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Integrated Pharmacology

整合药理学

（第2版）

MARK KESTER · KENT E. VRANA
KELLY D. KARPA

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（第2版）

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出版说明

知识整合是当前医学教育改革的一项重要内容。目前国内基础医学各门课程的教材基本上是以学科为单位单独编写的，缺乏学科之间知识的联系。为了推动医学教育改革，借鉴国外医学教材的编写模式，北京大学医学出版社经过充分调研，引进出版了世界著名医学出版集团Elsevier公司的“Integrated”系列教材。

在编写上，该系列书最大的特色就是在保持本学科知识体系完整的同时插入大量的“整合框”。这些“整合框”出现在需要链接到其他学科相关知识的位置，每个学科都有独特的标识。例如在《病理学》的细胞损伤一节，讲述缺氧时，会插入一个“生物化学整合框”，介绍生物化学中糖酵解的知识；在感染一节，出现NK细胞的时候，会插入一个“免疫学整合框”，介绍免疫学中NK细胞的知识；在凝血一节，则是插入一个“临床医学整合框”，介绍临床上凝血的实验室评估方面的知识……这些分布在各本书中的“整合框”，把各学科之间知识点连接起来，不但方便了读者学习，更是体现了学科整合的理念。

该系列书包括：

●整合生理学 ●整合病理学

●整合药理学 ●整合生物化学

●整合遗传学 ●整合免疫学与微生物学

该系列书可作为国内医学生整合课程教材、双语教学教材及来华留学生教材，也有利于医学教师拓展知识，方便备课；同时也是美国医师执照考试的优秀参考用书。

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To my past, present, and future: Lee and Allen Kester, Karen Kester, and Johanna and Saul Kester.

MK

To my best friend, confidante, and wife, Sheila, and the two reasons I do what I do—Caroline and Erin.

KEV

To Karl, Kyle, and Kieri – the three most important reasons that I "do" drugs (pharmacology).

KDK

Finally, to Professor Elliott Saul Vesell (founding Chair of Penn State Pharmacology), for putting the "art" in pharmacology.

Series Preface

How to Use This Book

The idea for Elsevier's Integrated Series came about at a seminar on the USMLE Step 1 Exam at an American Medical Student Association (AMSA) meeting. We noticed that the discussion between faculty and students focused on how the exams were becoming increasingly integrated—with case scenarios and questions often combining two or three science disciplines. The students were clearly concerned about how they could best integrate their basic science knowledge.

One faculty member gave some interesting advice: "read through your textbook in, say, biochemistry, and every time you come across a section that mentions a concept or piece of information relating to another basic science—for example, immunology—highlight that section in the book. Then go to your immunology textbook and look up this information, and make sure you have a good understanding of it. When you have, go back to your biochemistry textbook and carry on reading."

This was a great suggestion—if only students had the time, and all of the books necessary at hand, to do it! At Elsevier we thought long and hard about a way of simplifying this process, and eventually the idea for Elsevier's Integrated Series was born.

The series centers on the concept of the integration box. These boxes occur throughout the text whenever a link to another basic science is relevant. They're easy to spot in the text—with their color-coded headings and logos. Each box contains a title for the integration topic and then a brief summary of the topic. The information is complete in itself—you probably won't have to go to any other sources—and you have the basic knowledge to use as a foundation if you want to expand your knowledge of the topic.

You can use this book in two ways. First, as a review book . . .

When you are using the book for review, the integration boxes will jog your memory on topics you have already covered. You'll be able to reassure yourself that you can identify the link, and you can quickly compare your knowledge of the topic with the summary in the box. The integration boxes might highlight gaps in your knowledge, and then you can use them to determine what topics you need to cover in more detail.

Second, the book can be used as a short text to have at hand while you are taking your course . . .

You may come across an integration box that deals with a topic you haven't covered yet, and this will ensure that you're one step ahead in identifying the links to other subjects (especially useful if you're working on a PBL exercise). On a simpler level, the links in the boxes to other sciences and to clinical medicine will help you see clearly the relevance of the basic science topic you are studying. You may already be confident in the subject matter of many of the integration boxes, so they will serve as helpful reminders.

At the back of the book we have included case study questions relating to each chapter so that you can test yourself as you work your way through the book.

Online Version

An online version of the book is available on our Student Consult site. Use of this site is free to anyone who has bought the printed book. Please see the inside front cover for full details on Student Consult and how to access the electronic version of this book.

In addition to containing USMLE test questions, fully searchable text, and an image bank, the Student Consult site offers additional integration links, both to the other books in Elsevier's Integrated Series and to other key Elsevier textbooks.

Books in Elsevier's Integrated Series

The nine books in the series cover all of the basic sciences. The more books you buy in the series, the more links that are made accessible across the series, both in print and online.


