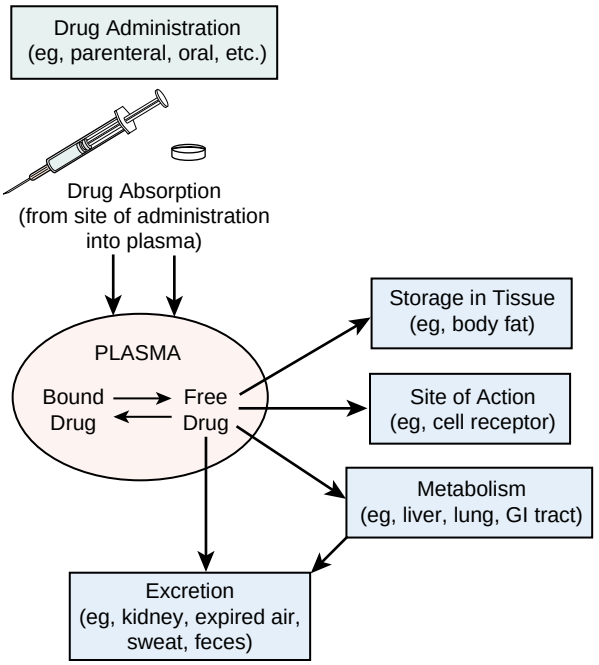

Figure 2–2 Entry and movement of drug molecules through the body to sites of action, metabolism, and excretion.

Distribution

Distribution involves the transport of drug molecules within the body. Once a drug is injected or absorbed into the bloodstream, it is carried by the blood and tissue fluids to its sites of pharmacologic action, metabolism, and excretion. Most drug molecules enter and leave the bloodstream at the capillary level, through gaps between the cells that form capillary walls. Distribution depends largely on the adequacy of blood circulation. Drugs are distributed rapidly to organs receiving a large blood supply, such as the heart, liver, and kidneys. Distribution to other internal organs, muscle, fat, and skin is usually slower.

An important factor in drug distribution is *protein binding* (Fig. 2–4). Most drugs form a complex with plasma proteins, mainly albumin, which act as carriers. Drug molecules bound to plasma proteins are pharmacologically inactive because the large size of the complex prevents their leaving the bloodstream through the small openings in capillary walls and reaching their sites of action, metabolism, and excretion. *Only the free or unbound portion of a drug acts on body cells.* As the free drug acts on cells, the decrease in plasma drug levels causes some of the bound drug to be released.

Protein binding allows part of a drug dose to be stored and released as needed. Some drugs also are stored in muscle, fat, or other body tissues and released gradually when plasma drug levels fall. These storage mechanisms maintain lower, more even blood levels and reduce the risk of toxicity. Drugs that are highly bound to plasma proteins or stored extensively in other tissues have a long duration of action.

Drug distribution into the central nervous system (CNS) is limited because the blood–brain barrier, which is composed of capillaries with tight walls, limits movement of drug molecules into brain tissue. This barrier usually acts as a selectively permeable membrane to protect the CNS. However, it also can make drug therapy of CNS disorders more difficult because drugs must pass *through* cells of the capillary wall rather than *between* cells. As a result, only drugs that are lipid soluble or have a transport system can cross the blood–brain barrier and reach therapeutic concentrations in brain tissue.

Drug distribution during pregnancy and lactation is also unique (see Chap. 67). During pregnancy, most drugs cross the placenta and may affect the fetus. During lactation, many drugs enter breast milk and may affect the nursing infant.

Metabolism

Metabolism is the method by which drugs are inactivated or biotransformed by the body. Most often, an active drug is changed into one or more inactive metabolites, which are

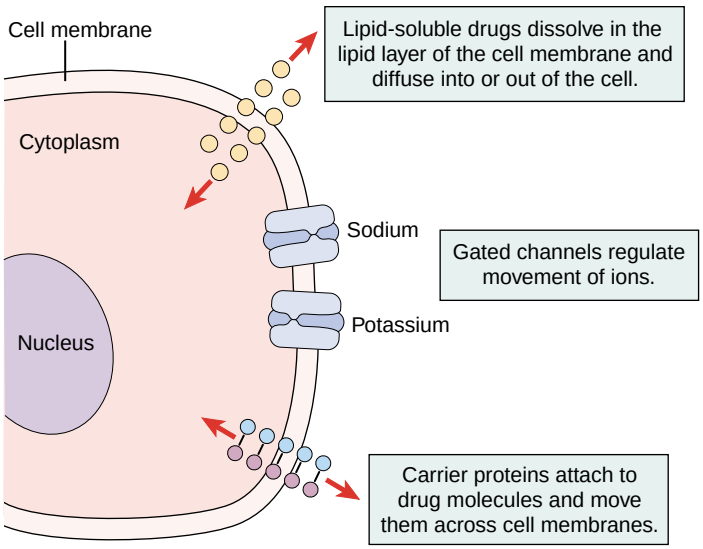

Figure 2–3 Drug transport pathways. Drug molecules cross cell membranes to move into and out of body cells by directly penetrating the lipid layer, diffusing through open or gated channels, or attaching to carrier proteins.