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Principles in General Pharmacology

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To our children

Christopher, Diane, Karen, R.J., Valerie

Jonathan

Sean

Preface

This book deals with principles in general pharmacology—the key ideas that are applied to virtually all drug classes—and thus seems to us the proper subject matter with which to launch the *Springer Series in Pharmacologic Sciences*. The book is designed to meet the modern need for a better understanding of pharmacologic principles. It is an intermediate text directed mainly, but not only, to students who have completed a first course in pharmacology and who now need greater detail on concepts fundamental to understanding much of the research literature—especially the parts that are quantitative. Physicians having a special interest in pharmacology will also find much useful information here. The book integrates topics that we have included in several courses to health science students in graduate and professional schools in recent years. The "principles" are those key concepts that are applicable to a wide range of drug classes and include pharmacokinetics, drug biotransformation, receptor interaction, and the key ideas underlying the expression and interpretation of dose–response data. These concepts have their roots in the more basic sciences of physics and chemistry. Some readers may feel that we omitted concepts that might be considered "principles"; hence we have used the preposition "in," not "of," in the title of this book.

Because its individual chapters are essentially self-contained, the book can be used in a variety of courses. For example, Chapters 1, 2, and 4 are suitable for the "principles" sections of introductory courses in pharmacology of the kind given in most professional schools. Instructors teaching graduate pharmacology and pharmacy students will find that Chapters 1 to 5, 8, and 9 can form the basis of a one-semester course of 30–40 hours duration. The addition of Chapter 6 and 7, which present the fundamental physicochemical bases that underlie current thinking on chemical bonding and reaction kinetics, along with selected articles and other works cited from the literature, provide sufficient material for a two-semester graduate course.

We hope that this book, which combines the features of reference and text, will aid students and professionals alike in understanding drug actions. However, the literature in pharmacology, as in other scientific fields, is vast. Hence, we could

not cite many excellent articles and books. We have instead carefully chosen those that best illustrate or extend the topics of this volume. We urge the student to read as many of these as possible, for no single book, however thick, is sufficient to teach this subject.

Series Preface

Pharmacology is both a basic and a clinical science. In contrast to other basic medical sciences, however, this discipline is bolstered by an active world-wide pharmaceutical industry that produces hundreds of new drugs each year. Further, researchers often find new uses for existing drugs – even old ones – while they are studying mechanisms of their action. Many compounds have become tools for further exploration of physiologic mechanisms. The result has been a dramatic and continuous proliferation of information about drugs and the various biologic systems on which they act.

This virtual explosion of knowledge presents a real challenge to students as well as to clinicians and researchers who must keep abreast of developments in their own and adjacent specialties. This challenge is further intensified when the new facts and mechanisms are related to completely new concepts necessary for their understanding. Many such concepts have been formulated from recent studies and thus were not taught until very recently in graduate and professional school courses. The experienced clinician or researcher who wants to keep up must have the new facts *and* the new mechanisms.

The *Springer Series in Pharmacologic Sciences* was conceived with these objectives in mind. The aim will be to produce volumes, each dealing with a particular therapeutic area or pharmacologic theme, that integrate the facts with the concepts needed to understand their underlying mechanisms. Physicians have long realized the importance of understanding mechanisms as a basis for rational drug therapy. The integration provided in these books also lends to each the flavor of a textbook, yet our intention is to give more recognition to the research literature than is usually found in student textbooks. This design helps to make each book rather self-contained, thus minimizing the need to consult many individual articles and reviews.

It is well known that drugs are categorized in a variety of ways, e.g., according to gross or intimate pharmacologic action, site of action, chemical structure, therapeutic use, etc. Accordingly, the books of this series will reflect this diversity of classification. In every book, however, the aim of the authors and editors is to sort, integrate, and interpret from among the large body of facts and concep-

tual ideas, and to provide a volume of modest size that is useful to large numbers of clinical and basic scientists and their students.

Some areas of pharmacology will surely advance more rapidly than others. Thus there will be a need to update with second editions in some areas. In this regard, this series has an advantage over the single, thick, comprehensive work. Our intention is to meet the needs for updated editions while continuing to expand the scope of the series with brand new titles.