Anatomy and Embryology


Histology


Neuroscience


Biochemistry


Physiology


Pathology


Immunology and Microbiology


Pharmacology


Genetics

Acknowledgments

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And to Madelene Hyde, who joined the team as we finished this project.

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To Ms. Elaine Neidigh and Ms. Vicki Condran for administrative and secretarial assistance.

To all of the above, we offer our heartfelt gratitude and appreciation that you can all work so well with such difficult personalities as ours.

Preface

It's all about integration. In fact, integration is essential for the study of pharmacology. Practitioners must consider mechanisms of action, adverse effects, and contraindications for any given drug to ensure proper and safe use by patients. Crucial to these considerations is a thorough understanding of the biochemistry, physiology, and anatomy of the targets affected by the drug. Thus, the overarching concept of the Elsevier Integrated Review series is to consider each basic science discipline within the overall context of all the other basic sciences. The foundation of clinical medicine requires that all basic sciences be integrated across disciplines. To facilitate this important learning paradigm, we have created Integration Boxes in this second edition of the text that highlight an essential pharmacologic principle that can be dramatically reinforced with information from another basic or clinical science discipline. This mode of learning facilitates deeper understanding and more complete memory of the concept.

It's also all about forging a team. Frequently, pharmacology is taught only by basic research-based scientists. We have taken a different and more dynamic approach. The team behind Elsevier's Integrated Review Pharmacology is composed of basic science researchers and educators as well as pharmacists and clinicians. It is our concept that integration must occur not only between "-ologies," but also between practitioners who prescribe, dispense, and create drugs. In this way, basic research scientists, with one voice, can effectively describe mechanisms of action for a drug, the clinician can highlight adverse effects, and the pharmacist can discuss potential interactions with other drugs and/or alternative/complementary medicines. These coordinated interactions among PhDs, MDs, and PharmDs are now the core of Penn State College of Medicine's clinically relevant and organ-based pharmacology curriculum.

It is also about voice—one consistent voice. Each chapter reflects the input of each of the three authors, reflecting an integration of basic, clinical, and pharmaceutical sciences. Each chapter includes Top 5 Lists of important concepts and case-based learning questions that reinforce the Integration Boxes.

It is also about "new and improved." Since the first edition was published, more than 100 new drug entities have come to market. More importantly, over the last several years, we have seen a revolution in pharmacologic agents. With the advent of "biologics," or genetically engineered drugs, the promise of personalized and targeted therapies is closer at hand. The second edition of Elsevier's Integrated Review Pharmacology highlights these new pharmacologic options.

It's also about color. To facilitate reinforcement of key concepts, we use a go (green) and stop (red) strategy in all our Integration Boxes and Figures. That is, if a drug turns off (antagonist) a receptor or enzyme, it is set in a red (actually purple) oval; if a drug activates (agonist) the receptor or enzyme, it is set in a green oval. In addition, we use a large red "X" to denote specifically where a drug inhibits a signaling cascade.

In the end, it's all about the students. Elsevier's Integrated Review Pharmacology provides students a rich tapestry from which to draw conclusions about specific drug classes. Detailed information is provided for major drugs in each of the classes. More importantly, this book provides students with the tools necessary to deal with the myriad new drugs that are presently moving through pharmaceutical drug evaluation "pipelines" or are first being contemplated or discovered by academic or industrial scientists. For the student, it should be more than just memorization of every minor adverse side effect for each and every drug. It's really about applying the principles of pharmacology to evaluate and assess the usefulness and effectiveness of new drugs as they come to market. Indeed, a core competency for the health care professional of the twenty-first century is to become a lifelong learner. We hope that we have provided the pharmacologic foundation for such an educational journey.

Mark Kester, PhD
Kent E. Vrana, PhD
Kelly D. Karpa, PhD, RPh

Editorial Review Board

Contents

Pharmacokinetics 1

CONTENTS

Pharmacokinetics is all about delivery—drug delivery, that is—ensuring that an optimal concentration of drug reaches its specific target. Obstacles to drug delivery include absorption, metabolism, elimination, and distribution of drug to other body compartments. In the end, it all boils down to a dynamic equilibrium—balancing a drug's absorption and distribution with its metabolism and elimination.

A complete understanding of any drug must take into account the mechanism of action, potential side effects, and interactions with other drugs. To fully understand how drugs work, practitioners (this includes physicians, pharmacists, nurses, and physician assistants) must know the general pharmacokinetic and pharmacodynamic characteristics of the prescribed drug to maximize therapeutic benefits and avoid toxicity. Pharmacokinetic principles covering the integrated processes of drug absorption, distribution, metabolism (biotransformation), and excretion cooperatively determine the drug concentration at the receptor site. Pharmacodynamic mechanisms determine how drug/receptor molecular interactions produce pharmacologic effects by altering intracellular signaling mechanisms (see Chapter 2).

