activity for Candida species, is fungicidal for Aspergillus, and is active against Fusarium species and Scedosporium apiospermum. Adverse effects include rash, abnormal liver function (fluconazole); peripheral edema, worsened congestive heart failure (itraconazole); hepatotoxicity (ketoconazole); and transient ocular toxicity (voriconazole). Drug interactions can occur: azoles inhibit metabolism of certain drugs (eg, sulfonylureas, warfarin, digoxin, cyclosporine, tacrolimus); azole serum levels are reduced by other drugs (eg, rifampin, isoniazid, carbamazepine).

Flucytosine is a nucleoside analog that disrupts pyrimidine metabolism in the fungal cell nucleus. The agent is fungicidal for Candida species, C. neoformans, and some strains of Aspergillus but not for other commonly encountered fungi. Resistance emerges rapidly during flucytosine monotherapy, so use of this drug is limited to combination therapy (with amphotericin B). Major adverse effects include bone marrow depression, GI toxicity, increased liver function test results, and cutaneous reactions. Caspofungin is a noncompetitive inhibitor of 1,3 beta-D-glucan synthase, an enzyme responsible for formation of an essential cell wall component in many pathogenic fungi and Pneumocystis carinii cysts. Caspofungin has good activity against Aspergillus, Candida, and Histoplasma species. The primary role of this drug is for treatment of refractory invasive aspergillosis and Candida esophagitis. The agent is usually well tolerated; rash or GI toxicity occurs rarely.
Figure 10-29 Nature of Viral Infections

Unlike fungi and bacteria, viruses lack both cell walls and cell membranes. Viruses consist of either double- or single-stranded DNA or RNA encased in a protein coat (capsid) and can reproduce only by invading a host cell and using its machinery. DNA viruses enter a host cell nucleus and are transcribed into mRNA, which is translated into virus-specific proteins. Infected cells usually die. Most RNA viruses do not depend on host cells for replication but on either enzymes in the virion, which can synthesize its own mRNA, or viral RNA acting as its own mRNA. Influenza virus, however, needs active transcription in a host cell nucleus. Despite a growing arsenal of antiviral drugs, viruses are the most elusive and defiant of all pathogens—as evidenced by the common cold. Immunization against viral infections such as measles, mumps, influenza, and chickenpox is the primary therapeutic approach. Two major infections for which antivirals are often used include influenza and herpesvirus infections.
Clinical Features of HSV Encephalitis

Typical features of acute onset of fever, headache, mental status and behavior changes with or without focal signs localizing to temporal lobe (dysphasia and bizarre behavior may localize). Seizure activity is common, often within 1 week of initial symptoms.

MRI demonstrating temporal lobe involvement is a diagnostic cornerstone.

PCR amplification of HSV DNA from cerebrospinal fluid provides major diagnostic information and is very sensitive.

HSV encephalitis CSF cytology and chemical studies typically show:
- WBC: moderate
- RBC: +/-
- Protein: moderate
- Glucose: normal

Reactivation of varicella zoster

Lumbar puncture for analysis of CSF viral DNA, cytology, and chemistries

**Figure 10-30 Herpesviruses**

Human herpesviruses (eg, herpes simplex virus types 1 and 2 [HSV-1 and HSV-2], varicella-zoster virus [VZV], human cytomegalovirus [CMV]) are found worldwide and often infect immunocompetent and immunocompromised patients. HSV-1 causes diseases of the mouth, face, skin, esophagus, or brain; HSV-2 causes diseases of the genitals, rectum, skin, hands, or meninges. HSV infections may be primary or an activation of a latent infection, eg, VZV is a cause of chickenpox first and then herpes zoster (shingles). The main physical finding in shingles is a rash that may be preceded by paresthesias or pain along the involved sensory nerve. Herpes encephalitis, a serious infection, is the most common viral infection of the CNS. It presents with general symptoms (fever, headache, decreased consciousness, lethargy) and may be localized to the brain or also involve mucous and cutaneous membranes. Antiviral agents can reduce morbidity, mortality, and duration of symptoms of most HSV infections.
Lesions of Herpes Simplex

Regional lymphadenopathy, common in genital herpes

Marked edema and vesicle formation in primary herpes

Autoinoculation lesions

Ulcerative lesions of genitalia

**Figure 10-31 Acyclovir and Famciclovir**

Acyclovir, an analog of guanosine, is activated by monophosphorylation via viral thymidine kinase and then is phosphorylated via host cell enzymes to a triphosphate form that is a substrate for viral rather than cellular DNA polymerase. It binds to HSV DNA polymerase, is incorporated into viral DNA, and prevents chain elongation. This selective affinity leads to more drug in virus-infected versus healthy cells. Acyclovir is used for initial or recurrent HSV, herpes zoster, and VZV infections. The drug is also used in prophylaxis of HSV and CMV infections in immunocompromised patients but is slightly effective for CMV disease (CMV does not produce thymidine kinase and is thus resistant). Adverse effects depend on route of administration: topical use may cause contact dermatitis, oral use can cause GI effects, and rapid IV infusion may cause renal dysfunction in predisposed patients. Famciclovir is similar to acyclovir but has better bioavailability, which allows for less frequent dosing.
**Cytomegalovirus Pneumonia**

**Figure 10-32 Ganciclovir**

Ganciclovir is similar to acyclovir but somewhat distinct. CMV does not produce thymidine kinase, so ganciclovir is the drug of choice in infections caused by CMV, because enzymes other than thymidine kinase in CMV-infected cells facilitate phosphorylation of the drug. Ganciclovir is used for serious CMV infections, especially retinitis, in immunocompromised patients or patients at risk for CMV disease; it prevents CMV disease in solid organ transplant recipients and HIV-infected patients. The most common adverse effect with IV and oral ganciclovir is bone marrow suppression (anemia, leukopenia, neutropenia, thrombocytopenia). Common adverse effects of intravitreal ganciclovir implants include vitreous hemorrhage and retinal detachments. Valganciclovir is similar to ganciclovir but has better bioavailability, which allows for less frequent dosing.
Influenza Virus and Its Epidemiology

Electron microscopic appearance of influenza $A_2$ virus; filaments and spherical forms ($\times 10,000$)

Virus viewed in section at much higher magnification ($\times 300,000$)

Influenza virus invasion of chorionicallantoic membrane cell of chick embryo. A. Attachment to cell membrane. B. Fusion of viral envelope with cell membrane. C. Penetration into cell cytoplasm.

Diagram of influenza virus budding from plasma membrane of infected cell

Hemagglutinin spikes
Neuraminidase spike
Double lipid layer of virus capsule
Protein layer

RNA
Polypeptides
Cell membrane
Cell cytoplasm

Figure 10-33 Influenza and Its Treatment

Influenza, an acute infection, is transmitted by inhalation. Epidemics are usually caused by type A virus; sporadic infections are usually caused by type B. Influenza and the common cold are similar, but the former usually produces more systemic symptoms (eg, high fever, headache, myalgia). Persons at high risk for influenza are the elderly, patients with chronic respiratory and cardiovascular diseases, and health care workers and others who come into contact with high-risk patients. Immunization is preferred to antivirals, which must be given early (within 48 hours). Antiviral drugs do have specific uses, eg, in vaccine-allergic patients and in outbreaks with variants not covered by a vaccine. Amantadine and rimantadine are anti-RNA drugs used for type A virus that block viral penetration of host respiratory epithelial cells; they also block viral uncoating after host cell penetration. Zanamivir (inhaled) and oseltamivir (oral) inhibit viral neuraminidase and are used for type A or B infections.
Acquired through sexual intercourse and exchange of blood, breast milk, and placenta, HIV attacks and binds to the CD4 receptor on CD4+ cells, T helper cells, and T cells. After HIV fuses with the cell, it releases RNA and enzymes needed for replication within the host cell. The single-stranded RNA is transcribed by reverse transcriptase to double-stranded DNA, which is incorporated into the genetic material of host cells via the integrase enzyme. HIV then uses the machinery of the infected cells to produce viral particles that break away from host cells, are cleaved by protease, and can infect other host cells by the same process. Over time, HIV causes host cell lysis and prevents production of new CD4+ cells. AIDS and opportunistic infections arise with decreasing CD4+ cells counts and an increasing viral load. Advances in drug therapy have changed the diagnosis of HIV infection from a death sentence to a life with chronic disease.
The first agents developed for HIV, NRTIs suppress viral replication by inhibiting nucleoside reverse transcriptase (converts viral RNA into DNA); non-NRTIs (NNRTIs) also inhibit this enzyme. NRTIs are used with PIs, NNRTIs, or both to treat HIV. NRTIs are also used to prevent maternal-fetal HIV transmission and infection after occupational exposure (eg, needlesticks). Adverse effects are drug specific, eg, zidovudine causes bone marrow suppression and myopathy; didanosine, zalcitabine, and stavudine cause peripheral neuropathy and pancreatitis; lamivudine and abacavir cause fatal hypersensitivity. All NRTIs can cause GI upset and possibly fatal lactic acidosis. NNRTIs can replace a PI in 3-drug regimens that would use 2 NRTIs and a PI. NNRTI adverse effects include rash (eg, Stevens-Johnson syndrome), hepatotoxicity, and CNS effects. All PIs and NNRTIs (not NRTIs) are metabolized by cytochrome P-450 in the liver, and drug interactions may occur with PIs and NNRTIs but are less likely with NRTIs.
Protease inhibitors inhibit HIV protease, an enzyme needed for proteolysis of viral polyprotein precursors into functional proteins (required for HIV to be infectious). Inhibition leads to formation of noninfectious viral particles. PIs are used with other antiretrovirals to treat HIV; for postexposure prophylaxis, PIs are used with the NRTIs zidovudine and lamivudine. Major adverse effects of PIs include hyperlipidemia; glucose intolerance, insulin resistance, and diabetes; and adipose redistribution syndrome (lipodystrophy, dorsocervical fat pad [buffalo hump], increased abdominal fat, peripheral lipoatrophy). In addition, ritonavir can cause oral paresthesias and GI upset; indinavir can cause kidney stones and hyperbilirubinemia; nelfinavir can cause diarrhea; and amprenavir can cause rash, GI upset, and oral paresthesias. Atazanavir is an azapeptide that can be given once daily and has fewer lipid side effects than other PIs. Its main adverse effect is indirect hyperbilirubinemia with or without jaundice or scleral icterus.
**Figure 10-37 Other Antiretroviral Agents for AIDS: Tenofovir and Enfuvirtide**

