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Lippincott 's Illustrated Reviews

Pharmacology

Lippincott图解

药 理 学

2nd edition

Mary J. Mycek
Richard A. Harvey
Pamela C. Champe

（英文影印版）

中国协和医科大学出版社

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Preface

Who will find this book useful

Lippincott's Illustrated Reviews: Pharmacology integrates and summarizes the essentials of medical pharmacology for (1) students in the health-related professions who are preparing for licensure examination [for example, the United States Medical Licensure Examination (USMLE) Step 1], and (2) professionals who wish to review or update their knowledge in this rapidly expanding area of biomedical science. The *Illustrated Review* uses an information-intensive, outline format along with summary figures and practice questions to teach this complex material.

How to use this book

OUTLINE TEXT *Lippincott's Illustrated Reviews: Pharmacology* uses a unique expanded outline format which allows the rapid review and assimilation of facts and concepts. The current knowledge in the field of medical pharmacology has been "predigested" and the relevant information has been recast in a hierarchical organization. Important topics are shown in bold print, whereas the names of drugs are featured in an italic typeface. This organization enables the reader to readily scan a page to locate specific information or to find a particular drug. A phonetic pronunciation guide for drug names assures that the reader will have a conversational familiarity with the therapeutic agents described in the book. Each chapter starts with a chart that lists and classifies the drugs to be discussed in that chapter. This permits the reader to immediately understand and remember the significant relationships among the facts and concepts.

ILLUSTRATIONS *Lippincott's Illustrated Reviews:Pharmacology* contains more than 400 original illustrations, each carefully crafted to compliment and amplify the text. This volume features a new kind of diagram in which pharmacologic processes are illustrated with a blend of graphics and explanations. This marriage of words and art allows the reader to integrate a body of knowledge without the distraction of constantly shifting from text to illustrations. For example, to sort out the intricacies of neurotransmitter synthesis and release in an ordinary textbook would require repeated skipping from text to figures. By contrast, the *Illustrated Review* (see for example, Figure 4.3, p.37) reveals the major steps and their significance at a glance.

CROSS-REFERENCES WITHIN THIS BOOK *Lippincott's Illustrated Review:Pharmacology* not only permits the easy assimilation of pharmacologic facts and concepts but also provides an extensive network of more than 400 cross-references to other relevant information in the volume. Thus, when readers encounter a new block of information, they are immediately directed by page citations to related material that reinforces and expands the original information. This elaborate matrix of references provides a cross fertilization that increases learning and retention. The student ends up with the "the big picture."

CROSS-REFERENCES TO OTHER BOOKS IN THE SERIES A unique feature of this volume is the large number of references to *Lippincott's Illustrated Reviews: Biochemistry*, which is the biochemistry volume in the Lippincott series. Designated as InfoLink references, they are located at the end of each chapter. This permits a reader with an interest in learning additional information related to a particular topic to readily locate relevant material covered in the biochemistry review. InfoLink also emphasizes the interrelationships between these biomedical disciplines—a skill that is increasingly being tested by the USMLE, Step I.

QUESTIONS AND ANSWERS A total of more than 200 practice questions (of the types used by the National Board of Medical Examiners and other standardized test writers) are included at the end of each chapter so that readers can check their progress in mastering the material. Answers with explanations are provided so that the reader knows both the correct answer and also why the distractors in the multiple choice questions are incorrect. These answers and their explanations are juxtaposed with the original questions in a special section at the end of the book. Thus readers can confirm the correct answers to a group of study questions without the disorientation of flipping from page to page.

FINDING INFORMATION An extensive index of more than 4000 entries permits the reader to instantly locate specific information. The index includes commonly used trade-names of drugs.

Readers should thumb through this carefully coordinated review of therapeutically useful agents . . . . they may be surprised that learning pharmacology can be so enjoyable!

Acknowledgments

We are grateful to the many friends and colleagues who generously contributed their time and effort to help us make this book as accurate and as useful as possible. We would like to acknowledge the contributions of Drs. Zigmund Kaminski, Edward J. Flynn, Lester A Sultatos, Uri Lopatin and Kafui DeMasio who provided many helpful comments. We would particularly like to express our thanks to Dr. Bruce Fisher whose clinical insights and suggestions were invaluable in clarifying confusing concepts. We highly value the additional support of our other colleagues at Robert Wood Johnson Medical School and in New Jersey Medical School. We (RAH and PCC) owe a special thanks to our Chairman, Dr. Masayori Inouye, who has encouraged us in this and other teaching projects. We would also like to thank Dr. Victor Gruber, the Director of the National Medical School Review, for sharing his insights into educational mechanisms for effectively integrating the biomedical sciences.

