Review of Medical Pharmacology

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7th Edition

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Preface

In preparing the seventh edition of this book, the authors have again attempted to emphasize those aspects of pharmacology that serve the clinical needs of the student and practitioner in medicine, dentistry, nursing, and pharmacy. As in previous editions, the discussion of certain theoretical and research aspects of pharmacology has been drastically limited in order to keep the size and cost of the book within reasonable limits.

Because learning how to think clearly about drugs is one of the student's most obvious and most difficult duties, one of the chief aims of this book is to foster a skeptical attitude toward all new drug claims. We hope the clinician will maintain a close working familiarity with the general and specialty sources of current information on new drugs listed on pp 3 and 30 of this text as well as the promotional literature supplied by the manufacturer. The physician should check with the pharmacist when necessary to determine what dosage forms and sizes are available locally.

We wish to express our thanks to all who have helped with the preparation and upkeep of this *Review* and particularly Drs. Mervin J. Goldman, Paul F. White, and Richard D. Mamelok. We appreciate hearing from our readers, and we welcome suggestions from students and others who may have ideas for making the book more accurate and useful. We are pleased to be able to say that this book has achieved a substantial readership out of the country in both the English language editions and in German, Italian, Japanese, Portuguese, and Spanish translations, with French and Chinese translations also in preparation.

The Authors

San Francisco
September, 1980

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Part I. General Information

Introduction | 1

Pharmacology, for the purpose of this book, is considered to be the body of information that underlies the effective and safe use of drugs in the diagnosis, prevention, or treatment of disease. However, pharmacology includes many controversial areas, and opinion begins to diverge with the very definition of the field. From the point of view of the practicing physician and medical student rather than the research specialist, pharmacology is a derived or applied science. Understanding how drugs are used and progress in drug therapy require the application and development of special information from many areas, especially organic and analytical chemistry, biochemistry, physiology, and the various clinical specialties.

Many research- and laboratory-oriented pharmacologists prefer to regard pharmacology also as a basic science and view it as a valid field of investigation independent of its immediate applications. Their approach would emphasize some of the headings in the outline below and minimize others. The emphasis of this book reflects the teaching responsibility of pharmacologists toward students in the professions rather than the needs of research pharmacologists. It deliberately blurs any distinction between pharmacology and therapeutics.

The discussion of most of the groups of drugs in the following chapters of this book is organized according to the outline that begins below. However, several chapters on general pharmacologic or therapeutic subjects precede the chapters in which the drug groups are discussed. Whether these general discussions should be read before or after a store of specific pharmacologic information is acquired depends upon the individual student. The following brief review of the conventionalized outline of what a practitioner should consider before using a particular drug should allow study of the general chapters to be deferred if desired.

History

Information about the history of the development or introduction of a drug group to therapy is not essential to its proper use. The history, however, is usually interesting and often important in the formation of attitudes toward current problems. The brief history of pharmacology at the end of this chapter divides the subject somewhat arbitrarily into periods. The historical sketches that appear in some chapters are usually selected to illustrate one of the generalizations presented in the outline of the history.

Chemistry

Data on the structure and chemical properties of compounds used as drugs have different relevance to different workers and may be of greater or lesser interest to different workers. One interested in the synthesis of new drugs requires information of a different kind from what is needed by a person whose ultimate interest is biologic and practical.

A. Chemical and Pharmacologic Classification: A key problem or concept that will be repeatedly emphasized is that the many hundreds of available drugs can be classified into a reasonable number of drug groups and subgroups rather than as so many individual agents. The most important function of the information on chemical structure given in the tables or figures is to demonstrate the similarity of related drugs within a group and to suggest a basis for establishing subgroups when important differences are present. In a few cases, minor changes in chemical structure may lead to major changes in the nature or specificity of biologic effect. However, the proliferation of drugs within most groups is not necessarily due to the synthesis of significantly different compounds but is related to the marketing of compounds that are merely imitative of the prototype in the group or subgroup.