Simply put, pharmacology is the science that studies the effects of drugs on the body (Table 1-1). A drug is any substance that alters the structure or function of living organisms. A poison is any substance that irritates, damages, or impairs the body's tissues. It is worth noting that all drugs, if given in large enough doses, have the potential to be toxic because all drugs are associated with some adverse effects. Thus the practitioner is responsible for hitting the bull's eye or, in pharmacology language, the therapeutic window—a concentration of drug at the active site that exerts a biologic response without exerting a toxic effect. The underlying principles of drug therapy can be reduced to four key statements:

- The intensity and duration of drug action depend on the time course of drug concentration at the receptor.
- Optimal steady-state drug concentration must be maintained at receptor sites to sustain the pharmacologic effect.
- Practitioners control these drug concentrations through selection of appropriate dose, dosage interval, and route of drug administration.
- The physical properties and mathematical models that determine drug absorption, distribution, metabolism, and excretion ultimately are responsible for drug/drug interactions and potential toxic side effects.

Pharmacokinetics can be reduced to mathematical equations, which determine the transit of the drug throughout the body, a net balance sheet from absorption and distribution (in) to metabolism and excretion (out). By understanding these mathematical equations, practitioners are able to determine optimal dosing for patients with impaired or altered mechanisms of absorption, metabolism, or excretion resulting from diet, genetics, environment, disease, allergy, behavior, and other drugs (prescription, nonprescription, and complementary or alternative medicines). Together, these complicating issues are known as *host factors* and represent the interface of environment, genetics, and pharmacology.

ABSORPTION

Absorption is the process of delivering a drug into the bloodstream. Drugs can be administered by a variety of routes: orally (PO), intravenously (IV), intramuscularly (IM), rectally

TABLE 1-1. Pharmacology Terminology

TERM	DEFINITION
Pharmacology	The study of drugs and their effects on the body
Drug	Any substance that alters the structure or function of a living organism
Poison	Any substance that irritates, damages, or harms tissues
Pharmacokinetics	The study of the rates and movements of drugs through the body
Absorption	The process of getting a drug from its site of delivery into the bloodstream
Distribution	The process of getting a drug from the bloodstream to the tissue where its actions are needed
Biotransformation	Conversion of a drug molecule to a more water-soluble form
Elimination	The process of removing a drug from the body

(PR), topically, and via inhalation. Ultimately, to exert systemic effects, drugs must reach the vasculature. Unexpected alterations in absorption can significantly affect therapeutic goals, and certainly there are pros and cons associated with each route of administration, which will be discussed. The general physical principles that govern the rate of absorption, regardless of the route by which the drug was administered, are passive diffusion, concentration gradients, lipid solubility, drug ionization, size of the drug, and dosage form of the drug.

For a drug to be absorbed—to enter the bloodstream—the drug must cross biologic barriers. For orally administered drugs, barriers include the epithelial cells lining the gut and the endothelial cells of the vasculature. Most drugs move down their concentration gradients from an area of high concentration to an area with a lower drug concentration. This movement, called *passive diffusion*, requires no energy expenditure but does depend on the size (molecular weight) of the drug and the lipid solubility of the drug. Most drugs cross biologic barriers by passive diffusion.

On the other hand, a few drugs cross biologic barriers using active transport mechanisms. In this case, the drug moves "uphill" against its concentration gradient—from an area of low concentration to an area with higher concentration. This type of transport requires energy expenditure, typically adenosine triphosphate. Some ions, vitamins, and amino acids are absorbed in this way.

For drugs that are absorbed by passive diffusion, the lipid solubility of the drug is a key determinant for predicting how well the drug will be absorbed. Drugs that are lipid soluble easily pass through the lipid bilayer of cell walls. As a general rule, the more carbon atoms and the fewer oxygen atoms a drug has, the more lipid soluble the drug is. However, the problem with lipid solubility is that a drug must be *lipid soluble* (hydrophobic) enough to pass through cell membranes but *water soluble* (hydrophilic) enough to dissolve in aqueous fluids (gastric juice, bloodstream). If a drug is too water soluble, it will not penetrate cell membranes. An example of an extremely water-soluble class of drugs is the aminoglycoside antibiotics. When used to treat systemic infections, aminoglycosides must be given IV because the drugs are not absorbed when administered PO. On the other hand, drugs such as phenytoin and griseofulvin are so lipid soluble that it is difficult for these agents to dissolve in aqueous media. Because of the need to be both lipid soluble and water soluble simultaneously, most drugs are administered as either weak acids or weak bases (i.e., a molecule that fluctuates between charged and uncharged states at physiologic pH).

PHYSIOLOGY

Fick's Law of Diffusion

Fick's law of diffusion states that, in a steady state of diffusion, the flux of a substance is proportional to the concentration gradient in the system. To be precise,

$$J = -DA\frac{\Delta c}{\Delta x}$$

where J is the net flux (rate of diffusion), D is the diffusion coefficient, A is the area available for diffusion, and $\Delta c/\Delta x$ is the concentration gradient. This equation concerns moving from areas of high drug concentration to areas of lower drug concentration.