Without talented artists, an Illustrated Review would be impossible, and we have been particularly fortunate in working with Michael Cooper throughout this project. His artistic sense and computer graphics expertise have greatly added to our ability to bring alive pharmacology "stories" for our readers. We also wish to thank Jo Gershman, who was a contributing artist.

The editors and production staff of the Lippincott William & Wilkins were a constant source of encouragement and discipline. We particularly want to acknowledge the tremendously helpful, supportive, creative contributions of our editor, Richard Winters, whose imagination and positive attitude helped us out of the valleys. Final editing and assembly of the book has been greatly enhanced through the efforts of Janet Greenwood and Mary Beth Murphy. Finally, the authors give thanks to Drs. Marilyn Schorin and Sewell Champe for their unfailing personal and professional support of this project, and to the late John Mycek for his encouragement.

Lippincott's Illustrated Reviews: Pharmacology

2nd edition

Contents

Absorption, Distribution, and Elimination of Drugs

1

I. OVERVIEW

The aim of drug therapy is to prevent, cure, or control various disease states. To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic, yet nontoxic levels are obtained. The clinician must recognize that the speed of onset of drug action, the intensity of the drug's effect, and the duration of the drug action are controlled by four fundamental pathways of drug movement and modification in the body (Figure 1.1). First, drug absorption from the site of administration permits entry of the therapeutic agent (either directly or indirectly) into plasma (input). Second, the drug may then reversibly leave the blood stream and distribute into the interstitial and intracellular fluids (distribution). Third, the drug may be metabolized by the liver, kidney, or other tissues. Finally, the drug and its metabolites are eliminated from the body (output) in urine, bile, or feces. Chapters 1 and 2 describe how knowledge of these processes influences the clinician's decision as to the route of administration, drug loading, and dosing interval.

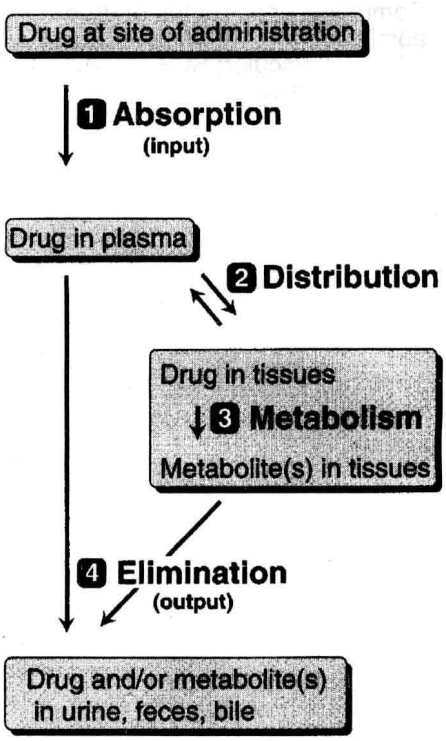

Figure 1.1
Schematic representation of drug absorption, distribution, metabolism and elimination.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined primarily by the properties of the drug (such as water or lipid solubility, ionization, etc.) and by the therapeutic objectives (for example, the desirability of a rapid onset of action or the need for long-term administration or restriction to a local site). There are two major routes of drug administration, enteral and parenteral. (Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration.)

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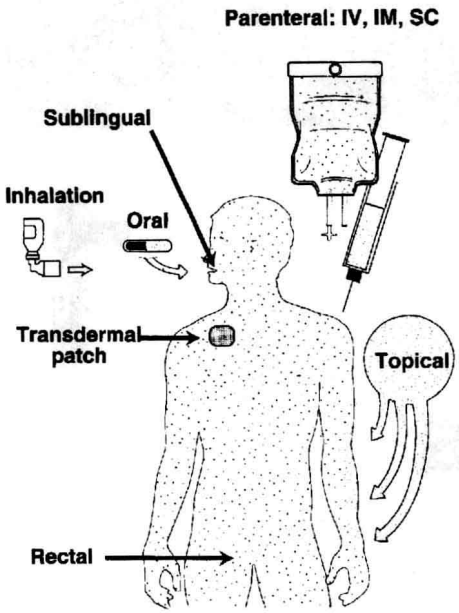

Figure 1.2
Commonly used routes of drug administration. (IV=intravenous; IM=intramuscular; SC= subcutaneous).

