or *down-regulation*). Prolonged inhibition of normal cellular functions with an antagonist may increase receptor number or sensitivity. If the antagonist is suddenly reduced or stopped, the cell becomes excessively responsive to an agonist (a process called receptor *up-regulation*). These changes in receptors may explain why some drugs must be tapered in dosage and discontinued gradually if withdrawal symptoms are to be avoided.

Nonreceptor Drug Actions

Relatively few drugs act by mechanisms other than combination with receptor sites on cells. These include:

1. Antacids, which act chemically to neutralize the hydrochloric acid produced by gastric parietal cells and thereby raise the pH of gastric fluid
2. Osmotic diuretics (eg, mannitol), which increase the osmolarity of plasma and pull water out of tissues into the bloodstream
3. Drugs that are structurally similar to nutrients required by body cells (eg, purines, pyrimidines) and that can be incorporated into cellular constituents, such as nucleic acids. This interferes with normal cell functioning. Several anticancer drugs act by this mechanism.
4. Metal chelating agents, which combine with toxic metals (eg, lead) to form a complex that can be more readily excreted.

VARIABLES THAT AFFECT DRUG ACTIONS

Expected responses to drugs are largely based on those occurring when a particular drug is given to healthy adult men (18 to 65 years of age) of average weight (150 lb [70 kg]). However, other groups of people (eg, women, children, older adults, different ethnic or racial groups, and clients with diseases or symptoms that the drugs are designed to treat) receive drugs and respond differently than healthy adult men. Therefore, current clinical trials are including more representatives of these groups. In any client, however, responses may be altered by both drug- and client-related variables, some of which are described in the following sections.

Drug-Related Variables

Dosage

Although the terms *dose* and *dosage* are often used interchangeably, dose indicates the amount to be given at one time and dosage refers to the frequency, size, and number of doses. Dosage is a major determinant of drug actions and responses, both therapeutic and adverse. If the amount is too small or administered infrequently, no pharmacologic action occurs because the drug does not reach an adequate concentration at target cells. If the amount is too large or administered too often, toxicity (poisoning) may occur. Because dosage includes the amount of the drug and the frequency of administration, overdosage may occur with a single large dose or with chronic ingestion of smaller amounts. Doses that produce signs and symptoms of toxicity are called *toxic doses.* Doses that cause death are called *lethal doses.*

Dosages recommended in drug literature are usually those that produce particular responses in 50% of the people tested. These dosages usually produce a mixture of therapeutic and adverse effects. The dosage of a particular drug depends on many characteristics of the drug (reason for use, potency, pharmacokinetics, route of administration, dosage form, and others) and of the recipient (age, weight, state of health, and function of cardiovascular, renal, and hepatic systems). Thus, the recommended dosages are intended only as guidelines for individualizing dosages.

Route of Administration

Routes of administration affect drug actions and responses largely by influencing absorption and distribution. For rapid drug action and response, the IV route is most effective because the drug is injected directly into the bloodstream. For some drugs, the IM route also produces drug action within a few minutes because muscles have a large blood supply. The oral route usually produces slower drug action than parenteral routes. Absorption and action of topical drugs vary according to the drug formulation, whether the drug is applied to skin or mucous membranes, and other factors.

Drug–Diet Interactions

Food may alter the absorption of oral drugs. In many instances, food slows absorption by slowing gastric emptying time and altering GI secretions and motility. When tablets or capsules are taken with or soon after food, they dissolve more slowly; therefore, drug molecules are delivered to absorptive sites in the small intestine more slowly. Food also may decrease absorption by combining with a drug to form an insoluble drug–food complex. In other instances, however, certain drugs or dosage forms are better absorbed with certain types of meals. For example, a fatty meal increases the absorption of some sustained-release forms of theophylline. Interactions that alter drug absorption can be minimized by spacing food and medications.

In addition, some foods contain substances that react with certain drugs. One such interaction occurs between tyramine-containing foods and monoamine oxidase (MAO) inhibitor drugs. Tyramine causes the release of norepinephrine, a strong vasoconstrictive agent, from the adrenal medulla and sympathetic neurons. Normally, norepinephrine is active for only a few milliseconds before it is inactivated by MAO. However, because MAO inhibitor drugs prevent inactivation of norepinephrine, ingesting tyramine-containing foods with an MAO inhibitor may produce severe hypertension or intracranial