B. Structure-Action Relationships: A few drugs have been "designed" in the sense that chemical theory predicted a desired biologic effect. For example, most of the antimetabolites introduced since the sulfonamides are compounds whose pharmacologic effect and usefulness were predicted. However, the great majority of drugs now in use derive from prototypes that were natural products and from later synthetic counterparts whose chemistry was patterned after the natural product. Drugs whose discovery was purely accidental or stemmed from the empirical preparation and screening of a large number of compounds without a justifiable theoretic basis also contribute to currently used drugs. Much structure-action speculation is retrospective and is of limited practical importance. The application of structure-action theory to the problems of the mechanisms of drug action, on the other hand, represents one of the ultimate goals of

pharmacologic thought. The tentative data available are discussed along with the relevant drugs.

Absorption, Distribution, Metabolism, & Excretion

These properties—(1) absorption from the gastrointestinal tract or injection site, (2) distribution of the drug intra- or extracellularly throughout the body, (3) metabolism or biotransformation of the drug, and (4) its excretion—are discussed together because there are several unifying chemical concepts. The lipid barrier model suggests that the barrier to distribution provided by cells or the cell wall will allow the transfer of lipid-soluble, nonpolar molecules preferentially to water-soluble substances. A more lipid-soluble substance would enter parenchymal cells, but its excretion would be slowed because it would also be well reabsorbed at the renal tubules. The metabolism or biotransformation of drugs by conjugation or chemical alteration converts them to more polar, more water-soluble metabolites that can be more rapidly excreted. The metabolites are usually inactive—ie, drug action is terminated by metabolism—in which case the details of the transformation are of limited practical importance except in following the rate of excretion. However, some metabolites are active or toxic. Some of the possible metabolic pathways are discussed in Chapter 2.

Pharmacologic Actions

A. Mechanisms of Action: Discussions of the mechanisms of action of a drug usually involve separate discussions at the physiologic and biochemical levels. For most drugs, it will be possible to make some statement about the mechanism of action at the level of the organ or functional system or tissue. The site of action, for example, may be localized to an organ such as the spinal cord or even to a functional system such as internuncial or polysynaptic pathways. In a number of cases, drug action can be explained by an action on chemical mediators liberated by the cell.

Below the organ or tissue level, at the biochemical or subcellular site of drug action, information is available in only a few cases. Some drugs are known to be inhibitors of specific enzymes; a few are metabolic antagonists; and several other biochemical mechanisms have been defined. For most drugs, however, the ultimate mechanism of action is unknown.

It is frequently said that an understanding of mechanism of action is a prerequisite to the rational use of drugs. Such understanding is certainly the goal. However, drugs used in the absence of such information will continue to act after the mechanism of action has been defined exactly as they have during the period of their empirical use.

B. Effects: The observed effects on as many organ systems and tissues as are influenced—ie, the descriptive pharmacology—is the crucial part of the discussion of each drug group, since it underlies and explains most of the therapeutic and toxic actions of the drug.

Clinical Uses

The possible therapeutic applications of a drug group cannot simply be listed. Not all of the suggested or even commonly accepted indications for the use of a drug are supported by convincing clinical studies. One cannot even assume that all of the marketed drugs are active. The problems of the clinical evaluation of drugs are discussed in a general way in Chapter 3. For the individual drug groups, the indications are listed, and some discussion of the methods of establishing usefulness and therapeutic effectiveness is given.

Adverse Reactions

The use of drugs is not without many dangers and discomforts. Before any drug or combination of drugs is used, the possible toxic effects must be considered, so that the physician can be prepared to treat toxic reactions and so that some judgment can be made about the possible benefits as compared with the possible toxic effects. A general discussion of the toxicity of therapeutic agents is presented in Chapter 6. In the discussion of each drug, adverse reactions are listed under one or more of the following categories:

A. Side-Effects: Under this category are discussed effects that are often unavoidable if adequate doses of the drug are given.