Ronald J. Tallarida
Philadelphia, 1988

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General Principles: History and Overview

Introduction

Today there are drugs for treating virtually every ailment. Not all drug treatments are curative; in fact, most are only ameliorative. Yet, we are better equipped today than ever before in treating disease. For example, at the turn of this century more than 13% of all American children died before their first birthday. The fatal diseases were principally pneumonia, influenza, and tuberculosis.[3] The improvement in life expectancy during this century is, for the most part, largely due to advances in medicine, and an important component of that advance is the availability of new drugs. Most of the drugs used today have come from laboratory research. Only a few (e.g., digitalis and morphine) are products of ancient cultures, most of the others in the modern pharmacopeias having come from the synthetic chemistry laboratory.

It is interesting to note what the major classes of today's drugs are, based on use. Some indication of these classes and their relative rank is afforded by a sampling of prescription drugs in the United States, as shown in Table 1.1.

Though borrowing heavily from biochemistry, physiology, and even physics, pharmacology is today very much a science in its own right. It is a dynamic field, buoyed by advances in basic research that often apply to clinical situations. Its subject matter is now considered "core" in most medical school curricula, although this aspect of the education of the American physician is relatively recent. The first American professorship of pharmacology, awarded to John J. Abel, was established in 1891 at Michigan, but it was not until the mid-1930s, when chemotherapeutic drugs arrived, that pharmacology became deeply rooted as a separate discipline in the doctor's education.

Tracing the history of pharmacology, or even its significance in the formal education of physicians, is beyond the scope of this brief volume. Several excellent sources for historical information exist.[1,2] Even an historical tracing of pharmacologic principles will not be formally done, for such a task, with the space available, would result in something that is very incomplete. Yet, some minor historical perspective seems in order.

TABLE 1.1. Drug classification ranked according to pharmacologic action or therapeutic use.[a]

Rank	Drug group
1	Cardiovascular
2	Antibiotics
3	Analgesics
4	Antibacterials/antiseptics
5	Tranquilizers
6	Diuretics
7	Decongestants/expectorants
8	Antiarthritics
9	Antihistamines
10	Gastrointestinal preparations
11	Contraceptives

[a]Based on the number of different preparations within the category as determined from a sampling of new and refill prescriptions in US retail pharmacies. A particular drug may lie in more than one category. From Tallarida RJ: Most-Prescribed Drugs–1985. Philadelphia, W.B. Saunders Co. 1985, pp. 219–230. Reprinted by permission.

Historical Perspective

In a general sense, "principles," those key points that apply to many drug groups, emerged in the first half of the 19th century when the active ingredients were isolated from natural preparations. Crude forms that had been used for ages became subject to quantitative analysis. With this quantitative precision it became possible to relate dose to response and thus instilled confidence in both the doctor and the patient. The London mathematician J.W. Trevan (1887–1955) would ultimately show in 1927 that the response to a fixed and precise dose in living material obeyed a normal distribution. The isolation of pure forms stimulated researchers to look for new compounds, or make alternatives to these natural products. The rise of chemistry aided in this effort. Products made at this time could now be screened for toxicity and effectiveness.

That a relation exists between the chemical structure of a compound and its biological activity was hypothesized by James Blake (1814–1893) and confirmed by his studies of inorganic salts. This work provided one of the earliest pieces of evidence for specific binding sites (receptors), for if the physiochemical composition of a drug influenced its activity, it was reasonable to suppose the existence of binding sites that specifically "recognized" the drug.

As chemistry advanced, the quest for new drugs and an understanding of their properties advanced. The accelerated pace led, for example, to a wide exploration for anesthetics and to the systematic work of Benjamin W. Richardson (1828–1896), who studied alcohols and hydrocarbons. Richardson discovered the importance of the number of carbon atoms in relation to the single-dose toxic

effects of these compounds, the kind of study that now falls within molecular pharmacology. He also found and explored the dilation of blood vessels by amyl nitrate after Antoine Balard (1802–1876) made the compound and Thomas Brunton (1844–1916) reported its success in treating anginal pain. Brunton also noted the inotropic action of digitalis and its consequent diuretic action. Pharmacology was emerging as a science and textbooks on the subject appeared, such as that by Carl Ludwig (1816–1895): *Textbook of Pharmacology, Therapeutics and Materia Medica*, which was published in London in 1885.

Antagonistic drug action, a key concept in both theoretical pharmacology and modern therapeutics, was systematically studied by Thomas R. Fraser (1841–1920), who examined the antagonism between atropine and physostigmine. The latter compound, an alkaloid extract from the calabar bean, is today well known for its prominent parasympathetic effects.