A. Enteral

1. **Oral:** Giving a drug by mouth is the most common route of administration, but it is also the most variable, and requires the most complicated pathway to the tissues. Some drugs are absorbed from the stomach; however, the duodenum is often the major site of entry to the systemic circulation because of its larger absorptive surface. [Note: Most drugs absorbed from the gastrointestinal (GI) tract enter the portal circulation and encounter the liver before they are distributed in the general circulation (Figure 1.3). First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than 90% of *nitroglycerin* is cleared during a single passage through the liver.] Ingestion of drugs with food can influence absorption. The presence of food in the stomach delays gastric emptying time so that drugs that are destroyed by acid, for example, *penicillin*, become unavailable for absorption (see p. 302). [Note: Enteric coating of a drug protects it from the acidic environment and may prevent gastric irritation. Depending on the formulation, the release of the drug may be prolonged, producing a sustained-release preparation.]

2. **Sublingual:** Placement under the tongue allows the drug to diffuse into the capillary network and therefore to enter the systemic circulation directly. Administration of an agent by this route has the advantage that the drug bypasses the intestine and liver and is not inactivated by metabolism.

3. **Rectal:** Fifty percent of the drainage of the rectal region bypasses the portal circulation; thus the biotransformation of drugs by the liver is minimized. Both the sublingual and the rectal routes of administration have the additional advantage that they prevent the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally or if the patient is already vomiting. [Note: The rectal route also is commonly used to administer antiemetic agents.]

B. Parenteral

Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal (GI) tract, and for agents such as *insulin* that are unstable in the GI tract. Parenteral administration is also used for treatment of unconscious patients and under circumstances that require a rapid onset of action. Parenteral administration provides the most control over the actual dose of drug delivered to the body. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each has its advantages and drawbacks.

1. **Intravascular:** Intravenous (IV) injection is the most common parenteral route. For drugs that are not absorbed orally, there is often no other choice. With IV administration, the drug avoids the GI tract and, therefore, first-pass metabolism by the liver. This route permits a rapid effect and a maximal degree of control over the circulating levels of the drug. However, unlike drugs present in the GI tract, those that are injected cannot be recalled by

strategies such as emesis or binding to activated charcoal. Intravenous injection of some drugs may introduce bacteria through contamination, induce hemolysis, or cause other adverse reactions by the too rapid delivery of high concentrations of drug to the plasma and tissues. Therefore, the rate of infusion must be carefully controlled. Similar concerns apply to intra-arterially (IA) injected drugs.

2. **Intramuscular (IM):** Drugs administered intramuscularly can be aqueous solutions or specialized depot preparations—often a suspension of drug in a nonaqueous vehicle, such as ethylene glycol or peanut oil. Absorption of drugs in aqueous solution is fast, whereas that from depot preparations is slow. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. An example is sustained-release *haloperidol decanoate* (see p. 130), whose slow diffusion from the muscle produces an extended neuroleptic effect.

3. **Subcutaneous (SC):** This route of administration, like that of IM injection, requires absorption and is somewhat slower than the IV route. SC injection minimizes the risks associated with intravascular injection. [Note: Minute amounts of *epinephrine* are sometimes combined with a drug to restrict its area of action. *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.] Other examples of drugs utilizing SC administration include solids such as silastic capsules containing the contraceptive *levonorgestrel* that are implanted for long-term activity (see p. 268), and also programmable mechanical pumps that can be implanted to deliver *insulin* in some diabetics.

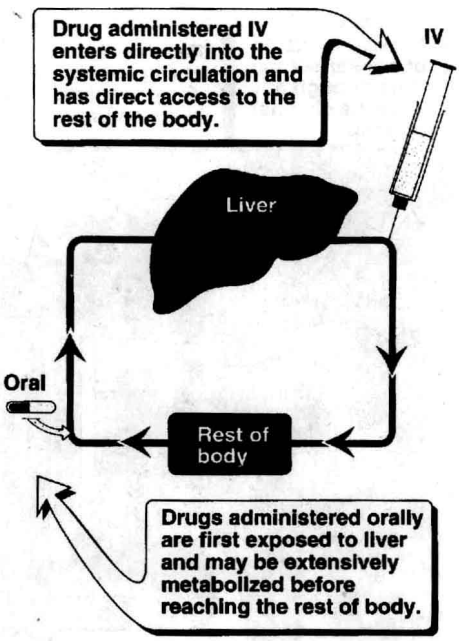

Figure 1.3
First-pass metabolism can occur with orally administered drugs. (IV = intravenous).