B. Overdosage Toxicity: Toxic effects of this type are dose-related—ie, their incidence increases as the dose level is increased.

C. Allergic Reactions: These reactions are not dose-related but depend upon the altered reactivity or hypersensitivity of the patient, usually induced by prior contact with the drug that has acted as an antigen.

D. Drug Abuse: A special form of toxicity is the use for nontherapeutic purposes of drugs that act on the central nervous system. The misuse of the individual drug is discussed in the relevant chapters (eg, alcohol; see Chapter 24), but the general problem of drug abuse and habituation is discussed in Chapter 7.

Contraindications & Cautions

For each drug, there are situations in which its use invites disaster. Most of the contraindications to the use of a drug are predictable from its effects and are easily remembered. Some are unexpected or easily overlooked. For each drug, therefore, a list of contraindications and cautions is presented. This checklist in a text or in the physician's mind should be reviewed before a drug is ordered for any patient.

Most contraindications are disease entities or altered physiologic states—eg, morphine is contraindicated in head injury. In other situations, the possible interaction of a drug with one previously administered dictates caution. Drug interactions are discussed at this point in each chapter, and a general discussion of the topic is presented in Chapter 6.

Preparations, Choice of Drug, & Dosage

In many chapters, all of the drugs in a group will be discussed as if there were no differences between them or as if the newer compounds did not differ from

the prototype. In many cases, it does not matter which of a large number of similar compounds is selected for use. In most drug groups, however, there will be compounds or subgroups of compounds that are more efficacious for a particular purpose than others, and these will be discussed when such difference does exist. The importance of the general principles of the technic of drug administration discussed in Chapter 4 will be apparent to the practitioner. These principles should be reviewed by the student when the selection and ordering of drugs for patients becomes one of his or her responsibilities.

An especially confusing factor is the multiplicity of names involved. Each drug has a generic or public name—eg, penicillin G—but in addition may be given a protected or trademark name by one or by many different manufacturers or distributors.

The dosages included in this text are in most instances those that are generally accepted or those suggested by the manufacturer. In some cases, a more conservative position on dosage has been adopted. When drugs are known to cause frequent or dangerous toxic reactions; when establishment of a maintenance dose is difficult, when parenteral administration requires special precautions, or when the drug is unfamiliar to the prescriber, the manufacturer's package insert or other current FDA-monitored sources of information should be consulted before the drug is administered.

References

A. Chapter References: The references at the end of each chapter are chosen to guide the student to further reading in areas that are judged to be rapidly changing, controversial, or unfamiliar. The emphasis is on the clinical aspects of the drug group, and most of the references are chosen from a few of the most readily available journals. The best source of additional reading or references depends on the library facilities available and on whether the seeker's interest is primarily in the clinical or laboratory aspects of the subject.

B. General References: The following texts contain comprehensive discussions of specific drug groups and of the general problems of pharmacology:

Goldstein A, Aronow L, Kalman SM: *Principles of Drug Action*, 2nd ed. Wiley, 1974. [Highly recommended when rigorous theoretical approach is needed.]

Goodman LS, Gilman A (editors): *The Pharmacological Basis of Therapeutics*, 5th ed. Macmillan, 1975. [Comprehensive text.]

Sollman T: *A Manual of Pharmacology*, 8th ed. Saunders, 1957. [Useful for data on old and obscure drugs.]

Access to the current research aspects of pharmacology is often provided by one of the following annual or serial publications:

The *Annual Review of Pharmacology* catalogs the literature by subject area. Comprehensive, research-centered reviews may be located by searching the indices of the following publications or their equivalents in specialized areas: *Pharmacological Reviews*, *Advances in Pharmacology and Chemotherapy*, *Progress in Drug Research*, and *Progress in Medicinal Chemistry*.

