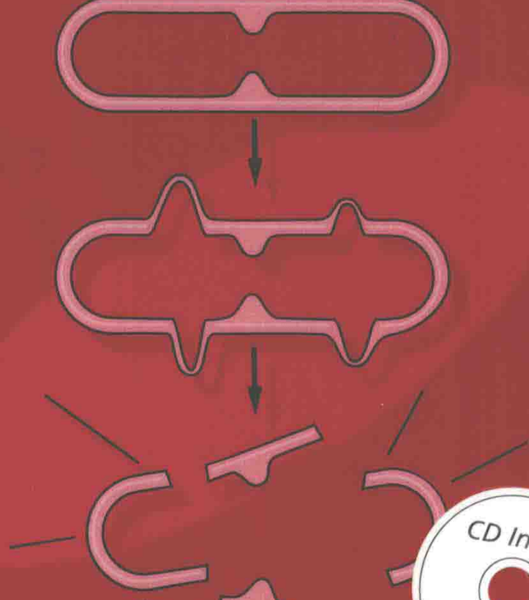
PDQ

PrettyDarnedQuick

Pharmacology

Second Edition

Gordon E. Johnson



CD Inside

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[*] *PDQ* (Pretty Darned Quick)

Writing the dedication for a book is never easy, particularly for a married man with six children. You know that each and everyone of them will be looking in this space to make sure that his or her name is here. So, to maintain our happy home, and pay all my political debts, I dedicate this book to:

Mary-Jane (wife, mother, and benevolent dictator)
Dorothy
Ian
Warren
Louise
Ted
and
Becky

However, the story does not end here, for I must also dedicate this book to the cascade of grandchildren who have tumbled into our lives. For it is to these 12 products of biotechnology that I owe my greatest debt. Thus, to Christina, Angela, Gillian, Megan, Kelsey, Sarah, Vanessa, Victoria, Renee, Graham (finally a boy!), Trevor, and Ryan, I dedicate this text. Who knows what drugs we may have by the time they are in a position to write their own books.

Preface

Pharmacology can be a most difficult subject to master. There appears to be so much to learn. Students can not be blamed if, overcome with the detail of individual drugs, they miss the basic concepts underlying the use of an entire group of agents. We encourage students to view our subject from a distance first, thus allowing an understanding of the basic principles of drug therapy before they commit to memory the properties of one drug after another. This is much easier said than done. It is hard to stand back and view the whole lake, if you are just learning to swim and are being swamped by each new swell. This book is intended to help beleaguered students, in danger of becoming "phagocytosed" by facts, rise above the field of battle and take a global view of complex topics. Only then can they return to the detail that is so important in correct drug use.

PDQ Pharmacology, is a small book. It is not intended to stand on its own. Rather, it is meant to complement a good general pharmacology text. Several excellent texts have been cited in this book. By the same token, this book should not be used as a substitute for a good undergraduate course in pharmacology.

If *PDQ Pharmacology*, is not intended to replace a recognized text or substitute for a course in pharmacology, how then should it be used? First, it can provide a valuable learning aid during the time the course is being taught. Filled with figures and tables selected to illustrate important principles of drug action, it will assist students to grasp the concepts that underlie groups of drugs before they are asked to concentrate on the properties unique to each agent. *PDQ Pharmacology*, can also assist students in reviewing pharmacology. In those last frantic hours prior to an examination, when students wish to review the entire course or require a rapid answer to an individual problem, *PDQ Pharmacology*, will fill the current void.

Gordon E. Johnson, PhD
March, 2002

Contents

Part 1 Principles of Medical Pharmacology

1

Drug Absorption, Distribution, and Elimination

CHARACTERISTICS OF DRUG MOVEMENT ACROSS MEMBRANES

Drugs are Dissolved in Body Fluids

Most drugs are either weak acids or weak bases. When dissolved in body fluids, they exist in both the **ionized** and **nonionized** forms. *The ionized form* is usually water soluble, or lipid insoluble, and does not diffuse readily throughout the body. *The nonionized form* is usually less water soluble and more lipid soluble. It is more likely to diffuse across lipid membranes (Figure 1–1).