C. Other

1. **Inhalation:** Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as by intravenous injection. This route of administration is used for drugs that are gases (for example, some anesthetics), or those that can be dispersed in an aerosol. The route is particularly effective and convenient for patients with respiratory complaints (for example, asthma or chronic obstructive pulmonary disease) as drug is delivered directly to the site of action and systemic side effects are minimized (see p. 219).

2. **Intranasal:** *Desmopressin* is administered intranasally in the treatment of diabetes insipidus; salmon *calcitonin*, a peptide hormone used in the treatment of of osteoporosis, is available as a nasal spray. The abused drug, *cocaine*, is generally taken by sniffing.

3. **Intrathecal/Intraventricular:** It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid (CSF), such as *methotrexate* in acute lymphocytic leukemia (see p. 379).

4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* (see p. 343) is applied as a

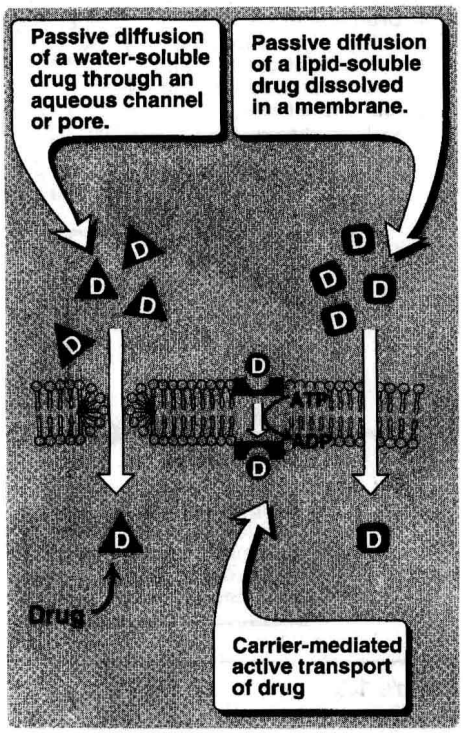

Figure 1.4
Schematic representation of drugs crossing cell membrane of epithelial cell of gastrointestinal tract.

cream directly to the skin in the treatment of dermatophytosis, and *atropine* (see p. 47) is instilled directly into the eye to dilate the pupil and permit measurement of refractive errors.

5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly depending upon the physical characteristics of the skin at the site of application. This route is most often used for the sustained delivery of drugs, such as the antianginal drug, *nitroglycerin* (see p. 175).

III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the blood stream. The rate and efficiency of absorption depend on the route of administration. For intravenous delivery, absorption is complete, that is, the total dose of drug reaches the systemic circulation. Drug delivery by other routes may result in only partial absorption and thus lower bioavailability. For example, the oral route requires that a drug dissolve in the gastrointestinal fluid and then penetrate the epithelial cells of the intestinal mucosa; disease states or the presence of food may affect this process.

A. Transport of drug from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by either passive diffusion or active transport.

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments, that is, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Lipid-soluble drugs readily move across most biological membranes, whereas water-soluble drugs penetrate the cell membrane through aqueous channels (Figure 1.4).

2. **Active transport:** This mode of drug entry involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate (see Figure 1.4). It is capable of moving drugs against a concentration gradient, that is, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels when binding to the enzyme is maximal.[1]

B. Effect of pH on drug absorption

Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a H^+ causing a charged anion (A^-) to form:[2]

[1,2]See p. 16 for Infolink references to other books in this series.

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

Weak bases (BH^+) can also release a H^+; however, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B).

$$BH^+ \rightleftarrows B + H^+$$

1. **Passage of an uncharged drug through a membrane:** A drug passes through membranes more readily if it is uncharged (Figure 1.5). Thus, for a weak acid, the uncharged HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the pK_a (Figure 1.6). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the stronger the acid. Conversely, the higher the pK_a, the stronger the base.] Distribution equilibrium is achieved when the permeable form of drug achieves an equal concentration in all body water spaces. Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.

2. **Determination of how much drug will be found on either side of a membrane:** The relationship of pK_a and the ratio of acid-base concentrations to pH is expressed by the Henderson-Hasselbalch equation[3]:

$$pH = pK_a + \log \frac{[\text{non-protonated species}]}{[\text{protonated species}]}$$

$$\text{For acids: } pH = pK_a + \log \frac{[A^-]}{[HA]}$$

$$\text{For bases: } pH = pK_a + \log \frac{[B]}{[BH^+]}$$

This equation is useful in determining how much drug will be found on either side of a membrane that separates two compartments that differ in pH, for example, stomach (pH 1.0 to 1.5) and blood plasma (pH 7.4). [Note: The lipid solubility of the nonionized drug directly determines its rate of equilibration.]