C. Clinical Evaluation: The clinical application and evaluation of drugs require the use of a literature distinct from the above. The journals of the several specialties and the better general medical journals are most useful, and the general problem is discussed in Chapter 3.

HISTORY OF PHARMACOLOGY

The discussion of some of the specific drug groups in the following chapters will begin with the history of their use or discovery. A survey of the history of drug therapy at this point serves as a way of outlining or organizing the entire subject. The data presented in subsequent chapters will illustrate the ideas outlined in this section.

Prescientific Period

The prototypes of many modern drug classes derive from natural products that have a long history of folk use. Scholars enjoy searching the records of the oldest cultures for references that can be interpreted as establishing the first use of a drug still used today. It is often assumed that our present more or less rational use of drugs and their natural progenitors in therapy grew out of the primitive experience. Actually, however, only a few folk remedies or contributions of the medicine of earlier cultures have been taken over directly. Most of the active natural products were used originally not as medicines but as magic tools, as arrow poisons in hunting or combat, as cosmetics, or even as a means of committing murder. The properties of opium have certainly been exploited for 3 millenniums, but the specific use of most natural products is based on the intervention of a relatively recent worker. In many cases, modern use could occur only when a sufficient nosologic basis had been developed—eg, only after fevers and dropsy were classified could cinchona bark and digitalis be used properly. Most of the drugs used in therapy prior to the modern period were abandoned along with bleeding and purging.

Therapy to 1800

The development of medicine and biology lagged far behind that of the other sciences. For medieval authoritarian systems, the physical sciences substituted observation, quantitative analysis, and the experimental method. Medicine actually regressed from Hippocratic empiricism and even late in the 18th century was scholastic and dependent on pure logic rather than observation. Many systems of medicine were developed, usually with a single pathologic process to

explain all disease. These attempts to reach a system of Newtonian unity and comprehensiveness actually inhibited observation and therefore progress.

There are more than a few exceptions to the above generalization, and medicine did have its great individuals. Vesalius, Paré, and Paracelsus were physicians of the Renaissance who trusted their own observations and experience.

More important to the history of therapy are the 17th century Englishmen—eg, Harvey and especially Sydenham—whose empiricism presaged the British clinical school.

First Applications of Experimental Method

At the time of the French Revolution, then, medicine was barely into its descriptive period, only anatomy having reached any maturity. Even general biology was still structural and taxonomic. François Magendie (1783–1855), an instructor of anatomy in Paris, then introduced the experimental method to medicine and biology. He studied the absorption of strychnine in order to challenge some of the vitalistic teaching of the period. A Javanese arrow poison (nux vomica) was administered by various routes and the resulting convulsions and asphyxia described. After studying the action in animals with the cord sectioned or destroyed, Magendie and his collaborating medical student accurately concluded that the spinal cord was the site of action of the active component, which was subsequently isolated and named strychnine. They presented their work in 1809 to the Paris Academy.

Magendie studied many other drugs and physiologic problems. His students isolated a number of alkaloids, and he published a formulary based on only pure, single compounds. His demonstration of the value of the experimental approach was influential.

Not the least of Magendie's contributions was to hire and encourage Claude Bernard (1813–1878). Unlike Magendie, who resisted all generalizations and compared his function as data collector to that of a junkman, Bernard not only contributed to every area of physiology but reflected on the methods of "experimental medicine," as the undifferentiated field of physiology-pharmacology-biochemistry was then called.

Clinical Research

For the development of modern medicine, a revolution in clinical medicine to restore the primacy of observation was as necessary as the application of the experimental method, and it too took place in France. After the Revolution, when all sciences broke with tradition and a new intellectual life was encouraged, the medical schools of the old regime (together with all universities) were simply abolished and new schools established within a few large hospitals. Clinical observations, especially those arising from the new technics of physical diagnosis, were correlated with autopsy data. Progress in the study and classification of disease entities was extremely great during the period 1825–1850. Cabanis, Pinel, and Bichat were the philosophic progenitors of the medical revolution, and Broussais should perhaps be called the founder of the Paris clinical school.