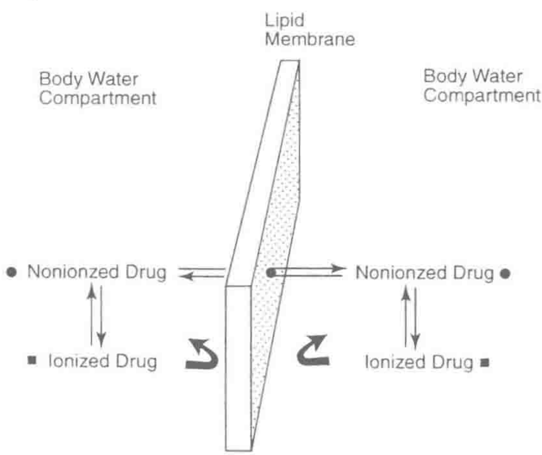

Figure 1–1 Diffusion of a drug across a lipid membrane. (After Johnson GE, Osis M, Hannah KJ. Pharmacology. In: Nursing Practice. Toronto (ON): W.B. Saunders, 1998.)

Ratio of C_i/C_n Drug Molecules

The ratio of ionized/nonionized (C_i/C_n) drug molecules depends on the pH of the environment and the pK_a of the drug in question.

Acids

$$HA \rightleftharpoons H^+ + A^-$$

	C_n	C_i
eg,	Salicylic Acid	Salicylate

When the pK_a of the drug = the pH of the media, then $C_i = C_n$.

Raising the pH has the effect of removing H^+ and driving the reaction to the right, therefore, increasing C_i. *Lowering the pH* has the effect of adding H^+ and driving the reaction to the left, therefore, increasing C_n.

Example: Salicylic acid has a pK_a of ~3.
At a pH of 3, $C_n = C_i$
At a pH < 3, $C_n > C_i$
At a pH > 3, $C_i > C_n$

Question: Would you expect salicylic acid to be mainly ionized or non-ionized in the stomach pH of 1?

Answer: Nonionized.

Bases

$$HB^+ \rightleftharpoons H^+ + B$$

	C_i	C_n
eg,	Morphine Sulfate	Morphine

When the pK_a of the drug = the pH of the media, then $C_i = C_n$.

Raising the pH has the effect of removing H^+ and driving the reaction to the right, therefore, increasing C_n. *Lowering the pH* has the effect of adding H^+ and driving the reaction to the left, therefore, increasing C_i.

Example: Morphine has a pK_a of ~ 8.
At a pH of 8, $C_n = C_i$
At a pH < 8, $C_i > C_n$
At a pH > 8, $C_n > C_i$

Question: Would you expect morphine to be mainly ionized or non-ionized in the stomach pH of 1?

Answer: Ionized.

OVERVIEW OF ABSORPTION, DISTRIBUTION, AND ELIMINATION OF DRUGS IN THE BODY (FIGURE 1–2)

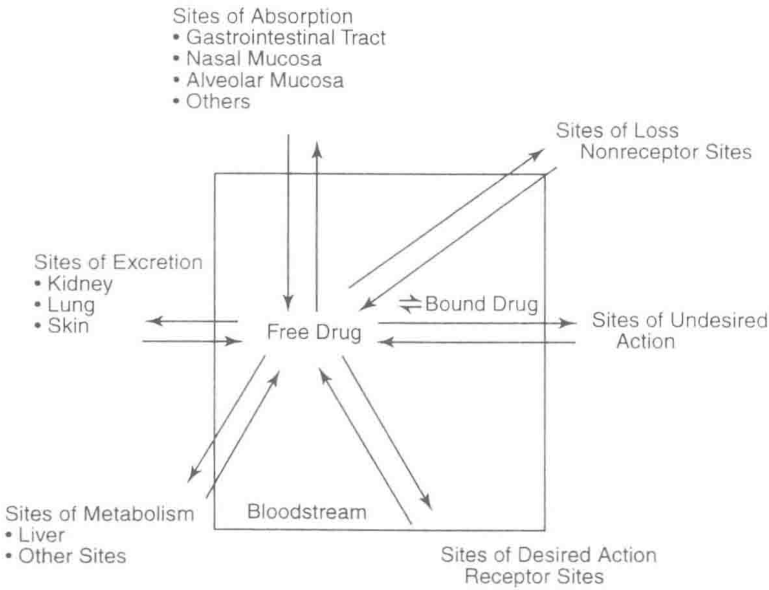

Figure 1–2 Characteristics of drug movement across membranes. (After Morgan JP. Alcohol and drug abuse, curriculum guide for pharmacology faculty. Rockville, MD: U.S. Department of Health and Human Services, 1985:3.)