Ionization

Weak acids and weak bases exist in solution as a mixture of ionized and un-ionized forms. Ionized drugs are poorly lipid soluble and do not readily cross lipid membranes, but they dissolve well in aqueous media. Un-ionized drugs, on the other hand, are highly lipid soluble and readily cross biologic membranes. Hence, the transfer of drug across a biologic barrier is proportional to the concentration gradient of the un-ionized form across the membrane; this is known as the *degree of ionization*. The ratio of ionized versus un-ionized fraction of drug depends on the pK_a (ionization constant) of the drug and the pH of the surrounding tissues or fluids. See Box 1-1 for an example.

Box 1-1. EFFECT OF pH ON THE IONIZATION OF SALICYLIC ACID (pKa = 3)

When pH = 1 99% of salicylic acid is un-ionized
When pH = 2 90.9% of salicylic acid is un-ionized
When pH = 3 50% of salicylic acid is un-ionized*
When pH = 4 9.09% of salicylic acid is un-ionized
When pH = 5 0.99% of salicylic acid is un-ionized
When pH = 6 0.10% of salicylic acid is un-ionized

*By definition, the pKa of a drug is the pH at which 50% of the drug is ionized and 50% is un-ionized.

Box 1-2. EXAMPLES OF DRUGS BEST ABSORBED IN AN ACIDIC ENVIRONMENT

Aspirin	Iron
Calcium carbonate	Ketoconazole
Digoxin	Vitamin B_{12}

When the pH of the solution is below the pK_a, acids are preferentially un-ionized and bases are mostly ionized. On the other hand, when the pH of a solution is higher than the pK_a, acids are mostly ionized and bases are mostly un-ionized.

These principles may be illustrated in a different manner; in biochemistry, the following notation is often used to indicate the ionization status of weak acids:

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

In an acidic environment, such as the stomach, the weak acid, A^-, accepts a proton and becomes un-ionized. Therefore, in an acidic environment, an acidic drug is likely to be uncharged and thus preferentially absorbed. Alternatively, in an alkaline environment, acidic drugs are more likely to remain ionized and relative absorption is reduced. However, it should be realized that even though this generalization suggests that weak acids are preferentially absorbed at low pH, there is still relatively little, if any, absorption in the acidic environment of the stomach, an organ not suited for absorption. The stomach is mostly a storage depot for drugs rather than an organ for drug absorption. Thus the rate of gastric emptying into the intestines greatly affects the overall rate of absorption. Most drugs are absorbed in the intestines. The small intestines have the greatest capacity for absorption, because villi and microvilli markedly increase the absorptive surface area. The proximal areas of the small intestines (duodenum) primarily absorb drugs that are weak acids because of the acidic pH of stomach secretions. See Box 1-2 for examples of drugs that are best absorbed in an acidic environment.

Ammonia, NH_3, is an example of a weak base.

$$NH_3 + H^+ \rightleftharpoons NH_4^+$$

In contrast to weak acids, when a weak base is in an acidic environment and picks up a proton, the compound becomes ionized and, in this example, ammonium ion is preferentially formed. An alkaline drug is un-ionized in a high pH environment (such as in the small intestines) and thus more likely to be absorbed in this alkaline environment. The distal portions of the small intestines predominately absorb drugs that are weak bases because of the alkalinity of bile secretions. The key point to remember is that a weak acid is most likely to be absorbed when in an acidic environment, and an alkaline drug is preferentially absorbed in an alkaline environment. Even though weak acids are preferentially absorbed in acidic environments, they will still be absorbed, albeit to a lesser extent, in the proximal portion of the small intestines because of the large surface area designed for absorption (villi, microvilli).

BIOCHEMISTRY

The Henderson-Hasselbach Equation

The Henderson-Hasselbach equation states that there is a relationship between the pH of a solution and the relative concentrations of an acid and its conjugate base in that solution. Recall that the pKa (or ionization constant) is numerically equivalent to the pH of the solution when the molar concentrations of an acid and its conjugate base are equal.

Biochemists express this as the log ratio of protonated over unprotonated. In pharmacologic terms, this translates to:

$$\text{For acids (A): } \log \frac{A^-}{HA}\left(\frac{\text{unprotonated}}{\text{protonated}}\right) = pH - pKa$$

$$\text{For bases (B): } \log \frac{B}{BH^+}\left(\frac{\text{unprotonated}}{\text{protonated}}\right) = pH - pKa$$

For acids, the protonated form is unchanged and is the denominator. This is the more permeable chemical form. In contrast, for bases the protonated form is charged and is the denominator. However, this is the less permeable chemical form. In practical terms, this means that acids are preferentially absorbed under acidic conditions (pH below the pKa), whereas bases are preferentially absorbed at alkaline pH (higher than their pKa).