Progress in therapy was not equally rapid. Ineffective remedies had first to be eliminated. The resulting nihilistic attitude toward drugs and the emphasis on diagnosis have persisted. P.Ch.A. Louis (1787–1872), a successor to Broussais and Laennec, introduced his "numerical," or statistical, method of describing the natural history of disease and of evaluating therapy. His recognition of observer bias and other still current problems was especially influential in the USA through Oliver Wendell Holmes and others.

Germany & the Rise of the University

Not only were the French ideas immediately very influential in neighboring Germany, but, in response to the imperialism of Napoleon, the unification of Germany began during the period just described. Soon thereafter, the influence of the German university appeared, and by 1850 the Germans led the world in research. The German universities were provincial rather than national, and governmental support was increased because of interprovincial competitiveness. Students and faculty moved freely between schools, and the faculties were large enough so that time for research as well as teaching was available.

Experimental medicine differentiated into the separate basic sciences. In 1846, Rudolph Buchheim established the first laboratory for experimental pharmacology in Dorpat (Tartu), Estonia. His student, Oswald Schmiedeberg (1838–1921), together with the great physiologist Ludwig, became preeminent and trained many of the pioneers of modern pharmacology—whether German, American, British, or other.

American Pharmacology

It has not been many years since it was almost true that syphilis and general anesthesia were the only contributions of the New World to medicine. American medical education initially followed the British provincial pattern, which meant that most practitioners were trained by apprenticeship. However, as British medical training improved during the 19th century with the dominance of hospital schools, American training deteriorated as proprietary and sectarian (eg, homeopathic, chiropractic) undergraduate schools proliferated. Each state controlled licensing of its practitioners, and degrees of doubtful validity were accepted as licenses. A few superior or privileged men were trained at Edinburgh, Paris, and, later, in Germany, but little investigational medicine existed.

In the years just prior to 1890, the State Boards of Medicine began to move against the worst incompetents in medicine, and a few isolated universities began to respond to the social need. The first American pharmacologist, J.J. Abel, returned from his training in Germany to an appointment at the University of Michigan.

An important stimulus to scientific medicine in

the USA was provided by Johns Hopkins University. A graduate school more or less patterned after the German university was opened in 1876, and soon thereafter the hospital (1889) and a medical school (1893) were established. J.J. Abel moved from Michigan to Hopkins and trained most of the academic leaders in pharmacology for the next generation.

The reorganization of the American Medical Association in 1901 and the dramatization of the situation by the Flexner Report (1910) led to the disappearance of the proprietary schools and the emergence of the university-associated medical school. Clinical and laboratory research finally appeared in respectable amounts in the USA.

American pharmacology continued to lag in its development until after World War II, when unprecedented amounts of money were made available for research, first by voluntary agencies and then by the National Institutes of Health. Graduate programs made it possible for a student to enter pharmacology with a research degree rather than an MD, resulting in an increase in the numbers of pharmacologists but also in an alienation from medicine. Finally, the American drug industry expanded to match in size if not in originality its European counterpart.

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2 | Drug Biodisposition & Interactions

The metabolism of each drug or drug group must be studied separately. However, the discussion of this aspect of drug information in subsequent chapters can be greatly shortened by a preliminary general consideration here, since the several processes that occur between the time of administration of the drug and the termination of its activity are closely related. The absorption, the distribution within the body, and the excretion of a drug are related processes, since they all depend upon the passage of the drug across a series of cellular membranes of similar properties. These plasma membranes or "lipid barriers" are more permeable to uncharged, lipid-soluble drugs than to ionized, water-soluble molecules. The biotransformation or metabolism of drugs is generally a process by which drugs are rendered more water-soluble, less subject to renal tubular reabsorption, and, therefore, more readily excreted.