ROUTES OF DRUG ADMINISTRATION

Sublingual

Drugs are absorbed through the oral mucosa. May be useful if a drug

1. irritates the stomach,
2. is destroyed in the stomach, or
3. is inactivated during its first pass through the liver.

Only an appropriate method of administration for a drug that

1. dissolves rapidly in saliva,
2. does not irritate the oral mucosa, and
3. is lipophilic.

Oral

1. Drugs are absorbed from the stomach and the duodenum.
2. Drug absorption is better from the duodenum because of its larger absorbing surface.
3. The stomach can absorb acidic drugs and weakly basic drugs.

For a drug to be absorbed from the stomach or the duodenum, it must

1. be dissolved in the gastrointestinal (GI) tract,
2. have at least 1 molecule in 500 nonionized, and
3. have nonionized molecules with sufficient lipid solubility to pass through the GI mucosa.

Rectal

Drugs are administered rectally for a systemic effect if

1. they are irritating to the stomach,
2. the patient is nauseated,
3. the patient is too young or old to take the drug orally, or
4. a sustained effect is desired (of less value today because of the development of sophisticated sustained-release oral and topical products).

Drugs are also administered rectally for a local effect, such as the treatment of proctitis or hemorrhoids.

Parenteral

Intravenous — immediate effect, danger of overdose.

Intramuscular — if the drug is dissolved in an aqueous media, absorption occurs rapidly; if the drug is administered as a suspension, absorption is prolonged.

Subcutaneous — absorption is almost as rapid as the intramuscular injection of a drug dissolved in an aqueous preparation.

Inhalation

For a systemic effect — effect starts immediately.

For a local effect — acts on the bronchioles.

DRUG DISTRIBUTION IN THE BODY

Initially

Drugs are carried in largest amounts to the most richly perfused tissues, such as the adrenals, brain, heart, lungs, kidneys, and muscles.

Later

Drugs then undergo redistribution within the body, being retained in tissues for which they have affinity, for example, in fat for lipophilic drugs (Figure 1–3).

Plasma Protein Albumin

Drug molecules may be bound to plasma proteins in the bloodstream, usually albumin. While bound to plasma proteins, drug molecules are inactive because they cannot leave the vascular system and enter the tissues. Once the level of free drug in the plasma falls, bound drug molecules diffuse off the plasma proteins in order to maintain a constant bound/free ratio (Figure 1–4).

Blood-Brain Barrier

Brain capillary endothelial cells have no pores to allow diffusion. In addition, glial connective tissue is attached to the basement membrane of cap-

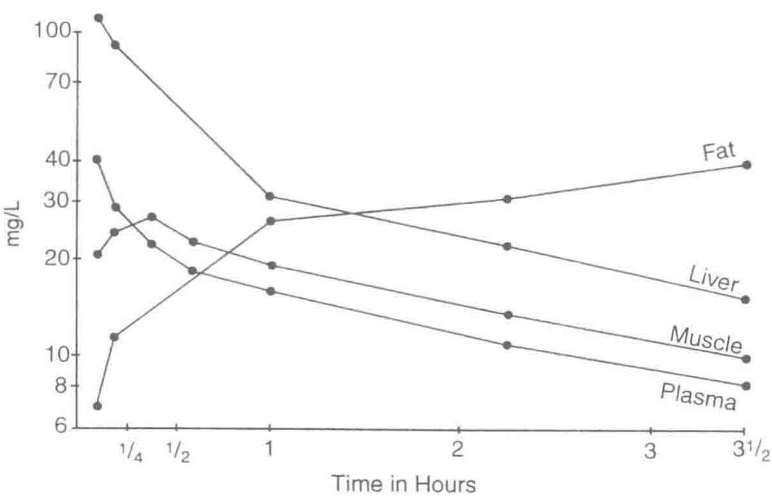

Figure 1–3 Time distribution of thiopental in a dog. Note the high levels found initially in the liver and the muscle, and the subsequent redistribution to fat. (After Brodie BB. Distribution and fate of drugs: therapeutic implications. In: Binns TB, ed. Absorption and distribution of drugs. Edinburgh: E and S Livingston, 1964:246.)