*Tenofovir* is a nucleotide analog that, like NRTIs, inhibits nucleoside reverse transcriptase and suppresses DNA viral replication. Unlike NRTIs, it does not require intracellular phosphorylation to an active form; it acts rapidly and is a potent inhibitor of the enzyme. It is active against most NRTI-resistant HIV strains and is reserved for treatment-experienced patients. GI-related adverse effects are common; renal failure and Fanconi syndrome are the more serious effects. *Enfuvirtide*, a peptide that prevents viral fusion with CD4+ cell membranes, is used for HIV infection in treated patients who have HIV replication despite antiviral therapy. The most common adverse effects are injection-site reactions and (in clinical trials) bacterial pneumonia. Because of high cost, complicated dosing, and adverse effects, enfuvirtide is reserved for highly motivated patients who have failed previous regimens and have few options. Both drugs are used in combination with other antivirals.
CHAPTER 11

DRUGS USED IN NEOPLASTIC DISORDERS

OVERVIEW

The original goal of chemotherapy was not quite as virtuous as that of today, since the first antineoplastic agents (nitrogen mustards) were created to be chemical warfare poisons in World War I. Decades after researchers observed myelosuppressive effects of mustard gas, the goals continue to evolve. At first, the aim was to slow tumor growth; whereas investigators now focus on quality of life, remission, and, sometimes, even cure. Most agents, especially older ones, do not discriminate between normal and abnormal cells and thus affect all proliferating cells, including those found in bone marrow, buccal and GI mucosa, and hair follicles. Most such drugs therefore cause nausea, vomiting, stomatitis, alopecia, and myelosuppression. Newer agents are designed to act more selectively and target components and processes that are unique to cancerous cells, which allows for both safer and more effective treatments.

The pharmacologic principles of chemotherapy are based on the biology of cells, specifically cell division. Antineoplastic agents cause cytotoxicity by targeting events, such as DNA synthesis, that occur during phases of the cell cycle—G₀, G₁, S, G₂, and M. These agents are classified according to these effects on the cell cycle or by other characteristics of their mechanism of action.

Antimetabolites (folate, purine, adenosine, and pyrimidine analogs, and substituted ureas), which are structurally similar to naturally occurring metabolites required for DNA and RNA synthesis, exert their effects either by competing with or by substituting for normal metabolites. Antimetabolites are cell cycle specific; they act during the S phase and are most effective against rapidly growing tumors.

Alkylating agents (eg, nitrogen mustards, nitrosoureas, and platinum compounds) bind to nucleophilic groups on cell constituents, which causes alkylation of DNA, RNA, and proteins. This class is most effective against rapidly dividing cells and is not cell cycle specific.

Popularly known as spindle poisons, microtubule inhibitors are plant-derived substances that are cytotoxic because they interfere with the mitotic spindle. The spindle consists of chromatin and microtubules, which are responsible for the metaphase of mitosis. This class includes vinca alkaloids, taxanes, and estramustine.

Steroid hormones affect development of 4 major types of cancer—breast, endometrial, ovarian, and prostate. Breast cancer is classified and treated according to the reactivity of the tumor to estrogen, the main hormone involved in the tumor's growth. Hormone-positive tumors are treated with estrogen antagonists and aromatase inhibitors. A primary treatment method for prostate cancer involves medical androgen ablation via gonadotropin-releasing hormone (GnRH) analogs (with effects on luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) or surgical ablation. Antiandrogens, also used for prostate cancer, block the actions of androgens, whether testicular or adrenal in origin, by interacting with cytosolic androgen receptor sites in all target tissues, including the prostate, hypothalamus, and pituitary.

The aim of antibody-based therapy is to target tumor cells selectively while bypassing healthy cells, thus optimizing efficacy while minimizing toxicity. Monoclonal antibodies are synthetic proteins that can attract immune cells to a tumor or deliver a cytotoxic to a tumor without activating the immune system. Unconjugated antibodies can be used to trigger immune system activation against malignant cells, promote programmed cell death (apoptosis), or interfere with growth factor signals to cancer cells. Conjugated antibodies are attached to radioactive particles or immunotoxins and serve as "guided missiles," delivering their cytotoxic attachments directly to tumors.
To replicate, both normal and cancer cells proceed through the cell cycle, which is divided into $G_0$, $G_1$, $S$, $G_2$, and $M$ (mitosis) phases. In the postmitotic $G_1$ phase, cells produce many enzymes required for DNA synthesis. In the $G_2$ phase, cells are resting but are still viable and can enter cell division. During $S$ phase, DNA content doubles in preparation for cell division. In premitotic $G_2$ phase, additional protein and RNA synthesis occurs. Antineoplastic agents cause cytotoxicity by affecting events occurring during these phases. Drugs that destroy cells only during a certain phase are cell cycle specific; cell cycle-nonspecific agents destroy cells independently of the phases. Chemotherapy is most effective against replicating tumor cells. Cell cycle-nonspecific agents, however, can be useful against tumors with few replicating cells. Chemotherapy is given intravenously, orally, intramuscularly, or subcutaneously or as a bolus injection, a short infusion, or a continuous infusion.
Aside from a few hematologic malignancies, most tumors show only a partial, fleeting response to monotherapy. Combination chemotherapy provides higher and more durable response rates by displaying efficacy against a broader range of cell lines in heterogeneous tumors, preventing or slowing development of resistance, and providing maximal cell kill (a measure of the number of tumor cells killed by drugs in relation to dose). Combination chemotherapy has thus become the standard for most malignancies. Selection of agents for regimens is based on the following principles: Only agents with demonstrated activity as monotherapy against the specific type of tumor should be selected. All agents within the regimen should have different mechanisms of action (which often has additive or synergistic effects). To minimize unacceptable toxicity, agents should not have overlapping adverse effects. To optimize efficacy and minimize resistance, the optimal dose and schedule of the drugs should be used.
In autologous transplantation the patient is the source of the stem cells (the patient is the donor and the host at the same time). When the stem cells come from another person who is a histocompatible donor, this is called *allogeneic transplantation*.

**Figure 11-3 Adverse Effects of Chemotherapy**

Most agents, especially older ones, do not discriminate between normal and abnormal cells and thus affect all proliferating cells, including those found in bone marrow, buccal and GI mucosa, and hair follicles. This nonselective feature helps to explain toxicities associated with these drugs. To some extent, most such agents cause nausea, vomiting, stomatitis, alopecia, and myelosuppression. Although most adverse effects are transient, certain ones (cardiac, pulmonary, and bladder toxicity) can be irreversible. Adverse effects can be minimized via supportive care therapy such as antiemetics for nausea and vomiting, erythropoietic agents and hematopoietic colony-stimulating factors for anemia and neutropenia, antihistamines and corticosteroids for hypersensitivity reactions, and chemoprotective agents such as mesna and amifostine for organ toxicity. A more intense measure involves harvesting bone marrow from a patient before myelosuppressive therapy and then reimplanting it after treatment.
**Figure 11-4 Folate Analogs: Methotrexate**

One of the oldest and most studied antineoplastic drugs, methotrexate (MTX) is structurally related to folic acid and is its antagonist: it inhibits dihydrofolate reductase (converts folic acid to the active tetrahydrofolate acid). Cells’ inability to use folate leads to reduced synthesis of thymidine and other building blocks (e.g., DNA, RNA, proteins) essential to cell function. Cell death results. MTX is used for different cancers—e.g., colorectal carcinoma, hematologic cancers (leukemias, lymphomas), and breast, lung, head, neck, and ovarian cancers. Common toxicities depend on dose: myelosuppression, erythema, stomatitis, alopecia, nausea, vomiting, diarrhea. More serious effects are hepatotoxicity, renal failure, and neurologic toxicity. Folic acid has no effect on MTX toxicity; leucovorin bypasses MTX-blocked dihydrofolate reductase, replenishes folate stores, and can prevent life-threatening neutropenia and mucositis, but it cannot protect against MTX-induced organ damage.
Figure 11-5 Purine Analogs: Mercaptopurine and Thioguanine

An analog of hypoxanthine and guanine, mercaptopurine (6-MP) is a prodrug that is converted in cells to active nucleotide metabolites. Thioguanine acid is one such metabolite, which interferes with metabolic reactions needed for RNA and DNA biosynthesis. This metabolite also causes inhibition of the first step in purine biosynthesis or converts to another ribonucleotide that can cause feedback inhibition. 6-MP is primarily used to treat acute lymphatic (lymphocytic, lymphoblastic) leukemia. Adverse effects include dose-related bone marrow suppression, diarrhea, hyperpigmentation, hyperuricemia, and hepatotoxicity (when used with doxorubicin and at certain doses). The toxicity of oral 6-MP is increased when given with allopurinol. Thioguanine (6-TG) is also a purine analogue that is structurally and functionally related to 6-MP. Both agents share similar uses and toxicities. Unlike 6-MP, however, 6-TG is not potentiated by allopurinol.
Metastases from pancreas
Most common sites:
1. Regional nodes
2. Liver
3. Lung and pleura
4. Intestine
5. Peritoneum

Moderately common sites:
6. Adrenal
7. Bone
8. Diaphragm
9. Gallbladder
10. Kidney

Occasional sites:
11. Heart
12. Mediastinum
13. Bladder
14. Ovary
15. Supraclavicular nodes
16. Muscle or subcutaneous tissue

Figure 11-6 Pyrimidine Analogs: 5-Fluorouracil
5-Fluorouracil (5-FU) is an inactive prodrug that, when converted to its active metabolite, inhibits methylation of deoxyuridyllic acid to thymidyllic acid, which leads to a lack of thymidine, a nucleoside of DNA. 5-FU also inhibits RNA formation by incorporating itself into the nucleic acid chain. The agent is used to treat solid tumors of the colon, rectum, breast, stomach, and pancreas. 5-FU is poorly absorbed orally and can cause severe GI toxicity, so it is given intravenously, intrahepatically, or topically. Blood dyscrasias, especially leukopenia, are the most common adverse effects; others are stomatitis and diarrhea, which can be severe in certain patients; hand-foot syndrome (painful, erythematous, swollen palms and soles); and cardiac toxicities (chest pain and tightness, dyspnea, cardiogenic shock). Alopecia is uncommon, and nausea and vomiting are usually mild.
Clinical Signs of Breast Cancer

Dimpling of skin over a carcinoma is caused by involvement
and retraction of Cooper ligaments. Pectoralis contraction
may enhance dimpling if fascia is involved.