Molecular Weight

Absorption is slow for drugs that are large in size or that possess "bulky" or oxygenated side chain groups. Most drugs are 250 to 450 Da in size and can readily cross membranes.

Dosage Form

Many drugs are available in multiple dosage forms. The formulation of a drug affects the drug's absorption and onset of action. Consider, for example, an orally administered drug that is available as a tablet, a capsule, a liquid suspension, and a liquid solution. To be absorbed, the solid tablet must disintegrate into small particles, which must then dissolve into aqueous gastrointestinal fluids. On the other hand, drugs that are formulated into capsules can skip the disintegration step because capsules contain drugs that are already in small particle form. A drug suspension contains even smaller particles than capsules. With liquid formulations, the drug has already been dissolved. Hence, drugs that are available as liquid formulations are absorbed faster than drugs that are suspensions, suspensions are absorbed more rapidly than capsules, and capsules are absorbed more rapidly than tablets (Fig. 1-1).

Routes of Administration

The enteral (relating to the alimentary canal) route of administration is the safest, most economical, and most convenient way of administering drugs. Orally, sublingually, and rectally administered medications are in this category.

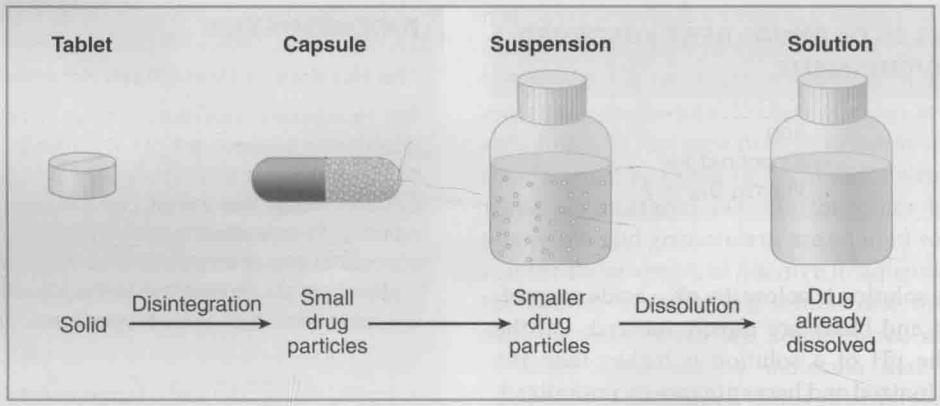

Figure 1-1. Disintegration and dissolution characteristics of various dosage forms.

ANATOMY

Drug Absorption

The first-pass effect is a major mechanism that determines the ultimate concentration of a drug in the plasma. Based solely on the anatomy of the body, drugs absorbed beyond the oral cavity are transported to the liver via the portal vein, where most drugs are metabolized to less active metabolites. After metabolism in the liver, drug metabolites are transported to the systemic circulation by the hepatic vein.

Sublingual and Oral

Medications that are administered sublingually dissolve under the tongue, without chewing or swallowing. Absorption is very quick, and higher drug levels are achieved in the bloodstream by sublingual routes than by oral routes because (1) the sublingual route avoids first-pass metabolism by the liver (Fig. 1-2), and (2) the drug avoids destruction by gastric juices or complexation with foods. Remember that drugs absorbed from the gut travel first to the liver via the portal vein. Drugs absorbed through the intestine may, thus, reach systemic circulation at a concentration significantly below the initial dose. The keys to understanding drug absorption are highlighted in Box 1-3.

Ideally, for a drug to be delivered sublingually, the drug should dissolve rapidly, produce desired therapeutic effects with small amounts of drug, and be tasteless. Examples of commonly prescribed sublingual tablets include nitroglycerin, loratadine, mirtazapine, and rizatriptan (Table 1-2).

Some diseases alter rates of drug absorption. For example if gastrointestinal motility is dramatically increased, as in inflammatory bowel diseases (Crohn disease, ulcerative colitis) or malabsorptive syndromes (celiac sprue), absorption of some drugs may be reduced (Table 1-3). On the other hand, absorption of other drugs may be increased in patients with these inflammatory gut disorders, because gastrointestinal membranes often do not remain intact as a consequence of these autoimmune diseases. Alternatively, consider situations in which gastrointestinal motility is slowed (i.e., diabetic gastroparesis). Here, drug absorption could be enhanced as a result of prolonged contact time with the absorptive areas of the intestine. Likewise, there are drugs that alter the rate of absorption for other orally administered medications (Table 1-4).