In the qualitative, descriptive account presented here, it may seem that absorption, distribution, metabolism, and excretion are sequential processes. This is true only in retrospect after the drug has been excreted and its effect finally dissipated. At any given moment, a drug and a variety of metabolic products may be distributed in many compartments—eg, the drug in the lumen of the intestine, the drug and perhaps a conjugate within the cells of the intestinal mucosa, drug and metabolites in the plasma, etc—until excretion occurs in bladder urine, expired air, or feces. Each transfer or metabolic change occurs at its own rate and has its own equilibrium constant. As drugs are ordinarily given—ie, with the exception of a continuous intravenous infusion—a steady state is not achieved. The multiple and complex processes acting simultaneously and interdependently can be assessed by (1) quantitative determination of factors such as changes in plasma concentration with time and (2) kinetics of volume distribution, functional half-life clearance, metabolic alterations, etc of the drug.

DISTRIBUTION OF DRUGS WITHIN THE BODY

Unit Membrane or Plasma Membrane

The distribution of drugs within the body is hindered by a series of membranes. Some of these membranes, like the skin or a mucosal surface, may be many cells thick; but the barrier to distribution resides in the cell membrane, and some generalities about transport across this membrane apply to many sites.

A. The Lipid-Sieve Model: The unit or plasma membrane surrounds or forms the boundary of all cells and surrounds the nucleus and organelles. Fig 2–1 presents a model of the lipoprotein membrane based on chemical analysis and electronmicroscopic and x-ray diffraction technics. Studies of the permeability of this membrane lead to the conclusion that it is a fluid mosaic with at least 3 functional components. The major component, for drugs if not for most physiologically important substances, is the lipid membrane that is permeable to lipid-soluble molecules and impermeable to polar, water-soluble substances. The membrane must in addition contain pores that permit the passage of small water-soluble molecules such as urea, alcohol, electrolytes, and water itself. Finally, the membrane contains channels through which substances can move after they have combined with a specific carrier.

B. Mechanisms of Transfer Across Membrane:

1. Passive transfer–Transfer or transport is said to be passive when the membrane need not generate energy to carry out the process.

a. Filtration, as across the capillary wall, is not

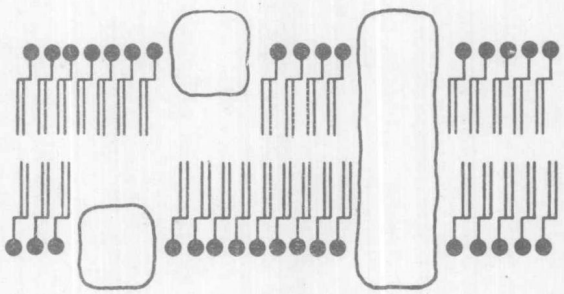

Figure 2–1. Hypothetical model of plasma membrane. The matrix of the membrane is a double layer of phospholipid molecules oriented with the polar heads in contact with intra- and extracellular water. Globular protein masses are embedded in the phospholipid bilayer with charged ionic residues projecting from the surface into water.

an important factor in limiting drug distribution.

b. Simple diffusion–If the rate of transfer across a membrane is proportionate to the concentration gradient, one infers that the process is one of simple diffusion. A water-soluble drug of low molecular weight such as alcohol may diffuse through the aqueous pores of the membrane. Water-soluble drugs of greater molecular weight either do not cross the membrane or are transported by an active process. Transfer by simple diffusion is then an important process for the distribution of lipid-soluble drugs. Many drugs—eg, ether or digitoxin—have a lipid solubility or oil-water partition coefficient that favors their transfer regardless of the pH of the medium. However, many drugs are either weak acids or weak bases, and the fraction of molecules present as the lipid-soluble un-ionized form to which the cell is preferentially permeable varies depending on the drug's pKa and the pH of the system. The pH within cells or of extracellular fluid cannot, of course, vary greatly. In order for a substance that is not actively transported to act intracellularly, it must either be lipid-soluble at all pHs or, if it is an amine or weak base, it must be largely in the un-ionized form at the pH of the body. It is possible, however, to alter the absorption or excretion of drugs by varying the pH of the gastric contents or the renal tubular urine.