Figure 11-7 Pyrimidine Analogs: Capecitabine

An oral, tumor-activated antineoplastic, capecitabine is a fluoropyrimidine carbamate that undergoes enzymatic conversion to inactive intermediates. When it reaches the tumor, it is converted to active 5-FU by thymidine phosphorylase, an enzyme that is found at high levels in tumors and low levels in normal tissues. This drug, together with docetaxel, is used for patients with metastatic breast cancer and failure to respond to previous anthracycline-containing therapy. It is also indicated as first-line therapy for metastatic colorectal carcinoma. This drug has selective tumor activation, so common drug-related adverse effects (eg, alopecia, bone marrow suppression) are minimized. Its most common side effects include diarrhea, nausea, vomiting, fatigue, stomatitis, and hand-foot syndrome. Potentially serious risks associated with the drug include severe diarrhea, grade 3 or 4 neutropenia, thrombocytopenia, and reduced hemoglobin levels.
**Clinical Presentation of Leukemias**

Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL).

**Peripheral blood examination:**

AML: High WBC counts, predominating blasts. Neutropenia or thrombocytopenia.

ALL: Pancreatopenia, WBC count may be elevated or low. Monoclonality is indicative of acute leukemia (specific T- and B-cell surface markers identify the subset of leukemia).

CML: High WBC count with mature neutrophils with early occasional myeloid forms and an occasional blast. Low leukocyte alkaline phosphatase score. Elevated platelet count, with dysmorphism and large size. Elevation of basophil count and blasts is seen in accelerated phase of this disorder.

CLL: Elevated WBC count. Mature lymphocytes with "smudged" or broken cells are prevalent.

Hepatomegaly (CML)

**Bone marrow examination:**

AML: Hypercellularity with blast count greater than 30%.

ALL: Monoclonality is indicative of acute leukemia (specific T- and B-cell surface markers identify the subset of leukemia). Presence of Philadelphia chromosome (Ph) in a subset of ALL confers a poor prognosis.

CML: Presence of Ph. More than 30% blasts count characterizes blast crisis.

CLL: Diffuse infiltration with mature lymphocytes.

Signs of bleeding, petechiae, purpura (AML, ALL)

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**Pyrimidine analogs**

Cytarabine and Fludarabine

Incorporated into DNA; inhibits chain elongation

**Pyrimidines**

Cytidine, Thymidine, Uridine

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**Figure 11-8 Pyrimidine Analogs: Cytarabine and Fludarabine**

Cytarabine is a pyrimidine antagonist that inhibits conversion of cytidine to deoxycytidine, which interferes with DNA synthesis. It may also be incorporated into DNA and stop chain elongation. The drug is useful for hematologic malignancies—chronic myelocytic leukemia, lymphoblastic leukemia, acute lymphocytic and nonlymphocytic leukemias, meningeal leukemia. Cytarabine is synergistic with other drugs, including alkylating agents, thiopurines, and anthracycline antibiotics. Although fludarabine is a purine analog, its pharmacologic action is similar to that of cytarabine. It is effective for chronic lymphocytic leukemia, NHL, and acute leukemia. The major toxic effect of both drugs is myelosuppression, which often leads to neutropenia. Other side effects with cytarabine include neuropathies, alopecia, GI distress, hepatic toxicity, hypersensitivity, and corneal toxicity; those of fludarabine include severe neurotoxicity, GI effects, stomatitis, rash, and somnolence.
Figure 11-9 Pyrimidine Analogs: Gemcitabine

Gemcitabine is structurally and pharmacologically similar to cytarabine. The major distinctions between the two are the longer half-life and higher tissue concentration of gemcitabine. Gemcitabine was specifically developed to extend the activity of cytarabine to nonhematologic malignancies including pancreatic cancer, non-small cell lung cancer, advanced breast cancer, ovarian cancer, and cervical cancer. This drug also has activity as second-line therapy in Kaposi sarcoma. Common adverse effects include myelosuppression (dose limiting), flu-like symptoms (occasionally dose limiting), fatigue, fever, peripheral edema, proteinuria, cutaneous reactions (radio-sensitizing effects), and GI effects. The drug may also cause adult respiratory distress syndrome and cardiac dysfunction (myocardial infarction, CHF, atrial fibrillation).
Hydroxyurea blocks conversion of DNA bases by blocking ribo-
ucleotide reductase; it does not affect RNA or cell proteins. 
Hydroxyurea causes cells to arrest at the G1-S interface, which 
is a period of maximal sensitivity to radiation, so concomitant 
hydroxyurea and radiation therapy causes synergistic toxicity. 
Hydroxyurea is used to treat neoplasms including melanoma, 
chronic myelocytic leukemia, and inoperable ovarian cancer. 
The agent is given orally to patients with chronic myelogenous 
leukemia who are in blast crisis (advanced disease in which the 
number of immature, abnormal leukocytes in bone marrow and 
blood is quite high). Hydroxyurea is also used as adjunctive ther-
apy to radiation for epidermoid carcinomas of the head and neck. 
Bone marrow suppression (leukopenia) is the most common 
adverse effect. Nausea, vomiting, diarrhea, constipation, and 
mucositis may also occur. Severe and sometimes fatal hepatitis and 
secondary leukemias have also been associated with this drug.
Mechlorethamine evolved from its first use as a chemical weapon to medicine, specifically for Hodgkin disease, mycosis fungoides, and malignant pleural effusions. This alkylating agent releases Cl⁻ to form a highly reactive ethylene-immonium ion. In tissues, the ionic form alkylates the nitrogen atom of a guanine residue in DNA, which causes DNA strand cross-linking and then DNA mutation or breakage or both. Proliferating cells, especially cells in G₁ and S phases, are most sensitive to the drug. Use of this agent is limited by its vesicantlike toxicities, which include nausea, vomiting, skin eruptions, ototoxicity, neurotoxicity, and severe myelosuppression. Melphalan is pharmacologically similar to mechlorethamine but is mainly used for palliation of multiple myeloma and nonresectable epithelial ovarian cancer. Leukopenia and thrombocytopenia are major adverse effects; others include pulmonary infiltrates and fibrosis, nausea and vomiting, amenorrhea, alopecia, sterility, and mucositis.
Both cyclophosphamide and ifosfamide are pharmacologically related to nitrogen mustards. These drugs are biotransformed by the cytochrome P-450 system to active mustard metabolites, which act as alkylating agents and form cross-links in the DNA. The first drug is used for a wide variety of cancers—colorectal and cervical cancers, Wilms tumor, pulmonary adenocarcinoma, breast and ovarian carcinoma, leukemias, lymphomas, neuroblastoma, retinoblastoma, bladder carcinoma, and soft tissue sarcomas.

Ifosfamide is used in refractory testicular cancer, soft tissue sarcomas, lymphomas, and cancers of the head and neck, breast, lung, cervix, and ovaries. Although ifosfamide has fewer effects, both drugs have similar toxicities, including alopecia, nausea and vomiting, diarrhea, myelosuppression, and hemorrhagic cystitis (can lead to bladder fibrosis). The last can be prevented by hydration and use of mesna, which inactivates toxic metabolites. Ifosfamide can also cause neurotoxicity.
Large, hemispheric glioblastoma multiforme with central areas of necrosis; brain distorted to opposite side.

Biopsy specimens

Nitrosoureas

Carmustine and lomustine are both nitrosoureas that are cytotoxic via alkylation of DNA and RNA and inhibition of protein synthesis. Both drugs are highly lipid soluble and can therefore enter CSF. As a result, the agents are useful for treatment of brain tumors. Carmustine wafer implants are used as an adjunct to surgery and radiation in patients with newly diagnosed high-grade gliomas and as an adjunct to surgery for patients with recurrent glioblastoma multiforme to prolong survival. Major adverse effects include myelosuppression (delayed with carmustine), pulmonary fibrosis, nausea and vomiting (severe with carmustine), and renal toxicity. Seizures and brain edema are the most common adverse effects associated with carmustine wafer implants. One major difference between the 2 agents is the administration route: carmustine is given intravenously, and lomustine is given orally.
Platinum compounds act as alkylating agents and form covalent bonds with the nitrogen atom of guanine to disrupt DNA, RNA, and protein synthesis. Cisplatin is used for solid tumors—lung, ovarian, head and neck, testicular, and cervical. Adverse effects include neurotoxicity, ototoxicity, GI effects, and nephrotoxicity. Carboplatin, a cisplatin analog with similar activity, is less emetogenic and less nephrotoxic and is used for patients with renal dysfunction. Oxaliplatin, the newest platinum agent, is similar to the other drugs but has a distinct use: combination with 5-FU for metastatic colon or rectal carcinoma after failed therapy with 5-FU and irinotecan. Oxaliplatin causes sensory peripheral neuropathy, neutropenia, GI effects, thromboembolism, and febrile neutropenia. Temozolomide, an imidazotetrazine (a new drug class), forms cytotoxic DNA cross-links. It is used for refractory anaplastic astrocytoma. Myelosuppression, GI distress, fatigue, constipation, and headache are adverse effects of temozolomide.
FIGURE 11-15 VINCA ALKALOIDS: VINCristine, VinBLASTINE, AND VINorelbINE