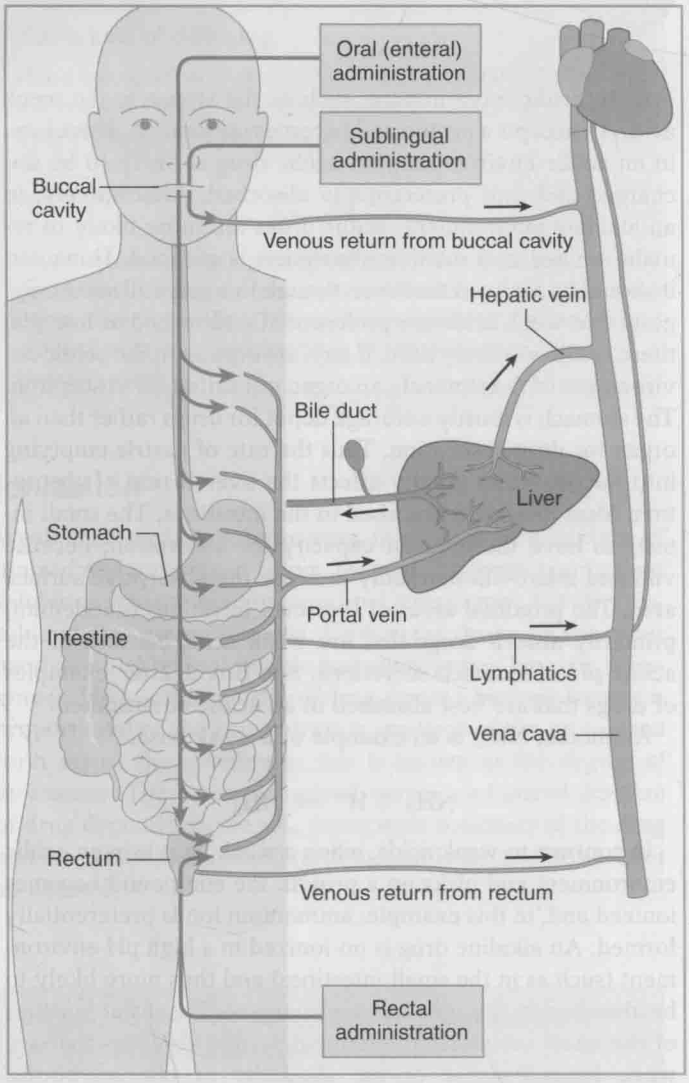

Figure 1-2. Drugs administered sublingually and rectally avoid first-pass metabolism in the liver.

Food can also affect absorption of drugs by either increasing, decreasing, or delaying the rate at which absorption occurs (Table 1-5). As a generalization, food tends to slow the

Box 1-3. KEYS TO DRUG ABSORPTION

- The biochemical properties of a drug determine the optimal route of administration.
- Optimal absorption of weak acids/bases depends on the pH of the gastrointestinal tract or surrounding environment.
- Gastrointestinal disease can affect the absorption of drugs.

TABLE 1-2. Drugs Commonly Prescribed Sublingually

DRUG	USE
Loratadine	Allergies
Mirtazapine	Anxiety
Nitroglycerin	Angina
Rizatriptan	Migraine headache

TABLE 1-3. Effect of Intestinal Disease on Drug Absorption

DISEASE	ABSORPTION INCREASED	ABSORPTION DECREASED
Celiac sprue	Aspirin Cephalexin Clindamycin Erythromycin Propranolol Sulfamethoxazole Trimethoprim	Acetaminophen Amoxicillin Penicillin V
Crohn disease	Clindamycin Propranolol Sulfamethoxazole Trimethoprim	Acetaminophen Cephalexin Methyldopa Metronidazole

TABLE 1-4. Drug Effects That Alter Absorption

EFFECT	DRUG
Changes in gastric or intestinal pH	H_2 blockers, antacids, proton pump inhibitors
Changes in gastrointestinal motility	Laxatives, anticholinergics, metoclopramide
Changes in gastrointestinal perfusion	Vasodilators
Interference with mucosal function	Neomycin, colchicine
Chelation	Tetracycline, calcium, magnesium, aluminum
Resin binding	Cholestyramine
Adsorption	Charcoal*

*Note that the final example is administered deliberately to alter drug absorption. The remainder display altered absorption as a side effect.

rate of gastric emptying. This results in slower absorption of many drugs. For this reason, drugs are often administered on an empty stomach—to increase absorption. However, if drugs are irritating to the gastrointestinal tract, a light, nonfatty meal may be recommended. There are other reasons to consider giving drugs with or without food. For example, penicillin V should be administered on an empty stomach (1 hour before meals or 2 to 3 hours after meals) because it is unstable in gastric acids. On the other hand, metoprolol and propranolol (β-blockers) should be taken with meals because food enhances their bioavailability. Although the oral route of administration is the most common, there are a few instances in which the oral route of administration should not be used (Box 1-4).