c. Carrier-facilitated diffusion–In this process, the substance to be transported combines with a carrier molecule at one membrane surface and dissociates from it at the other surface. The carrier, a protein, is specific for the transported ion or larger water-soluble molecule that would not otherwise traverse the membrane. The process is still one of diffusion, and a substance cannot be moved against a concentration gradient. Exchange diffusion is a common variation of carrier-facilitated diffusion in which the carrier combines with one substance at the outer surface to transport it inward and, having dissociated from the first substance, picks up a generally similar molecule at the inner surface and carries it to the outside.

2. Active transport–Active transport is carrier-facilitated but is able to move the substance against a chemical or electrical gradient. Performance of such work or active transport requires energy which is known, in the common examples, to be generated by the action of membrane ATPase. There are a variety of channels or pumps of this type. Each transports a specific chemical type—eg, sodium, organic acids—and related compounds compete for the capacity of the mechanism. Interference with the supply of energy inhibits the system noncompetitively.

Absorption

A. From the Gastrointestinal Tract: This discussion applies to the absorption of drugs after oral administration.

Small, neutral water-soluble molecules—eg, alcohol and water itself—are absorbed from the stomach, although the amount absorbed is limited by its rapid emptying time. The absorption of other drugs will vary depending on the pH, which is a function of the secretory state of the stomach. Aspirin, the most commonly used drug, is a weak acid that exists almost entirely in the non-ionized lipid-soluble form at the pH of the secreting stomach and is well absorbed from the stomach (Fig 2–2). Giving aspirin with a base or with food in order to reduce gastric irritation would increase the fraction present as the salt or water-soluble form

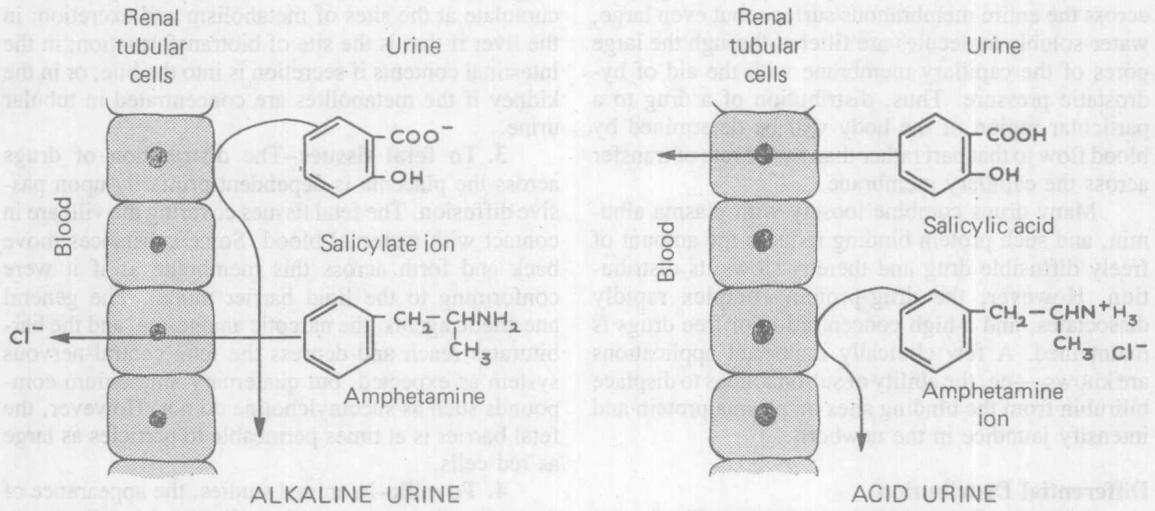

Figure 2–2. The influence of the pH of the medium on the diffusion of aspirin (acetylsalicylate) and amphetamine across a cellular barrier illustrated with a diagram of the renal tubule. The excretion of salicylic acid, a metabolite of aspirin, is increased if the renal tubular fluid is alkaline because it then exists as the ionized, less lipid-soluble salt form. The excretion of amphetamine, a weak base, is increased in an acid urine because it then is present as the salt rather than the lipid-soluble free base.

and slow its absorption to the rate normally observed in the small intestine.