These agents, derived from the periwinkle *Vinc* rosea, are cell cycle specific (inhibit mitosis). They bind to tubulin and prevent formation of microtubules (essential part of the mitotic spindle); chromosomes do not segregate correctly, and cell death ensues. CNS functions are also affected, which may account for neurotoxic effects. Vincristine is used for pediatric and adult acute leukemia, Hodgkin disease, lymphomas, multiple myeloma, neuroblastoma, Wilms tumor, and Kaposi sarcoma. Vinblastine, similar to vincristine, is also used for testicular cancer and renal cell carcinoma. Vinorelbine is mainly used for unresectable, advanced non–small cell lung cancer and breast cancer. All drugs may cause leukopenia, thrombocytopenia, acute uric acid nephropathy, ischemic cardiac toxicity, neurotoxicity, and cellulitis. The dose-limiting toxicities of vincristine include paresthesias, loss of tendon reflexes, neuritic pain, and muscle weakness; the dose-limiting toxicity of vinorelbine is granulocytopenia.
The taxanes docetaxel and paclitaxel both derive their activity from plants. The taxanes bind to tubulin but do not promote microtubule disassembly. Rather, they promote the assembly of microtubules from tubulin dimers and stabilize them by preventing depolymerization. The microtubules formed in the presence of taxanes are dysfunctional because they are too stable; cell death ultimately occurs. Both taxanes are used to treat ovarian cancer, breast cancer, non-small cell lung cancer, head and neck cancer, and AIDS-related Kaposi sarcoma. The drugs cause significant myelosuppression, with neutropenia being the major dose-limiting toxicity. Another important adverse effect is hypersensitivity reaction, which requires premedication with an $H_2$ blocker, corticosteroid, and diphenhydramine. Other effects include mucositis, alopecia, peripheral neuropathy, relatively mild nausea, and arrhythmias.
**Figure 11-17 Anthracyclines: Doxorubicin and Daunorubicin**

Isolated from a Streptomyces species, anthracyclines are cell cycle–specific antibiotics that bind tightly to DNA by intercalation and cause uncoiling of the double helix, which leads to strand breaks and prevents DNA and RNA synthesis. Another mechanism, which may produce cardiac toxicity, involves conversion of the drugs to toxic oxygen free radicals, to which cardiac tissue and tumors are vulnerable. Doxorubicin, one of the most widely used antineoplastics, has efficacy in various cancers (eg, carcinomas of the breast, prostate, thyroid, and lung; hepatoma; neuroblastoma; Wilms tumor). Daunorubicin is part of many initial remission induction regimens for leukemia (adult and pediatric acute lymphocytic and adult nonlymphocytic). A dose-limiting toxicity of both drugs is irreversible cardiotoxicity, which may be minimized by avoiding use with preexisting cardiac conditions, using dexrazoxane (a cardioprotectant), or using liposomal doxorubicin.
**Figure 11-18 Estrogen Antagonists: Tamoxifen and Toremifene**

The influence of estrogen in breast cancer is so critical that therapy now depends on whether a tumor is hormone dependent or independent. In the former, tumor cells have estrogen (ER) and progesterone receptors (are positive) and need these hormones for growth. In the latter, cells lack these receptors (are negative). Hormone-positive tumors are treated with estrogen antagonists such as tamoxifen, which has dual activity on ERs: antagonistic (inhibits cell proliferation, reduces tumors) and partial agonist effects (prevents bone demineralization in postmenopausal women). Tamoxifen increases risk of endometrial carcinoma and can cause hot flashes, deep vein thrombosis, pulmonary embolism, and retinal toxicity. Antiestrogens are avoided for ER-negative cancer, which does not respond to these drugs. Low-dose toremifene has similar effects (depletes ERs and is cytostatic for tumor growth), but higher doses produce more antitumor activity; therefore, it is used as second-line therapy after tamoxifen.
**Figure 11-19 Aromatase Inhibitors: Anastrozole, Letrozole, and Exemestane**

Aromatase inhibitors provide a more permanent cutoff of estrogen to cancer cells; they selectively and irreversibly bind to and inactivate aromatase, the main enzyme converting androgens to estrogens. These inhibitors have no partial agonist activity. Adrenal insufficiency caused by aminoglutethimide, the first drug developed, limited its use; the newer anastrozole, letrozole, and exemestane are better tolerated (no effects on corticosteroid or aldosterone biosynthesis). These drugs were first used as second-line therapy, but letrozole and anastrozole are now thought at least as good as, if not superior to, tamoxifen as first-line therapy for advanced breast cancer (and for adjuvant therapy). Adverse effects include hot flashes, musculoskeletal pain, and headache. In contrast to data for tamoxifen, no increased risk of uterine carcinoma or venous thromboembolism exists for the aromatase inhibitors. Premenopausal women with breast cancer and normal ovarian function should avoid aromatase inhibitors.
Androgen Deprivation in Metastatic Disease

Androgen receptor

Orchietomy removes primary androgen source.

Tumor growth

GnRH

LH

Testosterone

GnRH-analogs

5α-reductase

mRNA

5-DHT

dihydrotestosterone

DHT-receptor complex

Androgen-dependent tumor cell

Blockade of specific receptors in hypothalamic-pituitary-testicular axis and at cellular level can produce androgen deprivation of androgen-dependent prostate tumor cells.

"Escape" phenomenon in metastatic disease

Regression

Androgen deprivation destroys androgen-dependent cell lines.

Heterogeneous tumor

Homogeneous tumor

Death of androgen-dependent cell lines

Tumor contains heterogeneous population of androgen-dependent and androgen-independent cell lines. Androgen-deprivation therapy has no direct influence on androgen-independent cell lines.

Progression

Androgen deprivation does not retard growth of androgen-independent cell lines.

Decrease in size and number of lesions

Increase in size and number of lesions

Androgens stimulate prostate cancer cell growth, so main therapies involve medical (GnRH analogs) or surgical (orchietomy) androgen ablation. Leuprolide and goserelin have paradoxical effects on the pituitary: an initial release of LH and FSH and then down-regulation of GnRH receptors because of repeated dosing (negative feedback). This inhibition leads to reduced testicular steroidogenesis and lower serum testosterone levels. Both drugs are effective for palliation of advanced prostatic carcinoma and may be used in combination with flutamide or instead of diethylstilbestrol and orchietomy for initial treatment. GnRH may first cause a tumor flare (symptoms and pain) because of initial gonadotropin stimulation. Other adverse effects are hot flashes, blurred vision, injection site pain, and breast swelling. Leuprolide may be given as a depot intramuscular injection or as an implant that releases drug via osmotic-regulated technology. Goserelin is given as a pellet, injected under the skin.
Antiandrogens achieve total androgen blockade and are useful when GnRH analogs do not produce castration testosterone levels. These drugs block actions of androgens by interacting with cytosolic androgen receptor sites in all target tissues: prostate, hypothalamus, and pituitary. As monotherapy, antiandrogens may cause an increase in plasma testosterone, which may result from increased LH caused by the drugs' interference with negative feedback of androgens at the hypothalamic level. Because this effect could counteract antiandrogen actions in peripheral tissues, these drugs are given mainly to patients receiving GnRH analogs or are used as adjuvant therapy in orchiectomized patients for complete androgen blockade. Adverse effects include diarrhea, breast swelling and tenderness, and hepatotoxicity. Flutamide causes more diarrhea than do bicalutamide and nilutamide. Nilutamide has unique adverse effects: decreased visual accommodation, disulfiram-like reaction, and constipation.
Monoclonal Antibodies

Multiple metastases of small cell anaplastic (oat cell) carcinoma of lung to brain

CT scan showing metastatic nodules in cerebellum

Cerebellar metastasis of cutaneous melanoma

Breast cancer

Multiple metastases with edema

Figure 11-22 Unconjugated Antibodies: Trastuzumab, Alemtuzumab, and Rituximab

Trastuzumab, alemtuzumab, and rituximab are recombinant DNA-derived monoclonal antibodies (MoAbs). The first binds to human epidermal growth factor receptor 2 (HER2), a protooncogene in certain breast tumors. Natural killer (NK) cells identify the drug:MoAb complexes as abnormal, attach to the MoAb, and inhibit tumor growth. Alemtuzumab is directed against CD52 (an antigen on surfaces of normal and malignant B and T lymphocytes, NK cells, monocytes, and macrophages, and male reproductive tissues) and induces cell lysis. It is used for B-cell chronic lymphocytic leukemia in selected patients. Rituximab, a chimeric murine/human MoAb, binds to CD20, a cell cycle-regulating antigen found on more than 90% of B-cell NHL cells but not on stem, pro-B, or normal plasma or other normal tissues. Rituximab induces CD20+ B-cell NHL cell apoptosis and also recruits host immune cells to lyse B cells. These drugs can lead to serious cardiac, hypersensitivity, pulmonary, blood, metabolic, and mucocutaneous effects.
**Figure 11-23 Conjugated Antibodies: Ibritumomab Tiuxetan and Tositumomab and Iodine I 131 Tositumomab**

Ibritumomab tiuxetan and tositumomab and iodine I 131 tositumomab consist of a murine MoAb linked by a chelating agent to a radioisotope. The MoAb delivers the radioisotope to malignant sites, and the drugs, like rituximab, bind to the CD20 antigen. While the antibody induces apoptosis in CD20⁺ B cells, β emission from the radioisotope induces cell damage through formation of free radicals in target and neighboring cells. Both products are used for relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including follicular NHL that is refractory to rituximab. Both drugs are associated with prolonged and severe cytopenias (thrombocytopenia, neutropenia), which occur in most patients. Therefore, the products should not be given to patients with impaired bone marrow reserve or more than 25% lymphoma marrow involvement. Both drugs may cause serious infusion reactions (fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, nausea).

**Physical examination** including superficial lymph nodes and Waldeyer ring

**Lymphangiography** may be performed for evaluation of pelvic/retroperitoneal nodes.

**Staging laparotomy** may be performed in some CS1/II HD patients if a stage change impacts on treatment.

**Lumbar puncture** as clinically indicated, and in all high-grade NHL, HIV patients, NHL with bone marrow/epidural/nasopharyngeal/sinus/testicular disease.

**Gallium scanning** for evaluation of supravascular disease. **Positron Emission Tomography** (PET) is a more accurate approach available at some centers.