Rectal

Sometimes drugs are administered rectally via suppository or enema. Absorption from the rectum is erratic and unpredictable because the rectum contains no microvilli. In addition, most drugs irritate the rectum. However, rectal administration can be useful in patients who are unconscious or vomiting or in those with severe inflammatory bowel disease. An additional

TABLE 1-5. Effect of Food on Absorption of Selected Drugs

REDUCED ABSORPTION	DELAYED ABSORPTION	INCREASED ABSORPTION
Ampicillin Aspirin Atenolol Captopril Hydrochlorothiazide Tetracyclines Iron Levodopa Penicillamine Sotalol Warfarin	Acetaminophen Aspirin Cephalosporins Sulfonamides Diclofenac Digoxin Furosemide Valproate	Carbamazepine Diazepam Griseofulvin Labetalol Metoprolol Propranolol Nitrofurantoin

Box 1-4. WHEN TO AVOID GIVING DRUGS ORALLY

- If the drug causes nausea and vomiting
- If the patient is currently vomiting
- If the patient is unwilling or unable to swallow (e.g., child, mentally handicapped, unconscious)
- If the drug is destroyed by digestive enzymes (e.g., insulin)
- If the drug is not absorbed through the gastric mucosa (e.g., aminoglycosides)
- If the drug is rapidly degraded (e.g., lidocaine)

benefit of this route of administration is that the first-pass effect of the liver is avoided because a portion of the rectal blood supply (inferior and middle hemorrhoidal veins) bypasses hepatic portal circulation.

Parenteral

The parenteral routes of administration include any routes that bypass the gastrointestinal tract entirely. The IV route of administration is the quickest way to get a drug to its site of action, so IV drugs are of the greatest value during emergencies when speed is vital. Advantages and disadvantages of IV drug administration are found in Boxes 1-5 and 1-6.

IM and SC administrations are not affected by first-pass hepatic metabolism, but both routes of administration are directly affected by blood flow at the site of injection. Exercise, activity, and massage at the injection site increase blood flow, which speeds drug absorption by allowing drug contact with vasodilated capillaries.

Relatively large volumes of solution can be administered IM with less pain or irritation than SC injections. This route is particularly useful for lipophilic substances. IM aqueous solutions are typically absorbed within 10 to 30 minutes, although depot formulations have been designed for some drugs that promote gradual absorption over a prolonged period. Drugs administered SC are absorbed slightly more slowly than drugs administered IM. Patients are more likely to be able to give themselves SC injections (e.g., insulin) than to self-administer medications by any other parenteral route.

In the event of an overdose after IM or SC injections, absorption may be reduced by immobilizing the limb, applying ice, administering a vasoconstrictive agent (e.g., epinephrine), or applying a tourniquet.

Other examples of parenteral administration options are listed in Table 1-6.

Box 1-5. ADVANTAGES OF INTRAVENOUS ADMINISTRATION

- Drug immediately enters circulation
- Drug is rapidly distributed to tissues
- Rapid response
- Permits instant dosage titration
- Useful if drug is destroyed by gastric contents or heavily metabolized by the first-pass effect
- Allows maintenance of constant blood levels
- Large quantities can be administered for a long time
- Reduced irritation because of diluting/buffering by blood
- Always available (unconscious patients)

Box 1-6. DISADVANTAGES OF INTRAVENOUS ADMINISTRATION

- Once injected, the drug cannot be removed
- Injections given too rapidly can cause serious reactions if too much drug arrives at organs as a concentrated solution (respiratory, circulatory failure)
- Not suited for easy self-administration
- Must use sterile technique
- Discomfort with drug administration
- Irritation, allergy, overdoses difficult to manage

Inhalation

Anesthetic gases, metered-dose inhalers, and dry-powder inhalers all deliver drugs to the lungs. The smaller the particle size of the drug, the more likely the drug will reach the alveoli. Inhaled glucocorticoids and β-adrenergic agonists are often given to directly affect bronchial and alveolar targets, thus achieving efficacy with minimal systemic effects. However, it should be remembered that a proportion of inhaled drugs still reaches the systemic circulation.

Mucous Membranes

Several drugs are administered topically to mucous membranes of the eye, nose, throat, and vagina. Although typically only local effects are desired, some level of systemic drug absorption does occur through mucous membranes. In fact, some vaginal estrogen products are specifically formulated to provide systemic effects. Likewise, undesired systemic side effects can occur from drug administration to mucous membranes, such as when ocular β-blockers aggravate asthma or when nasally delivered corticosteroids contribute to osteoporosis, cataracts, or elevated intraocular pressure.

TABLE 1-6. Additional Parenteral Routes of Administration and Rationale for Use

SITE OF ADMINISTRATION	RATIONALE (EXAMPLE)
Intra-arterial	Local perfusion of an organ (cancer chemotherapy, radiocontrast agent)
Bone marrow (burn patients)	Other sites inaccessible
Intradermal	Allergy testing
Intracardiac	Emergency treatment of cardiac arrest
Intraperitoneal	Home dialysis; some ovarian cancer treatment protocols

Topical

In general, absorption through the skin is extremely slow. Absorption can be increased by incorporating drugs into fatty, lipid-soluble vehicles such as lanolin, by rubbing the application site to increase blood flow, or by applying a keratolytic (e.g., salicylic acid) to reduce the keratin layer. Drugs applied topically may be used either for their local effects (e.g., hydrocortisone) or for systemic effects (e.g., nitroglycerin, scopolamine, estrogen, nicotine). The latter examples are available as *transdermal* formulations and are time released.