Because the subject of pharmacokinetics is the movement of precise drug quantities throughout the body, pharmacokinetics could become a rigorous discipline only if methods of drug delivery could be made accurate. The first use of the hypodermic syringe by Alexander Wood (1817–1884) must therefore be regarded as a monumental advance in this branch of pharmacology, as well as in modern clinical medicine. The drug molecule must traverse many membranes (highly lipid structures) that divide the (largely aqueous) compartments of the organism. The studies of Hans H. Meyer (1853–1939) on the relative solubilities of compounds for fats and water, leading to the concept of the lipid/water partition coefficient, gave new insights that led to models patterned after the much studied diffusion of gases and studies of dilute solutions. Physical theories, along with chemical knowledge, therefore further permeated the discipline that is now known as pharmacokinetics. The physiochemical ideas provided a framework for the later precise studies of the biotransformation and elimination of drugs by Von Nencki (1847–1901), Von Mering (1849–1908), and Schmiedeberg (1838–1921).

Of course, the literature of the 20th century reveals an explosion in pharmacologic knowledge and much of the information has sharpened our definitions of key ideas or principles. The reader will become aware, while reading the chapters on quantitative pharmacology, that certain individuals are linked with certain ideas, so some additional sense of the history of the theoretical advances may emerge.

Principles

Just as the array of diseases is diverse, so, too, are the properties and actions of the drugs used to treat them. The results of laboratory research often seem at odds with clinical experience. Modell[4] has commented: "That a disparity should sometimes seem to exist generally arises through neglect of pertinent laboratory data or through improper interpretation or application." The point here is that, more often than not, properly evaluated laboratory findings are applicable to

clinical situations, but the evaluation of laboratory data requires an understanding of some basic principles—the main subject of this book. The fundamental concepts broadly applicable to all drugs or to wide classes of drugs are the principles. Some readers will undoubtedly feel that we have overlooked some concept that might be considered a "principle." If so it is because our use here of the word is purposely narrow, including only those ideas that have their roots in the more fundamental sciences of chemistry and physics and the inevitable mathematical concepts that are required for their proper expression. The broader use of the term "principle" shall unfold in the accompanying volumes of this series in which individual systems and drugs affecting them are discussed.

Overview of Pharmacologic Principles*

In order to be effective a drug must be absorbed into the bloodstream and arrive at its locus of action on the target organ. In its movement the drug molecule must traverse various membranes and enter the capillaries. Only the smallest molecules can diffuse through the membranes pores; therefore larger molecules will pass by diffusion only if they are soluble in the membrane. Because membranes are mainly lipid, drug molecules that are lipid-soluble pass more readily than those that are not. Nonionized particles have greater lipid solubilities than do ionized molecules; thus, the degree of ionization of the drug molecules is an important factor in a drug's absorption. The lipid solubility of a drug is frequently expressed in terms of its lipid/water partition coefficient, a measure of the relative affinity of the drug for a lipid solvent and water at some specified temperature. Most drugs are absorbed by passive diffusion.

Besides passive diffusion, other mechanisms of transport exist. Some compounds of low solubility penetrate membranes more easily than can be accounted for by passive diffusion. The transport of some of these compounds is aided by carrier molecules. For compounds that move against a concentration gradient (actually an electrochemical gradient because of an accompanying difference in electric potential), energy is required and the transport is described as "active." In both active and carrier-mediated transport the drug must be in solution.

Drugs exist in a variety of different physical forms: aqueous solutions, suspensions, capsules, tablets, etc. The physical form is an important factor in the absorption of a drug by a particular route. For oral administration, the most common route, the degree and rate of absorption as a function of the physical form are generally greatest for oral solutions, then suspensions, capsules, tablets, and coated tablets, in that order. Tablets are frequently coated in order to prevent destruction of the drug by the acidic gastric juice.

*The balance of this chapter is from Tallarida RJ: Most-Prescribed Drugs—1985. Philadelphia, WB Saunders, 1985, pp 261–274. Reprinted by permission.

Ionization and Absorption

Because ions have low lipid solubility, and since many drugs are weak acids and bases that tend to form ions, it is useful to discuss the conditions that determine the drug's degree of ionization. Ionized molecules do not readily traverse the highly lipid cellular membranes. The degree of ionization of a drug molecule depends on the pH of the medium containing the drug and a property of the drug called "pK." The computation of the degree of ionization of both acidic and basic drugs uses the Henderson–Hasselbalch equations. The ionization constant (K) is often expressed as the negative (common) logarithm, or pK value: $pK = -\log(K)$.