**Computerized tomography** (CT scan) with oral and intravenous contrast to evaluate chest/abdomen/pelvis and neck.

**Blood laboratory study**
- CBC, differential/platelets, ESR, electrolyte/chemistry panel, renal/liver function testing, alkaline phosphatase/LDH/β₂ microglobulin, HIV serology

**Bilateral marrow aspiration/biopsy** in most patients. Its use is debated with early-stage, asymptomatic HD, where it is rarely positive.
Chronic myeloid leukemia (CML)

**Peripheral blood examination:**
High WBC count with mature neutrophils with early occasional myeloid forms and an occasional blast. Low leukocyte alkaline phosphatase score. Elevated platelet count, with dysmorphism and large size. Elevation of basophil count and blasts is seen in accelerated phase of this disorder.

**Bone marrow examination:**

**Figure 11-24 Imatinib Mesylate**

Imatinib inhibits Bcr-Abl tyrosine kinase, the constitutive abnormal enzyme created by the Philadelphia chromosome (Ph) abnormality in chronic myeloid leukemia (CML). This enzyme is present in almost all patients with CML and some patients with acute lymphoblastic leukemia. Imatinib inhibits proliferation and induces apoptosis in Bcr-Abl+ cell lines as well as fresh leukemic cells from Ph+ CML. The agent, used orally, is indicated as first-line therapy in newly diagnosed patients with Ph+ CML in the chronic phase and after failure of interferon alfa therapy in patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase. Imatinib is also used for patients with Kit+ (CD117+) unresectable and/or metastatic GI stromal tumors. Main adverse effects include thrombocytopenia, neutropenia, liver enzyme increases, edema (responds to diuretics and dose reduction), muscle cramps, nausea (reduced by food and water ingestion), and diarrhea.
Large cell anaplastic carcinoma in middle of right upper lobe with extensive involvement of hilar and carinal nodes. Distortion of trachea and widening of carina.

Tumor composed of large multinucleated cells without evidence of differentiation toward gland formation or squamous epithelium. These cells produce mucin (stained red). Some tumors may be composed of large clear cells containing glycogen.

**Figure 11-25 Gefitinib**

*Gefitinib* is an orally active anilinoquinazoline derivative that inhibits intracellular phosphorylation of several tyrosine kinases, one of which is associated with epidermal growth factor receptor (EGFR). EGFR is expressed on the surface of many normal cells and cancer cells and is thought to play a role in growth, metastasis, angiogenesis, and resistance to apoptosis of non-small cell lung cancer cells. Gefitinib is approved as monotherapy and as third-line therapy (after failure of both platinum-based and docetaxel regimens) in patients with locally advanced or metastatic non-small cell lung cancer. Main adverse effects are diarrhea, nausea, vomiting, and dermatologic effects. Potentially fatal interstitial lung disease occurs rarely, more often in patients who received previous chemotherapy and, to a lesser extent, previous radiotherapy. Increased mortality has been noted in gefitinib-treated patients with concomitant idiopathic pulmonary fibrosis with worsening lung function.
**FIGURE 11-26 BORTEZOMIB**

Bortezomib is a reversible inhibitor of the 26S proteosome, a large protein complex that degrades ubiquitininated proteins. The ubiquitin-proteosome pathway is known to play a major role in intracellular degradation of numerous regulatory proteins involved in cell integrity, such as cell cycle control, cellular apoptosis, transcription factor activation, and tumor growth. Inhibition of the 26S proteosome disrupts cell proliferation and apoptosis, which leads to cell death. Bortezomib is given intravenously and is approved for patients with multiple myeloma who have received at least 2 previous types of therapy but had disease progression after the last therapy. Predominant adverse effects with bortezomib include pyrexia; pneumonia; diarrhea, nausea, and vomiting; dehydration; fatigue, malaise, weakness; thrombocytopenia; peripheral neuropathy; and anemia.
OVERVIEW

Many drugs that are used to treat skin disorders are also administered for systemic disorders, but for skin disorders, the drug formulation is usually designed in a way that limits their absorption and distribution to the skin surface. Systemic distribution in these cases is generally not desirable and can lead to an increased number or severity of adverse effects. In severe skin disease, however, systemic administration is appropriate, and oral preparations are available for such treatment.

Glucocorticoids are a commonly used drug class for treating skin disorders such as dermatoses because of their antiinflammatory, immunosuppressive, and other effects. Glucocorticoids alter gene expression in cells located in the dermis and epidermis by binding to glucocorticoid response elements on DNA. These drugs are transported to the cell nucleus after forming complexes with cytoplasmic receptors. Glucocorticoids include hydrocortisone, betamethasone, and clobetasol (for psoriasis).

Retinoids, a family of naturally occurring and synthetic vitamin A analogs, affect cell differentiation and proliferation by regulating transcriptional activity mediated by nuclear retinoic acid receptor subtypes. Commonly used retinoids include adapalene, isotretinoin, and tretinoin (for severe acne); acitretin (for severe psoriasis); bexarotene (for early-stage cutaneous T-cell lymphoma); andtretinoin (for cutaneous lesions of Kaposi sarcoma); and naturally occurring β-carotene (for reducing skin photosensitivity).

Other dermatologic agents include antimicrobial, antimalarial, antifungal, and antiviral drugs; drugs (primarily pyrethrins and pyrethroids) used to treat scabies and lice; cytotoxic and immune-modulating drugs; systemic antihistamines (to treat, for example, urticaria, angioedema, and cutaneous mastocytosis); drugs to treat pigmentation disorders; keratolytic agents, such as salicylic acid, urea, lactic acid, and colloidal or precipitated sulfur (to treat excess thickening of the outermost layer of the skin); selenium sulfide (to treat dandruff); and psoralens (eg, 8-methoxypsoralen) and porphyrins (used as photosensitizers to enhance phototherapy).
SKIN DISORDERS

FIGURE 12-1 ANATOMY OF THE SKIN

The skin is a complex, multicomponent organ. It is commonly classified into 3 anatomical regions and multiple subregions: the epidermis, which includes the strata corneum, lucidum, granulosum, spinosum, and basale; the dermis, which includes the papillary and reticular layers; and the subcutaneous tissue, which includes sweat glands. All layers are extensively supplied by blood vessels and innervated by motor and sensory neurons. Disorders of the skin can develop either as primary disease (localized to 1 or more layers of the skin) or as a secondary result of a systemic disease. Drugs for management of these disorders involve topical or systemic administration of medications to treat the dermal or systemic source of the problem. Major classes of drugs used in dermatologic pharmacology include glucocorticoids, antibacterials, antifungals, antivirals, antiparasitics, and retinoids.

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Figure 12-2 Alopecia

Alopecia—the loss or absence of hair, especially of the head—can be caused by illness, drugs, endocrine disorders, some types of dermatitis, hereditary factors, radiation, and physiologic processes such as aging. Drug therapy, when appropriate, involves topical steroids (e.g., clobetasol) or intradermal injections of triamcinolone for alopecia areata (defined patches, usually on the scalp or beard; occurs most often in children and in autoimmune diseases); minoxidil for androgenic alopecia (affects androgen-sensitive follicles on the scalp of men and women); and griseofulvin, itraconazole, or terbinafine for tinea capitis (fungal infection). Scarring (cicatrical) and permanent alopecias are treated with potent corticosteroids used topically or intralesionally on active inflammatory borders. Systemic drugs (e.g., acitretin, chloroquine, doxycycline, low-dose methotrexate, minocycline, prednisone, quinacrine, tetracyclines) may also be used if the disease type and extent warrant them.
Primary blister diseases are caused by defects in cell adhesion proteins. The defects are either inherited (usually apparent at or soon after birth) or occur in diseases (typically adult onset) in which cell adhesion proteins become target antigens for autoimmune responses. Blisters can also result from infectious, traumatic, or inflammatory processes. Therapeutic drugs include topical, intraleisional, or systemic corticosteroids or immunosuppressive agents (eg, azathioprine, cyclophosphamide, cyclosporine, dapsone) for bullous pemphigoid and pemphigoidlike diseases in which IgG autoantibodies attack certain basal keratinocyte proteins; high-dose systemic corticosteroids or mycophenolate mofetil (suppresses lymphocyte proliferation and antibody formation by B cells) for life-threatening pemphigus vulgaris; systemic prednisone for pemphigus foliaceus (affects desmosomes); and dapsone for paraneoplastic pemphigus (associated with lymphoproliferative disorders).
Eczema is an acute or chronic inflammatory skin condition characterized by the presence of 1 or more areas of pruritus (severe itching), erythema (redness), scaling (dry exfoliative shedding), macules (discoloration), papules (pimples), or vesicles (blisterylike sacs). Drugs, when needed, include oral antihistamines or topical corticosteroids for common cases of atopic dermatitis; antibiotics (antistaphylococcal or antistreptococcal) or topical tacrolimus or pimecrolimus for severe or recalcitrant cases of atopic dermatitis; systemic corticosteroids for severe contact dermatitis; topical zinc pyrithione, selenium sulfide, salicylic acid, or ketoconazole for seborrheic dermatitis; topical corticosteroids and emollients for stasis dermatitis (secondary to edema resulting from poor venous return); and antifungal drugs for dermatophytosis (tinea) (ringworm).
Psoriasis is a chronic relapsing skin disorder with distinctive lesions consisting of erythematous papules that coalesce into plaques with sharp borders and silvery, yellow-white scales in patients with advanced disease. It affects approximately 1% to 3% of the population and affects men and women about equally. Management depends on the degree of body surface area affected (topical drugs for <20% body area; systemic drugs for ≥20%), location and sensitivity of affected areas, degree of inflammation, and patient compliance with the therapy regimen. Drugs, when appropriate, include topical steroids (produce a rapid response, but tolerance develops; eg, fluocinonide); vitamin D analogs (eg, calcipotriene), which inhibit proliferation and normalize maturation of keratinocytes; retinoids (eg, tazarotene); and keratolytics (eg, salicylic acid, urea, and lactic acid). Certain drugs—eg, lithium, β blockers, antimalarials, and systemic steroids—can worsen psoriasis and should be avoided.
Figure 12-6 Scabies and Pediculosis