DISTRIBUTION

The process of translocating drugs from the bloodstream into the tissues is referred to as *distribution*. The apparent volume of distribution (Vd) describes the area of the body to which drugs are distributed and may be defined as the fluid volume required to contain all the drug in the body at the same concentration observed in the blood. The Vd may be calculated by dividing the total amount of drug in the body by the initial concentration of drug in the plasma (e.g., C_0 or plasma concentration at time zero). Remember, Vd assumes that the concentration of drug is the same in all locations throughout the body (which is not always true). Mathematically, Vd (in liters) is equivalent to

$$\frac{\text{Dose (mg)}}{\text{Concentration (mg/L)}}$$

Another way to think about Vd is that it is equal to the amount of space in the body that a drug needs to fill up. It should in no way be confused or associated with any particular physiologic compartment. In many cases, the volume of distribution is normalized to body weight and will then be expressed as units of liters per kilogram.

Vascularity is the most important determinant of distribution. After all, very little drug can be distributed to an area of the body that gets minute amounts of blood flow. Frankly, most drugs are not uniformly distributed. Drugs are typically distributed in several phases. In the first phase, drugs are distributed to high-flow areas such as the heart, liver, kidneys, and brain. In later phases, drugs are distributed to low-flow areas such as bones, fat, and skin.

There are many body compartments in which drugs can be distributed, and the Vd varies for each drug, depending on how widely distributed the drug is. Some drugs that circulate in the body tightly bound to albumin will remain primarily in the vasculature, a compartment with a Vd of about 5 L, the volume of plasma. Other hydrophilic drugs distribute to both the vasculature and extracellular fluid compartments, with a Vd of about 15 L. Still other agents distribute throughout all body fluids, including intracellular fluids, and possess a Vd of 40 L or more. With respect to Vd, some key points to understand are (1) when a drug has a large Vd, it means that a larger dose of drug will be needed to achieve a target drug concentration in the plasma; and (2) lipid-soluble drugs (hydrophobic) have a larger Vd than water-soluble drugs. In fact, lipophilic drugs can dissolve in fat and can accumulate in adipose tissues, yielding Vd greater than 100 L. Note that a drug may have a high Vd and distribute to peripheral compartments, but those compartments are not necessarily the sites of drug action. However, the real value of Vd is that it allows determination of steady-state dosing regimens when a particular concentration of drug is desired in the plasma.

Plasma Protein Binding

Numerous drugs bind nonspecifically to serum proteins, especially albumin, as well as other cell constituents in the skeletal system (bones, teeth, muscle), through a process known as nonspecific protein binding. Protein-bound drugs are not bioactive (i.e., protein-bound drugs have no therapeutic efficacy while bound nonspecifically to plasma proteins). Bound drugs cannot be filtered by the glomerulus nor are they subject to metabolism by microsomal P450 enzymes. Protein-bound drug can be thought of as a *reservoir*—with drug gradually released from nonspecific binding sites when plasma concentrations of the drug decline. For sports enthusiasts, think of plasma proteins as the hockey penalty box; when bound to plasma proteins, drugs (i.e., hockey players) can no longer participate in biologic activity, free distribution, metabolism, or excretion. On the other hand, unbound (or "free") drugs are able to distribute and bind to their specific receptor targets and exert biologic effects.

When a drug is nonspecifically protein bound, the disappearance of the drug from the blood is slowed, because only free drug (1) is metabolized by hepatic enzymes and (2) is filtered by renal glomeruli and eliminated. Because albumin is the primary plasma protein to which drugs bind nonspecifically, alterations in albumin levels can affect free drug concentrations (Table 1-7). Other plasma proteins that nonspecifically bind drugs include α_1-acid glycoproteins and lipoproteins.

There is a theoretical risk of drug-drug interactions any time a drug is greater than 80% protein bound. Drugs compete with one another for binding to plasma proteins, and drugs frequently displace each other. Consider the anticoagulant drug warfarin, which is greater than 99% protein bound. This means that less than 1% of warfarin is circulating freely, and it is this small amount of free drug that is therapeutically active. If a patient has been stabilized on a dosage of warfarin and another highly protein-bound drug is

TABLE 1-7. Free Drug Levels with Albumin Alterations

ALBUMIN LEVEL	ILLNESS	FREE DRUG LEVELS
Hyperalbuminemia	Dehydration	Decreased
Hypoalbuminemia	Burns	Increased
	Renal disease	Increased
	Hepatic disease	Increased
	Malnutrition	Increased