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movement of lipid-soluble drugs from the vehicle to the skin, but it may facilitate the movement of water-soluble drugs. Conversely, polyethylene glycol vehicles remove the perspiration and dehydrate the barrier, which decreases the permeability to drugs; such vehicles remove the aqueous medium through which water-soluble drugs may pass down into the stratum corneum but at the same time facilitate the transfer of lipid-soluble drugs from the vehicle to the skin.

Even in the absence of a vehicle, it is not clear what physicochemical properties of a drug favor cutaneous penetration, high lipid-solubility being a prerequisite, according to some authorities, and an ether–water partition coefficient of approximately one, according to others. Yet, the penetration of ethanol and dibromomethane are nearly equal, and other such enigmas exist. It is not surprising, then, that the effects of vehicles are not altogether predictable.

A general statement might be made that if a drug is quite soluble in a poorly absorbed vehicle, the vehicle will retard the movement of the drug into the skin. For example, salicylic acid is 100 times as permeant when absorbed from water than from polyethylene glycol and pentanol is 5 times as permeant from water as from olive oil. Yet, ethanol penetrates 5 times faster from olive oil than from either water or ethanol, all of which denies the trustworthiness of generalizations about vehicles.

Since the 1960s, there has been much interest in certain highly dielectric aprotic solvents, especially dimethyl sulfoxide (DMSO). Such substances generally prove to be excellent solvents for both water- and lipid-soluble compounds and for some compounds not soluble in either water or lipid solvents. The extraordinary solvent properties probably are due to a high polarizability and van der Waals bonding

other biological membranes by numerous drugs, including such large molecules as insulin. The mechanism is understood poorly. Such vehicles have a potential for many important uses, but they are at present only experimental, pending further investigations on toxicity.

From time to time, a claim is made that a new ingredient of a tablet or elixir enhances the absorption of a drug, and a comparison of plasma levels of the old and new preparations seems to support the claim. Upon further investigation, however, it may be revealed that the new so-called absorption adjuvant is replacing an ingredient that previously bound the drug or delayed its absorption; thus, the new "adjuvant" is not an adjuvant but rather it is only a nondeterrent.

Other Factors—A number of other less-well-defined factors affect the absorption of drugs, some of which may operate, in part, through factors already cited above. Disease or injury has a considerable effect upon absorption. For example, debridement of the stratum corneum increases the permeability to topical agents, meningitis increases the permeability of the blood–brain barrier, biliary insufficiency decreases the absorption of lipid-soluble substances from the intestine and acid–base disturbances can affect the absorption of weak acids or bases. Certain drugs, such as ouabain, that affect active transport processes may interfere with the absorption of certain other drugs. The condition of the *ground substance*, or "intracellular cement," probably bears on the absorption of certain types of molecules. Hyaluronidase, which depolymerizes the mucopolysaccharide ground substance, can be demonstrated to facilitate the absorption of some, but not all, drugs from subcutaneous sites.

Drug Disposition

The term *drug disposition* is used here to include all processes which tend to lower the plasma concentration of drug, as opposed to drug absorption, which elevates the plasma level. Consequently, the distribution of drugs to the various tissues will be considered under *Disposition*. Some authors use the term disposition synonymously with elimination, that is, to include only those processes which decrease the amount of drug in the body. In the present context, disposition comprises three categories of processes: distribution, biotransformation and excretion.

Distribution, Biotransformation and Excretion

The term *distribution* is self-explanatory. It denotes the partitioning of a drug among the numerous locations where a drug may be contained within the body. *Biotransformations* are the alterations in the chemical structure of a drug that are imposed upon it by the life processes. *Excretion* is, in a sense, the converse of absorption, namely, the transportation of the drug, or its products, out of the body. The term applies whether or not special organs of excretion are involved.

Distribution

The body may be considered to comprise a number of *compartments:* enteric (gastrointestinal), plasma, interstitial, cerebrospinal fluid, bile, glandular secretions, urine, storage vesicles, cytoplasm or intracellular space, etc. Some of these "compartments," such as urine and secretions, are open-ended, but since their contents relate to those in the closed compartments, they also must be included.

At first thought, it may seem that if a drug were distributed passively (ie, by simple diffusion) and the plasma concentration could be maintained at a steady level, the concentration of a drug in the water in all compartments ought to become equal. It is true that some substances, such as ethanol and antipyrine, are distributed nearly equally throughout the body water, but they are more the exception than the rule. Such substances are mainly small, uncharged, nondissociable, highly water-soluble molecules.

The condition of small size and high water solubility allows for passage through the pores without the necessity of carrier or active transport. Small size also places a limit on van der Waals binding energy and configurational complementariness, so that binding to proteins in plasma, or cells, is slight. The presence of a charge on a drug molecule makes for unequal distribution across charged membranes, in accordance with the Donnan distribution (see below). Dissociability causes unequal distribution when there is a pH differential between compartments, as discussed under *The pH Partition Principle* (see below). Thus, even if a drug is distributed passively, its distribution may be uneven throughout the body. When active transport into, or a rapid metabolic destruction occurs within, some compartments, uneven distribution is also inevitable.

The pH Partition Principle—An important consequence of nonionic diffusion is that a difference in pH between two compartments will have an important influence upon the partitioning of a weakly acidic or basic drug between those compartments. The partition is such that the un-ionized form of the drug has the same concentration in both compartments, since it is the form that is freely diffusible; the ionized form in each compartment will have the

concentration that is determined by the pH in that compartment, the pK and the concentration of the un-ionized form. The governing effect of pH and pK on the partition is known as the *pH partition principle*.