Scabies, a highly communicable skin disease caused by infestation by the mite *Sarcoptes scabiei* var. *hominis* (the itch mite), is characterized by extreme pruritus and widespread inflammatory papules, often scratched (abraded). The mainstay of pharmacologic therapy is the use of topical scabicides, such as permethrin and lindane (although lindane has a higher potential for CNS toxicity), or an oral antiparasitic agent (eg, ivermectin). Pediculosis is caused by infestation by *Pediculus capitis* (head louse), *Pediculus humanus* (body louse), or *Pthirus pubis* (pubic louse). Head lice and body lice are commonly treated with topical permethrin (but this agent should not be used for infants younger than 2 months or for pregnant or lactating women). Pubic lice (crabs) are treated with topical synergized pyrethrins; eyelashes are treated with petrolatum.
## Figure 12-7 Urticaria

Urticaria, which is characterized by a sudden general eruption of pale evanescent wheals or papules, results from fluid transudation from small cutaneous blood vessels. Histamine and other mediators are released, which leads to severe itching. Acute urticaria is usually treated with antihistamines if it is mild; corticosteroids are used if it is severe. Specific agents include the histamine H1 receptor antagonists cetirizine, ciproheptadine, diphenhydramine, fexofenadine, hydroxyzine, and loratadine. H2-receptor antagonists are sometimes added, or agents having mixed H1/H2-antagonistic action, such as certain tricyclic antidepressants (eg, doxepin), are used. Chronic urticaria is treated with attenuated anabolic steroids, nifedipine, dapsone, sulfasalazine, colchicine, methotrexate, hydroxychloroquine, UV-B light, or PUVA (psoralen plus UV-A light); ciproheptadine is useful for cold urticaria, and β blockers are useful for adrenergic urticaria.

### Substances Associated With Urticaria or Angioedema

<table>
<thead>
<tr>
<th>Blood products</th>
<th>Contactants</th>
<th>Drugs*</th>
<th>Foods</th>
<th>Inhalants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextran</td>
<td>Animal dander and saliva</td>
<td>Anesthetics</td>
<td>Berries</td>
<td>Animal dander</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Arthropods</td>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Cheese</td>
<td>Cigarette smoke</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Foods</td>
<td>Antiepileptic agents</td>
<td>Chocolate</td>
<td>Dusts</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>Latex</td>
<td>Aspirin</td>
<td>Eggs</td>
<td>Flour</td>
</tr>
<tr>
<td>Opioids</td>
<td>Marine forms</td>
<td>Bromides</td>
<td>Fish</td>
<td>Mold</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Medications (topical)</td>
<td>Cephalosporins</td>
<td>Milk</td>
<td>Pollen</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Plants</td>
<td>Chloroquine</td>
<td>Nuts</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Textiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulla drugs</td>
<td>Toiletry items</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Radiographic contrast media</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Vancomycin</td>
<td></td>
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</tbody>
</table>

*Almost any prescription or over-the-counter medication can cause urticaria.
OVERVIEW

Vitamin deficiencies have various causes, including an inadequate supply of the vitamin in the diet, inability of the body to absorb or utilize the vitamin, excessive degradation or excretion of the vitamin, general nutritional deficiency, disease, and vitamin-drug interactions.

Vitamins are commonly classified into those that are water soluble and those that are fat soluble. Water-soluble vitamins include the vitamin B family—thiamine (B₁), riboflavin (B₂), nicotinic acid (niacin) (B₃), pyridoxine (B₆), pantothenic acid, cyanocobalamin (B₁₂), biotin, and folic acid (folacin)—and vitamin C (ascorbic acid). Fat-soluble vitamins include vitamin A (retinol); the vitamin D family—calciferol (D₂) and cholecalciferol (D₃); vitamin E (α-tocopherol); and the vitamin K family—phyloquinone (K₁), menaquinones (K₂), and menadione (K₃).

Water-soluble vitamins typically have small body stores, and thus, the concentrations of these vitamins can readily be compromised in the presence of alcoholism, dieting (fads), prolonged anorexia, nausea, dysphagia, diarrhea, weight loss, advanced organ failure, and malabsorption. Fat-soluble vitamins are affected by any chronic deficiency in fat absorption, such as that occurring in short bowel syndrome, pancreatic insufficiency, bacterial overgrowth, celiac sprue, Whipple disease, and primary biliary cirrhosis.

Management of vitamin deficiency disorders can take many forms, including prevention (maintenance of adequate dietary intake), supplementation (usually oral, but the parenteral route is also used), treatment of an underlying disorder, and elimination of interactions with drugs.
VITAMINS

Vitamin A Deficiency

Principal food sources of vitamin A
Milk
Liver
Egg yolk
Kidneys
Cod liver oil
Certain fish oils
Principal food sources of carotene
Carrots
Tomatoes
Pimentos
Sweet potatoes
Apricots, yellow peaches
Leafy vegetables

Vitamin A Ester
Vitamin A
Carotene

Bile aids absorption of carotene.

Pancreatic secretions promote hydrolysis of vitamin A esters.

Vitamin A and carotene absorbed
Mineral oil dissolves and carries off vitamin A in stool.

Bloodstream

Esterase

Liver

Mobilization

Vitamin A esterified
Carotene converted to vitamin A

Principal deficiency manifestations

Xerophthalmia
Night blindness (effect on retinal rods)
Growth impairment
Hyperkeratinization of skin

Thyroid promotes conversion of carotene to vitamin A.

Figure 13-1 Deficiency of Vitamin A (Retinol) and Other Fat-Soluble Vitamins

Dietary sources of the fatsoluble vitamin A include milk fat, eggs, green leafy or yellow vegetables, and fish oil. Vitamin A is formed from precursors (α, β, and γ carotenoids) found in yellow pigments of fruits and vegetables (eg, apples, cabbage, cantaloupe, carrots, oranges, tomatoes). Diseases that result in malabsorption of fat or impaired storage of vitamin A in the liver are characterized by interference with growth, reduced resistance to infections, and disrupted epithelial cell structure and function. Principal manifestations of this deficiency include xerophthalmia (conjunctival dryness with epithelial keratinization), night blindness, and hyperkeratinization of skin. The main manifestations of other fat-soluble vitamin deficiencies include rickets (vitamin D), excessive steatorrhea (secretion of fat from sebaceous glands of skin; fatty stools) (vitamin E), and increased bleeding time (vitamin K). All these deficiencies are treated via supplementation.
The B vitamin group includes thiamine (B₁), riboflavin (B₂), nicotinic acid (niacin) (B₃), pyridoxine (B₆), pantothenic acid, cyanocobalamin (B₁₂), biotin, and folic acid (folacin). Major dietary sources are whole grains, whole brown rice, wheat germ, meats, fish, dairy products, and vegetables. Thiamine deficiency (beriberi) is characterized by peripheral neurologic, cerebral, and cardiovascular abnormalities. The disorder is more common in people with alcoholism, whose poor diet can lead to inadequate daily intake of thiamine. The principal manifestations of other vitamin B deficiencies include local seborrheic dermatitis on the face and scrotum (vitamin B₃); alterations in skin, blood, and CNS function (vitamin B₆); pernicious anemia (vitamin B₁₂); anorexia, nausea, vomiting, and dermatitis (biotin); and megaloblastic anemia, diarrhea, and weight loss (folic acid). All of these deficiencies are treated via supplementation.
Figure 13-3 Niacin or Nicotinic Acid Deficiency (Pellagra)

Deficiency of water-soluble niacin (nicotinic acid) or its amide (nicotinamide) results from dietary deficiency or impaired absorption. It is usually associated with diets lacking tryptophan-containing proteins and can occur secondary to gastrointestinal diseases or chronic alcoholism. This deficiency causes pellagra, which is characterized by cutaneous, gastrointestinal, mucosal, neurologic, and cognitive symptoms. The numerous cutaneous symptoms include cheilosis (reddened lips and fissures at the angles of the mouth), angular stomatitis (inflammation and fissures radiating from the corners of the mouth), and magenta-colored tongue (as seen in arboflavinosis). Involvement of the CNS progresses from general lassitude, disorientation, memory impairment, and confusion to delirium and clouding of consciousness. Treatment is by supplemental intake (parenteral if oral is not possible).
Deficiency of water-soluble vitamin C (ascorbic acid) results from impairment of the maintenance of the ground substance that binds cells together and is necessary for the formation and maintenance of collagen in connective tissues. The precise mechanism of this effect is not known but is thought to be due to the ability of vitamin C to participate in oxidation-reduction reactions. Symptoms of vitamin C deficiency (scurvy) include imperfect bone and tooth formation; swollen, congested, bleeding gums; anorexia; multiple ecchymoses (skin discoloration consisting of irregular hemorrhagic areas); and a positive Rumpel-Leede (Hess) capillary fragility test (for thrombocytopenia). Treatment is via supplemental intake.
**Figure 13-5 Fat-Soluble Vitamin-Drug Interactions**

**Vitamin A:** Because dietary fat and pancreatic lipase are necessary for absorption of vitamin A from the small intestine (see Figure 13-1), absorption is impaired by agents that modify this process, such as mineral oil, neomycin, and cholestyramine. Because ethanol competes with vitamin A as a substrate for alcohol dehydrogenase, excess ethanol consumption results in reduced conversion of retinol to retinal (which leads to, for example, night blindness).

**Vitamin D:** Drugs that bind bile salts interfere with gastrointestinal absorption of vitamin D; glucocorticoids interfere with hepatic metabolism of this vitamin; and hepatic enzyme inducers can accelerate conversion of vitamin D to its inactive metabolites.