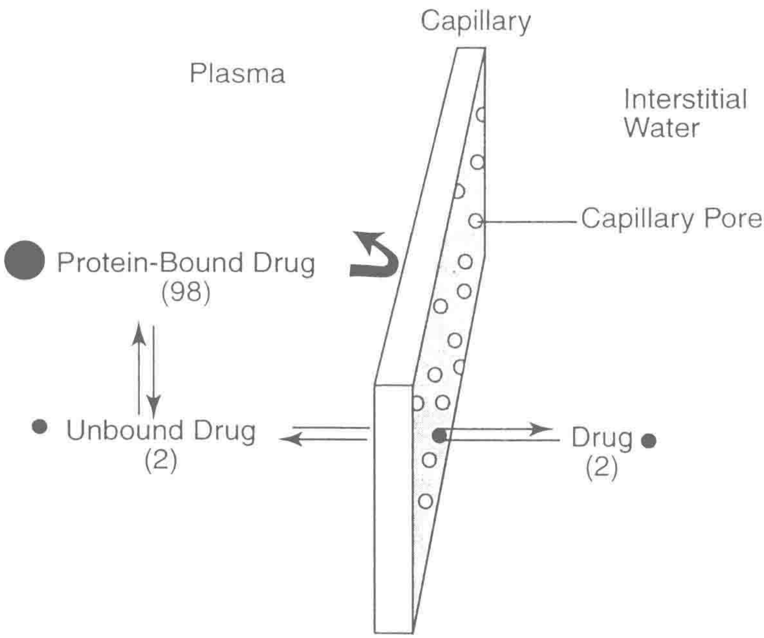

Figure 1–4 Schematic representation of the diffusion of a drug, which is 98% bound to plasma protein, across a capillary. (After Johnson GE, Osis M, Hannah KJ. Pharmacology. In: Nursing Practice. Toronto (ON): W.B. Saunders, 1998.)

illary endothelium. Together, these structural modifications are called the blood-brain barrier. Ionized molecules cannot enter the brain. Nonionized molecules, not bound to plasma proteins, enter the brain easily (Figure 1–5) because they are lipid soluble and can pass through the blood-brain barrier.

Placental Transfer Of Drugs

The mature placenta contains a network of maternal blood sinuses that interface with villi that carry the fetal capillaries. Drugs cross the placenta primarily by simple diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Placental transfer occurs less readily with drugs possessing a high degree of dissociation or low lipid solubility. The view that the placenta is a barrier to drugs is not correct. The fetus is, to at least some extent, exposed to essentially all drugs taken by the mother (Figure 1–6).

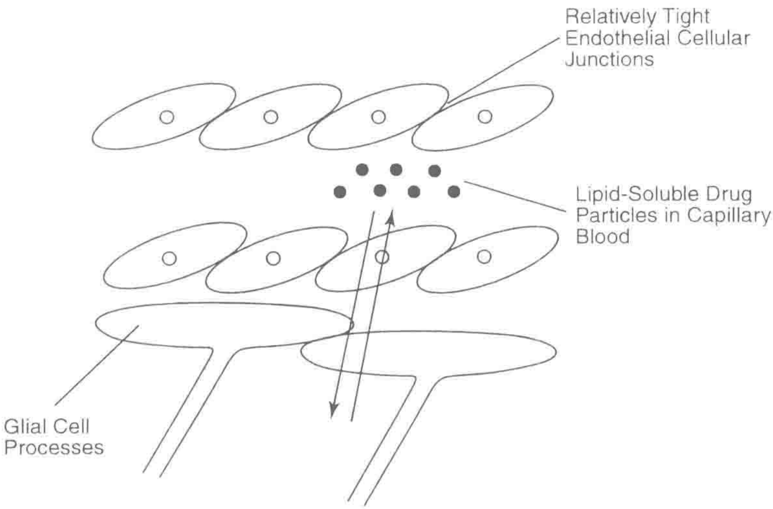

Figure 1–5 Blood-brain barrier. (After Morgan JP. Alcohol and drug abuse, curriculum guide for pharmacology faculty. Rockville, MD: U.S. Department of Health and Human Services, 1985:3.)