The degree of ionization depends on the pK of the drug and on the pH of the medium that contains the drug. For drugs that are weak acids, the ratio of nonionized to ionized concentrations is determined from the equation

$$pH = pK + \log_{10} \frac{(\text{ionized})}{(\text{nonionized})} \tag{1.1}$$

In contrast, drugs that are weak bases obey the equation

$$pH = pK + \log_{10} \frac{(\text{nonionized})}{(\text{ionized})} \tag{1.2}$$

As an example, consider acetylsalicylic acid, whose pK is approximately 3.3, in gastric juice of pH 3. The ratio of nonionized to ionized forms, computed from the Henderson–Hasselbalch equation, can be shown to be 1.99, that is, approximately twice as much is nonionized as is ionized, a situation that favors absorption. In contrast, diazepam, a weak base with pK of 3.3, has the ratio of approximately 2 of ionized to nonionized in the same gastric juice and, thus, exhibits, less absorption from the stomach. Of course, other factors besides ionization affect the absorption of drugs. These are outlined below and discussed in greater detail in Chapter 3 on pharmacokinetics.

Oral Administration

The most popular route of administration is the oral route, and drugs given this way must be absorbed from the stomach or the intestines. As previously discussed, the pH of the medium is one important factor in the absorptive process. The stomach juice is acidic, usually in the pH range 1 to 4, whereas in the duodeum the pH ranges from 5 to 6. The remainder of the intestine is neutral to slightly basic with a pH of about 8 in the lower ileum. These facts relate to ionization and its importance in absorption. Other factors, however, also affect absorption of orally administered rugs. (See Fick's law.) Because the intestines contain such a large absorptive area compared with that of the stomach, most of the absorption takes place in the small intestine. Solubility may depend on pH as well. A swallowed tablet must first disintegrate and then be dissolved if it is to enter the bloodstream. A drug that is not absorbed from the stomach must enter

the intestine; hence, the rate of gastric emptying is important for such a drug. As previously noted, in some cases it is undesirable for the drug to be soluble in gastric juice, for example, when the drug would be destroyed by the gastric juice, or when the drug is irritating to the gastric lining. In such cases enteric-coated tablets are used, for these resist dissolution in the stomach. Gastric irritation can sometimes be avoided by taking the drug with food or milk.

Some preparations are designed to be released at a controlled rate by using different coatings, each destroyed at a different rate, thereby releasing the drug molecules at a controlled rate. Many widely prescribed drugs are formulated as sustained-release or controlled-release preparations.

Portal Circulation

The liver is the most important organ for drug metabolism. The drug metabolite or metabolites may or may not have activity, or they may have activities that are much less than that of the parent drug. A drug in the blood is carried to the liver, resulting in a decrease of the drug's concentration (in time) at a rate that depends on the hepatic blood flow and the chemical machinery of the liver. The latter consists of numerous enzymes contained in the endoplasmic reticulum of the liver. Drugs taken orally are particularly susceptible to this enzymatic activity, since drainage from the gastrointestinal system is into the portal circulation, a direct route to the liver (further discussed in Chapter 4). For example, nitroglycerin is rapidly degraded in the liver; accordingly, the oral route is not used. Instead, nitroglycerin is administered sublingually (and, more recently, transdermally). Drainage from the mouth is into the superior vena cava and not into the portal circulation. Of course, it is necessary that a drug given this way be highly potent (such as nitroglycerin) since the amount absorbed from this route is small.

Parenteral Administration

Although the oral route is the most common and the most convenient, it cannot always be used for reasons previously mentioned. In such cases parenteral administration may be used. The important parenteral routes are subcutaneous, intramuscular, and intravenous. The subcutaneous route is used, provided that the drug is not too irritating and that the volume is reasonably small. This route usually results in fairly constant absorption. The insulin preparations are good examples of drugs given subcutaneously.

Drugs administered via the intramuscular route are often in solutions in oil and are absorbed at a slow, steady rate. This route is not used when bleeding may be a problem, as in patients on anticoagulant drugs. Sometimes this route is also painful because of its irritating effect on muscle and other tissue.

In contrast to the subcutaneous and intramuscular routes, which are extravascular, the intravenous route delivers the precise amount to the blood and delivers the drug to the target sight(s) more rapidly than do the other common parenteral routes. Usually intravenous administration must be slow and carefully moni-