**Vitamin K:** Coumarin anticoagulants can produce vitamin D deficiency.
**Vitamin B family:** Folate absorption, activity, or removal is affected by ethanol, phenytoin, and oral contraceptives; salicylates (compete with protein-binding sites); and methotrexate (folate antagonist). Vitamin B$_6$ is affected by ethanol (decreases coenzyme pyridoxal phosphate production); hydrazines (eg, isoniazid) (coenzyme inhibitors); cycloserine and penicillamine (coenzyme inactivators); and steroid hormones (coenzyme competitors). In turn, vitamin B$_6$ reduces levodopa efficacy or serum phenobarbital and phenytoin levels. Oral hypoglycemic biguanides, colchicine, ethanol, and aminosalicylic acid affect vitamin B$_{12}$ absorption. Isonicotinic acid hydrazide, 6-MP, and 5-FU cause niacin deficiency; niacin inhibits effects of sulfinpyrazone and probenecid. Riboflavin absorption is inhibited by thyroxine and drugs that increase intestinal motility. **Vitamin C:** Aspirin and oral contraceptives reduce plasma vitamin C levels; this vitamin can alter renal drug excretion.
CHAPTER 14

DRUG ALLERGY, ABUSE, AND POISONING OR OVERDOSE

OVERVIEW

Drug allergy, or allergic reaction to drugs, represents a type of adverse drug reaction. The effects are mediated by humoral (involving antibodies) or cell-mediated (e.g., T-lymphocyte) immunologic mechanisms and can lead to consequences that are short- or long-term, restricted to a specific organ or involving the whole body, and trivial or life-threatening. The clinical manifestations of allergic reactions to drugs are varied and can include anaphylaxis (anaphylactic shock, i.e., life-threatening changes in the vasculature [such as vasodilation and edema] and the bronchioles [such as bronchoconstriction] that are consistent with shock); bronchospasm; dermatitis; fever; granulocytopenia (abnormal reduction of the number of neutrophils, eosinophils, and basophils in the blood); hemolytic anemia (abnormal decrease in red blood cell number); hepatitis; lupus erythematosus-like syndrome; nephritis or pneumonitis (lung inflammation); thrombocytopenia (abnormal decrease in platelet number); and vasculitis (inflammation of blood or lymph vessels). Allergic reactions to drugs are typically characterized by the necessity for previous exposure to the drug or to a drug of similar chemical structure; lack of dose-related effect; similar manifestations independent of the drug (i.e., not related to the therapeutic or toxic effects of the drug); and nonresponsiveness to receptor antagonists of the drug.

Drug abuse (addiction) is a multifaceted problem, typically involving a complex combination of psychosocial contribut-
ing factors. Hereditary predisposition is also suspected to play a role in some cases. Drug abuse is perhaps most succinctly defined as the continued inappropriate nonmedical use of a drug in the face of known negative medical or other consequences. To some extent, every drug that produces a detectable psychic effect is abused by someone, somewhere in the world. In addition, many, perhaps most, drug addicts abuse more than 1 drug. Hence, the list of abused drugs is extensive and includes some substances that are thought of primarily as mood or physique enhancers or as "recreational" drugs (e.g., anabolic steroids, mushrooms, designer drugs, hallucinogens, inhalants, marijuana, nicotine). This chapter focuses on some of the major classes of therapeutic drugs that are abused.

Drug poisoning or overdose can be accidental (a result of medical errors or errors in the home) or intentional (suicide attempts). The substances involved include pharmaceuticals (most often analgesics and over-the-counter preparations), cleaning products, cosmetics, and plants or plant extracts. The symptoms and duration of the toxicity depend on the substance involved, the amount, and the site of exposure. The mechanisms can be specific (e.g., receptor-mediated reactions) or nonspecific (e.g., tissue necrosis). This chapter focuses on toxicity caused by selected pharmacologic agents.
Figure 14-1 Allergic Reactions to Drugs

Only a few drugs have a molecular size (>10,000 d) sufficient to induce an allergic reaction by themselves. Induction of an immune response more often occurs when a small drug molecule, metabolite, or excipient (inert substance in a prescription) covalently binds to some large endogenous macromolecule (carrier), such as a protein, and becomes allergenic. The immune system becomes sensitized during the initial exposure, although the allergic response is not elicited at this time. Antigen-specific antibodies of the T- and B-cell type proliferate in lymphatic tissue, and some remain there (as memory cells) and are clinically silent until reexposure to the antigen (drug-carrier complex). The response to reexposure can be quick and severe, even to a small dose of the drug. Four types of drug allergy are generally distinguished: anaphylactic, cytotoxic, immune complex vasculitis, and cell-mediated. Management generally involves treating the symptoms and supporting vital functions.
Figure 14-2 Type I (Acute, Anaphylactic) Reactions

After initial exposure to drug antigen (drug-carrier complex), macrophages and interleukins convert B cells into IgE/receptor-expressing cells that circulate in blood (as basophil granulocytes) or reside in tissues (as mast cells). Reexposure to drug antigen results in binding to paired IgE receptors and release of various chemical mediators such as histamine, kinins, serotonin, prostaglandins, leukotrienes, platelet-activating factor, and eosinophilic chemotactic factor. Histamine and other bioactive substances released into the bloodstream cause blood vessels to dilate and tissues to swell. The effect may be life-threatening if airway obstruction, blood pressure decrease, or heart arrhythmias occur. Type I reactions can have a rapid onset (minutes) and are similar to those seen in hypersensitivity reactions to insect stings, extrinsic asthma, and seasonal rhinitis.
**Figure 14-3 Type II (Cytotoxic, Autoimmune) Reactions**

If antigen (drug)-antibody (IgG) complexes adhere to a cell surface, the immune response can damage or kill the cell. This effect occurs because the binding of the complex activates complement, which is a family of proteins that circulate in the blood in an inactive form until activated by an appropriate stimulus. Activated complement is normally directed against microorganisms, but when directed against a cell, complement causes lysis and death of the cell, promotes phagocytosis, attracts neutrophil granulocytes (chemotaxis), and stimulates other inflammatory responses. An example is allergy to penicillin. Penicillin binds to red blood cells, antibodies bind to the penicillin, complement is activated, and the cell is damaged or dies, which leads to drug-induced autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia.
FIGURE 14-4 TYPE III (IMMUNE COMPLEX, SERUM SICKNESS, ARTHUS) REACTIONS

If drug antigen-antibody complexes adhere to cells of vascular tissue, the immune response can attack not only the antigen-antibody complex but also the healthy cells of the vessel to which the complex is attached. This result can cause damage or death of the vessel’s cells. Activated complement, inflammation, and vasculitis damage vessel walls and result in the symptoms of serum sickness, which include malaise, fever, rash, arthralgia (pain in a joint), lymphadenopathy, hepatitis, and characteristic rash and eruptions along the sides of the feet and hands.
When drug antigen is administered on or into the skin or mucosa, for example, binding to antigen-specific receptors expressed on T lymphocytes can occur. Binding stimulates lymphocytes to release signal molecules (lymphokines), which activate macrophages and provoke an inflammatory reaction in the surrounding area. This cell-mediated response (involving sensitized T lymphocytes) is slower than humoral immune responses (those involving antibodies). Drug-related substances that can cause type IV reactions include ethylenediamine, which is used as a drug-solubilizing agent, and EDTA, which is used as a preservative in many topical and ophthalmic preparations.

**Figure 14-5 Type IV (Cell-Mediated, Delayed-Hypersensitivity, Contact Dermatitis) Reactions**
Drug abuse involves 2 components: psychosocial (e.g., family situation, peer pressure) and endogenous (e.g., genetics, enzyme levels). Pharmacologic mechanisms of drug abuse involve CNS neurotransmitter systems that operate for therapeutic drug effects. An endogenous pleasure or reward pathway in the brain is important for motivation and learning (survival) and is thought to be excessively active—because of genetics, overuse, or other factors—in drug abuse. The brain reward circuit consists of neuronal pathways, cortical sites, and subcortical nuclei, especially within the limbic region. Primary among these are dopaminergic neurons in the ventral tegmentum that project to the nucleus accumbens and then to the cortex and other centers. Also, norepinephrine-containing neurons from the locus ceruleus project to the ventral tegmentum. Stimulation or disinhibition of dopaminergic neurons within the ventral tegmentum may be common to abuse of different substances.

**Figure 14-6  Brain Reward Circuit**

Brain reward circuits comprise dopaminergic neurons located in ventral tegmentum, which project to nucleus accumbens via medial forebrain bundle. Nucleus accumbens sends projections to cortex and other centers. Locus ceruleus projects to ventral tegmentum.
Effects of Alcohol on End Organs

Cellular damage

Ethanol

ADH pathway

Cytochrome P-450 pathway

Acetaldehyde

Free fatty acids

Phosphatidylcholine

Phosphatidylethanol

Intracellular free radicals interfere with cell membrane function and protein synthesis and alter DNA.

Acetaldehyde damages cytoskeleton and enzyme systems and induces antibodies against cell components.

Fatty acid esters interfere with protein synthesis and mitochondrial and cell membrane function.

Phosphatidylethanol alters regulatory and communication functions of cell membrane.

Alcohol causes end organ damage via ethanol metabolites and ethanol-generated compounds, which alter structure and function of cell components.

Organ damage

Cardiovascular damage includes arrhythmias and cardiomyopathy.

Immune system suppression increases risk of infection and some cancers.

Teratogenic effects may lead to fetal alcohol syndrome.

Increased risk of spontaneous abortion

Testicular atrophy and diminished libido

Anovulation and early menopause

Hepatic damage includes fatty liver, alcoholic hepatitis, and cirrhosis.

Neurologic damage ranges from Korsakoff dementia to subclinical cognitive defects.

Neurologic damage

Increased risk of spontaneous abortion

Testicular atrophy and diminished libido

Anovulation and early menopause

FIGURE 14-7 ETHANOL: DELETIOUS EFFECTS

Short- and long-term excess ethanol consumption leads to widespread problems for the individual and for society. The lifetime prevalence of ethanol dependence is estimated at 10% to 15%, and as many as 30% of male and 10% of female admissions to general hospitals are related to ethanol-associated disorders. Ethanol is rapidly absorbed from the GI tract and distributes to all cells in the body. It readily passes into the fetal circulation. Low concentrations of ethanol are safely metabolized in a 2-step process: first by alcohol dehydrogenase to acetaldehyde and then by aldehyde dehydrogenase to acetate. High concentrations saturate this pathway and give rise to toxic byproducts of alternative pathways. Because ethanol is so widely distributed throughout the body, the toxic consequences of excess ethanol consumption involve essentially every organ.
Alcohol Withdrawal

Expression and severity of symptoms vary with duration and degree of dependence and with recognition and treatment of early withdrawal.