DRUG ELIMINATION

Renal Excretion

Drugs are filtered, secreted, and reabsorbed by the kidneys (Figure 1–7).

Filtration: All drugs not bound to plasma proteins are filtered.

Secretion: Some acidic and basic drugs are secreted. This is an active process with transport maxima. Drugs that are secreted usually have short half-lives.

Reabsorption: Drug reabsorption from the renal tubules depends on the percentage of the drug in the nonionized form. Nonionized drug molecules are usually reabsorbed into the systemic circulation. Ionized molecules are not reabsorbed.

Metabolism

Kidneys cannot eliminate lipophilic drug molecules. Lipophilic drugs must first be transformed into ionized, or water-soluble, molecules before the kidney can excrete them. This process is referred to as drug metabolism. Although drug metabolism can occur in most tissues, the liver is the major organ involved in this process. Drug metabolism should not be equated with

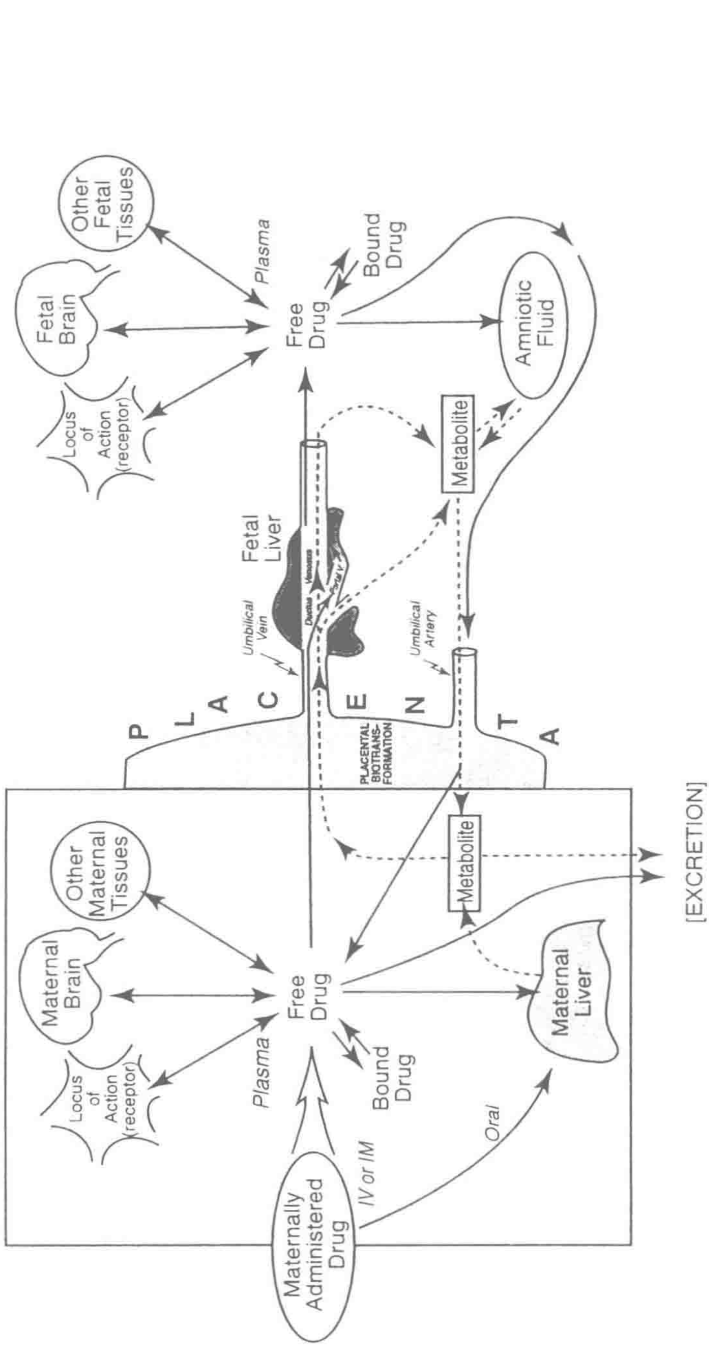

Figure 1–6 Drug distribution in a model of the maternal-placental-fetal unit. (After Mirkin BL. Drug distribution in pregnancy. In: Boreus L, ed. Fetal pharmacology. New York: Raven Press, 1972:22.)