C. Physical factors influencing absorption

1. **Blood flow to the absorption site:** Blood flow to the intestine is much greater than the flow to the stomach; thus absorption from the intestine is favored over that from the stomach. [Note: Shock

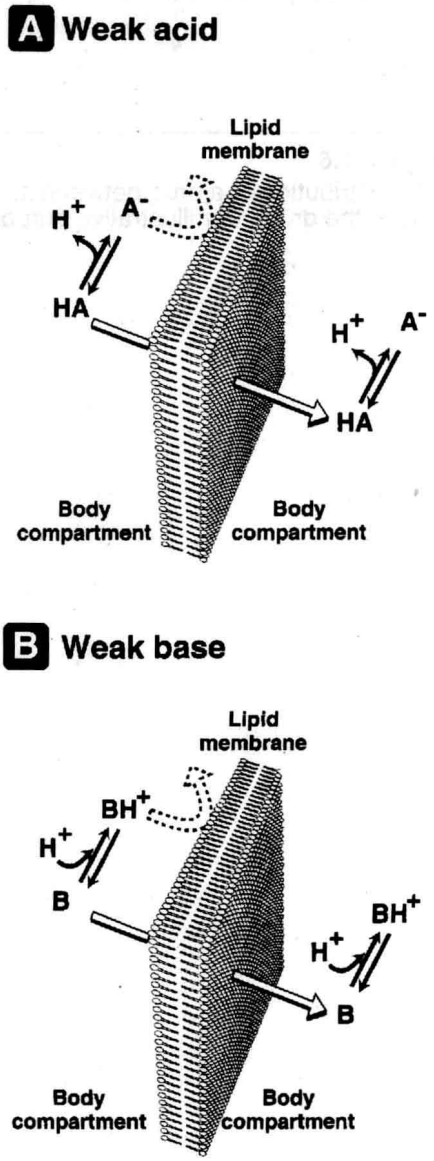

Figure 1.5
A. Diffusion of non-ionized form of a weak acid through lipid membrane; B. Diffusion of non-ionized form of a weak base through lipid membrane.

[3]See p. 16 for Infolink references to other books in this series.

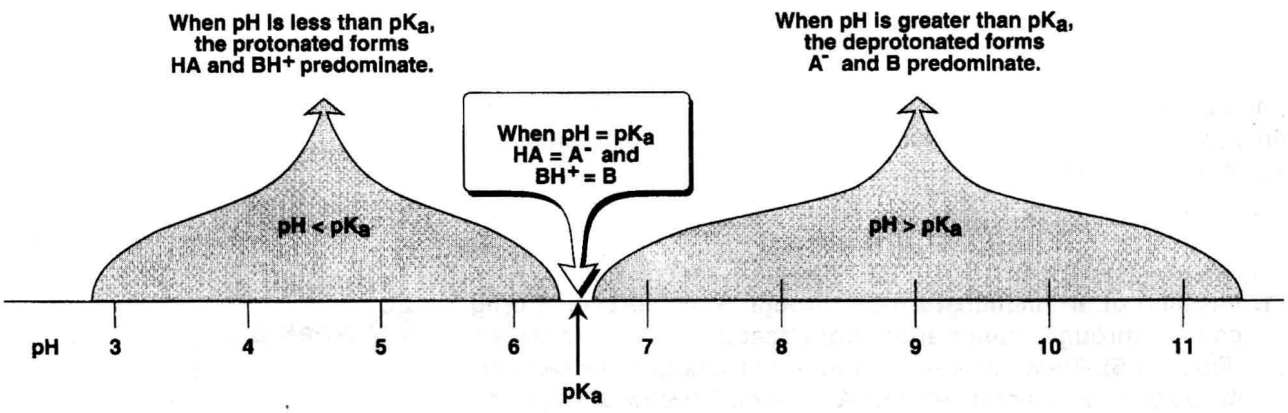

Figure 1.6
The distribution of a drug between its ionized and un-ionized form depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

severely reduces blood flow to cutaneous tissues, thus minimizing the absorption from subcutaneous administration.]

2. **Total surface area available for absorption:** Because the intestine has a surface rich in microvilli, it has a surface area about 1,000 times that of the stomach; thus absorption of the drug across the intestine is more efficient.

3. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions) prolongs gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

IV. BIOAVAILABILITY

Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form. For example, if 100 mg of a drug is administered orally and 70 mg of this drug is absorbed unchanged, the bioavailability is 70%.

A. Determination of bioavailability

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels achieved by IV injection, in which all of the agent enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plot-