Generalized seizures occur in 8% of cases. Focal or multiple seizures suggest other cause.

Stages of Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Hours after alcohol consumption</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(peak)</td>
<td>24</td>
<td>36-48 (peak)</td>
<td>48-72</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Mild-to-moderate anxiety, tremor, nausea, vomiting, sweating, elevation of heart rate and blood pressure, sleep disturbance, hallucinations, illusions, seizures</td>
<td>Aggravated forms of stage 1 symptoms with severe tremors, agitation, and hallucinations</td>
<td>Acute organic psychosis (delirium), confusion, and disorientation with severe autonomic symptoms</td>
</tr>
</tbody>
</table>

Stage 1 withdrawal usually self-limited. Only small percentage of cases progress to stages 2 and 3. Progression prevented by prompt and adequate treatment.

Figure 14-8 Ethanol Abuse: Treatment

Abrupt withdrawal from ethanol is accompanied by excitatory CNS signs such as delirium tremens and potentially lethal seizures. Medication management in the past was limited to disulfiram, which inhibits aldehyde dehydrogenase. The buildup of acetaldehyde produces an unpleasant reaction when ethanol is consumed and thereby provides a deterrent to excess ethanol use. Naltrexone and acamprosate (in Europe) are newer alternative choices.

Naltrexone is an opioid receptor antagonist that seems to have the additional (perhaps independent) property of reducing the chance of relapse when used in conjunction with psychosocial treatment. Acamprosate seems to enhance abstinence by a modulatory effect on the NMDA subtype of the glutamate receptor.
Opioid Withdrawal

Signs and Symptoms

- Sweating
- Dilated pupils
- Lacrimation
- Rhinorrhea
- Yawning

- Nausea
- Vomiting
- Diarrhea

- Locus ceruleus
  - Noradrenergic effects may be blocked by α₂ agonists.

- Insomnia and muscle aches mediated via μ receptors and relieved by μ agonists.

Noradrenergic effects of withdrawal (mediated via locus ceruleus) increase heart rate and blood pressure.

Blood pressure
Heart rate

<table>
<thead>
<tr>
<th>Days since last dose</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset and severity of withdrawal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity of opioid withdrawal varies with dose and duration of opioid use. Onset and duration of symptoms after last drug dose depend on half-life of particular drug.

**Figure 14-9** Withdrawal: Opioids, Benzodiazepines, and Barbiturates

Abrupt discontinuation of drugs used for long-term abuse results in withdrawal signs. In general, these signs are the opposite of those induced by the drug: withdrawal from CNS excitatory drugs is inhibitory, and withdrawal from CNS depressants is excitatory. The rate and severity of withdrawal are lessened by tapered cessation of drug use rather than abrupt cessation. Withdrawal that is too rapid, particularly from CNS depressant drugs such as ethanol and barbiturates, can be life-threatening. Withdrawal from opioids
**Figure 14-9 Withdrawal: Opioids, Benzodiazepines, and Barbiturates (continued)**

Involves influenza-like symptoms, diarrhea (rather than the opioid-induced constipation), and effects mediated through adrenoceptors. Opioid withdrawal can be ameliorated by opioid substitution (e.g., with methadone) or with α₂-adrenoceptor agonists. Withdrawal from benzodiazepines is generally mild after therapeutic (low) doses but can be severe (e.g., tachycardia) after long-term abuse of high doses.
Accidental or intentional overdose of sympathomimetics produces symptoms that mimic, in an exaggerated fashion, activation of the sympathetic subdivision of the ANS. Therefore, common effects of moderate overdose of these drugs include mydriasis, diaphoresis (profuse sweating), tachycardia, and hypertension; CNS excitation and seizures are common consequences of severe overdose. The sympathetic nervous system can be oversimulated either by drugs that act directly by binding to adrenergic receptors (e.g., α- or β-adrenoceptor agonists) or by drugs that act indirectly by enhancing release of norepinephrine (e.g., amphetamines), inhibiting the reuptake of norepinephrine (e.g., cocaine), or inhibiting the breakdown of adrenergic receptor--associated second messengers (e.g., inhibition of phosphodiesterase by high doses of xanthines such as caffeine and theophylline). Management of effects produced by overdose of these drugs typically involves supportive care.
Accidental or intentional overdose of cholinergic drugs produces symptoms that mimic, in an exaggerated way, activation of the SNS and the ANS. Because of excess stimulation at the site of pre-ganglionic cholinergic receptors in both the sympathetic and parasympathetic subdivisions, the action on the ANS is mixed. Thus, overdose can cause muscle paralysis, miosis or mydriasis, bradycardia or tachycardia, CNS stimulation or depression, salivation, lacrimation, diaphoresis, and diarrhea. Cholinergic receptors can be overstimulated by direct-acting agonists (e.g., acetylcholine, succinylcholine) or indirect-acting drugs that enhance the action of acetylcholine, such as organophosphates that inhibit acetylcholinesterase (e.g., phosystigmine, neostigmine, edrophonium, certain insecticides, nerve gases). Management of the effects produced by overdose of these drugs involves supportive care, especially of the respiratory system, and other measures.
Figure 14-12 Anticholinergic Drugs

Accidental or intentional overdose of anticholinergic drugs produces effects that result from blockade of nicotinic cholinergic receptors located on skeletal muscles in the SNS (e.g., effects of curare) and synapses of preganglionic neurons in the ANS (e.g., effects of nicotine), and/or from blockade of muscarinic cholinergic receptors located on smooth muscles, cardiac muscles, or glands in the ANS (e.g., effects of atropine and pilocarpine).

Overdose signs include skeletal muscle paralysis, mydriasis, tachycardia, decreased gastrointestinal activity, dry mucosa, dry skin, delirium, hallucinations, and seizures. Management of the effects produced by overdose of these drugs usually involves supportive care, particularly of the respiratory system, and other measures (for the autonomic signs).
FIGURE 14-13 SEROTONERGICS

Excess serotonin can result from the accidental or intentional overdose of drugs that directly activate serotonin receptors or, more commonly, from drugs that indirectly enhance serotonin levels by inhibiting presynaptic neuronal reuptake of serotonin or by inhibiting serotonin breakdown by monoamine oxidase. The latter category includes selective serotonin reuptake inhibitors, nonselective serotonin reuptake inhibitors, and MAOIs. Excessive serotonin activity produces a serotonin syndrome, which may include akathisia-like restlessness, muscle twitches and myoclonus, hyperreflexia, sweating, shivering and tremor, and possibly life-threatening seizures or coma.
Miosis (pinhole pupils)

Seen in poisoning by morphine and morphine derivatives, some types of mushrooms, cholinesterase inhibitors, parasympathomimetics, nicotine, chloral hydrate, sympatholytics, and some other compounds.

Periodic paralysis usually associated with hypokalemia but may also occur with hyperkalemia or normokalemia. Hyperthyroidism may also be associated with hypokalemic periodic paralysis.

Figure 14-14 Opioids

Accidental or intentional overdose of opioid agonists, such as morphine, codeine, or oxycodone, results in overstimulation of opioid receptors that are located throughout the CNS and in the periphery. Overdose of these drugs is characterized by miosis, constipation, hypothermia, hypotension, pulmonary edema, and possibly life-threatening respiratory depression, among other signs. Seizures can also occur. Metabolites of the drugs can produce additional toxicity (e.g., neuromuscular excitability by normeperidine and myocardial depression by norpropoxyphene). All effects that are produced by excess opioid receptor activation are reversed by administration of an opioid receptor antagonist such as naloxone. Multiple treatments with an antagonist may be required if the half-life of the antagonist is shorter than that of the agonist. High doses of antagonist may be needed against propoxyphene (and reversal of the toxic effect may still be incomplete).
Many products on the market have pharmacologic activity and can be obtained without a prescription. Some of these products contain single or multiple ingredients, such as antihistamines, decongestants, analgesics (e.g., nonsteroidal antiinflammatory drugs or acetaminophen). These drugs, as well as vitamins, health aids, and herbs, can produce toxicity in overdose or when taken together (too numerous to list here). An overdose scenario that highlights an important pharmacologic principle is that associated with acetaminophen (paracetamol). It is one of the safest drugs at therapeutic doses because it and its potentially toxic intermediate metabolites are rapidly metabolized in a glutathione-dependent pathway and then excreted. However, in overdose, depletion of glutathione allows accumulation of reactive metabolites that cause hepatic injury. If treatment with a glutathione substitute is initiated early enough, it provides a successful antidote.
Vomiting induced by the emetic syrup of ipecac is occasionally recommended for pediatric ingestions, being managed at home, in consultation with the poison center. It no longer has a role in the hospital management of poisonings.

### Toxins With a Specific Antidotal Therapy

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>β Blockers</td>
<td>IV glucagonos</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>IV calcium, glucagones</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Atropine, pralidoxime</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Cyanide kit</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Digibind®</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Ethanol, 4-methylpyrazole</td>
</tr>
<tr>
<td>Fluoride</td>
<td>IV calcium, magnesium</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>IV glucose</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>IV pyridoxine</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
</tr>
<tr>
<td>Methanol</td>
<td>Ethanol, 4-methylpyrazole</td>
</tr>
<tr>
<td>Methemoglobin producers</td>
<td>IV methylene blue</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Naloxone, naltrexone</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Sodium bicarbonate</td>
</tr>
</tbody>
</table>

**Figure 14-16 Management of Poisoning and Overdose**

Specific antidotes are available for only a limited number of drugs. However, most drug overdoses or poisonings can be successfully managed by using a combination of drugs (e.g., a receptor antagonist for opioids) and/or supportive care, with particular attention to vital organ functions, breathing, circulation, cardiac arrhythmias, seizures, and altered mental status. Benefit may also be derived from surface decontamination and, under certain restricted conditions, use of emetic agents or gastric lavage. Forced diuresis has unproven efficacy, but alkalization of the urine may delay gastric absorption of weak acidic drugs and enhance their urinary excretion (e.g., salicylates and barbiturates).
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