stances, such as glucuronic acid or sulfate. With chronic administration, some drugs stimulate liver cells to produce larger amounts of drug-metabolizing enzymes (a process called *enzyme induction*). Enzyme induction accelerates drug metabolism because larger amounts of the enzymes (and more binding sites) allow larger amounts of a drug to be metabolized during a given time. As a result, larger doses of the rapidly metabolized drug may be required to produce or maintain therapeutic effects. Rapid metabolism may also increase the production of toxic metabolites with some drugs, (eg, acetaminophen). Drugs that induce enzyme production also may increase the rate of metabolism for endogenous steroidal hormones (eg, cortisol, estrogens, testosterone, and vitamin D). However, enzyme induction does not occur for 1 to 3 weeks after an inducing agent is started, because new enzyme proteins must be synthesized. Rifampin, an antituberculosis drug, is a strong inducer of CYP 1A and 3A enzymes

Metabolism also can be decreased or delayed in a process called *enzyme inhibition*, which most often occurs with concurrent administration of two or more drugs that compete for the same metabolizing enzymes. In this case, smaller doses of the slowly metabolized drug may be needed to avoid adverse reactions and toxicity from drug accumulation. Enzyme inhibition occurs within hours or days of starting an inhibiting agent. Cimetidine, a gastric acid suppressor, inhibits several CYP enzymes (eg, 1A2, 2C, and 3A) and can greatly decrease drug metabolism. The rate of drug metabolism also is reduced in infants (their hepatic enzyme system is immature), in people with impaired blood flow to the liver or severe hepatic or cardiovascular disease, and in people who are malnourished or on low-protein diets.

When drugs are given orally, they are absorbed from the GI tract and carried to the liver through the portal circulation. Some drugs are extensively metabolized in the liver, with only part of a drug dose reaching the systemic circulation for distribution to sites of action. This is called the *first-pass effect* or presystemic metabolism.

Excretion

Excretion refers to elimination of a drug from the body. Effective excretion requires adequate functioning of the circulatory system and of the organs of excretion (kidneys, bowel, lungs, and skin). Most drugs are excreted by the kidneys and eliminated unchanged or as metabolites in the urine. Some drugs or metabolites are excreted in bile, then eliminated in feces; others are excreted in bile, reabsorbed from the small intestine, returned to the liver (called *enterohepatic recirculation*), metabolized, and eventually excreted in urine. Some oral drugs are not absorbed and are excreted in the feces. The lungs mainly remove volatile substances, such as anesthetic gases. The skin has minimal excretory function. Factors impairing excretion, especially severe renal disease, lead to accumulation of numerous drugs and may cause severe adverse effects if dosage is not reduced.

Serum Drug Levels

A *serum drug level* is a laboratory measurement of the amount of a drug in the blood at a particular time (Fig. 2–5). It reflects dosage, absorption, bioavailability, half-life, and the rates of metabolism and excretion. A *minimum effective concentration (MEC)* must be present before a drug exerts its pharmacologic action on body cells; this is largely determined by the drug dose and how well it is absorbed into the bloodstream. A *toxic concentration* is an excessive level at which toxicity occurs. Toxic concentrations may stem from a single large dose, repeated small doses, or slow metabolism that allows the drug to accumulate in the body. Between these low and high concentrations is the therapeutic range, which is the goal of drug therapy—that is, enough drug to be beneficial, but not enough to be toxic.

For most drugs, serum levels indicate the onset, peak, and duration of drug action. When a single dose of a drug is given, onset of action occurs when the drug level reaches the MEC. The drug level continues to climb as more of the drug is absorbed, until it reaches its highest concentration and peak drug action occurs. Then, drug levels decline as the drug is eliminated (ie, metabolized and excreted) from the body. Although there may still be numerous drug molecules in the body, drug action stops when drug levels fall below the MEC. The duration of action is the time during which serum drug levels are at or above the MEC. When multiple doses of a drug are given (eg, for chronic, long-lasting conditions), the goal is usually to give sufficient doses often enough to maintain serum drug levels in the therapeutic range and avoid the toxic range.

In clinical practice, measuring serum drug levels is useful in several circumstances:

- When drugs with a low or narrow therapeutic index are given. These are drugs with a narrow margin of safety because their therapeutic doses are close to their toxic doses (eg, digoxin, aminoglycoside antibiotics, lithium, theophylline).
- To document the serum drug levels associated with particular drug dosages, therapeutic effects, or possible adverse effects.
- To monitor unexpected responses to a drug dose. This could be either a lack of therapeutic effect or increased adverse effects.
- When a drug overdose is suspected.

Serum Half-Life

Serum half-life, also called *elimination half-life*, is the time required for the serum concentration of a drug to decrease by 50%. It is determined primarily by the drug's rates of metabolism and excretion. A drug with a short half-life requires more frequent administration than one with a long half-life.

When a drug is given at a stable dose, four or five half-lives are required to achieve steady-state concentrations and develop equilibrium between tissue and serum concentra-