To illustrate the principle, consider the partition of salicylic acid between the gastric juice and the interior of a gastric mucosal cell. Assume the pH of the gastric juice to be 1.0, which it occasionally becomes. The pK_a of salicylic acid is 3.0 (Martin[10] provides one source of pK values of drugs). With the Henderson–Hasselbach equation (see page 242) it may be calculated that the drug is only 1% ionized at pH 1.0.* The intracellular pH of most cells is about 7.0. Assuming the pH of the mucosal cell to be the same, it may be calculated that salicylic acid will be 99.99% ionized within the cells. Since the concentration of the un-ionized form is theoretically the same in both gastric juice and mucosal cells, it follows that the total concentration of the drug (ionized + un-ionized) within the mucosal cell will be 10,000 times greater than in gastric juice. This is illustrated in Fig 35-11. Such a relatively high intracellular concentration can have important osmotic and toxicologic consequences.

Had the drug been a weak base instead of an acid, the high concentration would have been in the gastric juice. In the small intestine, where the pH may range from 7.5 to 8.1, the partition of a weak acid or base will be the reverse of that in the stomach, but the concentration differential will be less, because the pH differential from lumen to mucosal cells, etc, will be less. The reversal of partition as the drug moves from the stomach to the small intestine accounts for the phenomenon that some drugs may be absorbed from one gastrointestinal segment and returned to another. The weak base, atropine, is absorbed from the small intestine, but, because of pH partition, it is "secreted" into the gastric juice.

The pH partition of drugs has never been demonstrated to be as marked as that illustrated in Fig 35-11 and in the text. Not only do many drug ions probably pass through the pores of the membrane to a significant extent, but also some may pass through the lipid phase, as explained above for the morphinans and mecamylamine. Furthermore, ion-pair formation in carrier transport also bypasses nonionic diffusion. All processes that tend toward an equal distribution of drugs across membranes, and among compartments, will cause further deviations from theoretical predictions of pH partition.

Electrochemical and Donnan Distribution—A drug ion may be distributed passively across a membrane in accordance with the membrane potential, the charge on the drug ion and the Donnan effect. The relationship of the membrane potential to the passive distribution of ions is expressed quantitatively by the Nernst equation (Eq 7, page 709) and already has been discussed. Barring active transport, pH partition and binding, the drug will be said to be distributed according to the electrical gradient or to its "equilibrium" potential. If the membrane potential is 90 mv, the concentration of a univalent cation will be 30 times as high within the cell as without; if the drug cation is divalent, the ratio will be 890. The distribution of anions would be just the reverse. If the membrane potential is but 9 mv, the ratio for a univalent cation will be only 1.4 and for a divalent cation only 2.0. It, thus, can be seen how important membrane potential may be to the distribution of ionized drugs.

It was pointed out under *Membrane Potentials*, page 707, that large potentials derive from active transport of ions but that small potentials may result from Donnan distribution. Donnan membrane theory is discussed in Chapter 14. According to the theory, the ratio of the intracellular/extracellular concentration of a permeant univalent anion is equal to the ratio of extracellular/intracellular concentration of a permeant univalent cation. A more general mathematical expression that includes ions of any valence is

$$\left(\frac{A_i}{A_e}\right)^{1/Z_a} = \left(\frac{C_e}{C_i}\right)^{1/Z_c} = r \qquad (8)$$

where A_i is the intracellular and A_e the extracellular concentration of anion, Z_c is the valence of cation, Z_a is the valence of anion, C_i is the intracellular and C_e the extracellular concentration of cation and r is the Donnan factor. The value of r depends upon the average molecular weight and valence of the macromolecules (mostly protein) within the cell and the intracellular and extracellular volumes. Since the macromolecules within the cell are charged negatively, the cation concentration will be higher within the cell, that is, $C_i > C_e$. Since a Donnan distribution results in a membrane potential, the distribution of drug ion also will be in keeping with the membrane potential.

The Donnan distribution also applies to the distribution of a charged drug between the plasma and interstitial compartment, because of the presence of anionic proteins in the plasma. Eq 8 applies by changing the subscript i to p, for plasma, and e to i, for interstitial. The Donnan factor, r, for plasma–interstitial space partition is about 1.05:1.

Binding and Storage—Drugs frequently are bound to plasma proteins (especially albumin), interstitial substances, intracellular constituents and bone and cartilage. If binding is extensive and firm, it will have a considerable impact upon the distribution, excretion and sojourn of the drug in the body. Obviously, a drug that is bound to a protein or any other macromolecule will not pass through the membrane in the bound form; only the unbound form can negotiate among the various compartments.

The partition among compartments is determined by the binding capacity and binding constant in each compartment. As long as the binding capacity exceeds the quantity

* The relationship of ionization and partition to pH and pK has been formulated in several different ways, but the student may calculate the concentrations from simple mass law equations. More sophisticated calculations and reviews of this subject are available.[6,11–16]

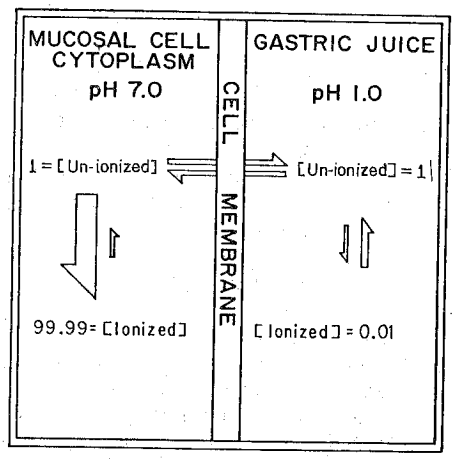

Fig 35-11. Hypothetical partition of salicylic acid between gastric juice and the cytoplasm of a gastric mucosal cell. It is assumed that the ionized form cannot pass through the cell membrane. The intragastric concentration of salicylic acid is arranged arbitrarily to provide unit concentration of the un-ionized form. *Bracketed values:*