The intracellular and luminal pH influences movement in both directions. Thus, weak bases given by parenteral injection can appear in the gastric contents via a reverse ion-trapping mechanism.

In the alkaline medium of the small intestine, those drugs that are weak bases exist as the free base and are well absorbed.

B. From the Urinary Tract: The pH of the urine is determined by the acid-base status of the patient, and alterations affect the ionization of drugs in a manner analogous to what takes place in the stomach. Examples of a weak acid (salicylic acid) and a weak base (amphetamine) are shown in Fig 2–2.

C. From Injection Sites: The rate of absorption from a subcutaneous or intramuscular injection site is related to the water solubility of the injected substance as well as the local blood flow. The rate of absorption can be slowed and the duration of action of a water-soluble drug prolonged by injecting it as an insoluble complex—eg, procaine penicillin or protamine zinc insulin.

D. From the Skin: The keratinized layer of the skin is a much less permeable barrier than the ordinary cell membrane, and the skin conforms to the lipid barrier model only if the keratinized layer is removed. Absorption of drugs after application to the skin or even penetration for a local effect is difficult to achieve and is discussed separately in Chapter 5. On the other hand, many drugs are well absorbed from the non-keratinized epithelium of the mucous membranes of the mouth or pharynx.

Transport Within the Vascular Compartment

Drugs readily leave the vascular compartment to enter the interstitial fluid. Lipid-soluble drugs pass across the entire membranous surface, but even large, water-soluble molecules are filtered through the large pores of the capillary membrane with the aid of hydrostatic pressure. Thus, distribution of a drug to a particular region of the body will be determined by blood flow to that part rather than by the rate of transfer across the capillary membrane.

Many drugs combine loosely with plasma albumin, and such protein binding reduces the amount of freely diffusible drug and thereby slows its distribution. However, the drug-protein complex rapidly dissociates, and a high concentration of free drugs is maintained. A few clinically important applications are known—eg, the ability of sulfonamides to displace bilirubin from the binding sites on plasma protein and intensify jaundice in the newborn.

Differential Distribution

A. To the Central Nervous System: The factors that determine whether or not a drug can reach and act on an intracellular site are similar throughout the body. The central nervous system is unusual in that drugs can reach extracellular sites only after passing through glial cells.

Capillaries in the central nervous system ("within the blood-brain barrier") cannot filter plasma into the interstitial space, because interstitial space is very limited in extent and the supporting glial cells are closely opposed to the capillary wall. Drugs that act on peripheral nerve tissue, presumably at an extracellular site, may not reach parenchymal central nervous system cells if the drugs are in a charged, lipid-insoluble form because of the so-called blood-brain barrier. Quaternary ammonium derivatives such as curare or acetylcholine, for example, exist entirely in the salt form at body pH and, after intravenous injection, do not act on the central nervous system however great their effect on peripheral nerve. They act on brain and spinal cord only if applied directly.

B. To Other Special Sites:

1. To lipid depots and other storage sites–Drugs with high intrinsic lipid solubility and low water solubility may accumulate in high concentration in the adipose tissues of the body—eg, thiopental or the chlorinated hydrocarbon type of insecticide. (The accumulation of thiopental in fat is discussed again below as an example of redistribution as a mechanism of terminating drug action.)

Some other examples of selective accumulation depend upon factors other than blood: tissue compartment coefficients. Colloidal and particulate drugs are taken up by the cells of the reticuloendothelial system; heavy metals concentrate in bone. Physiologically important substances may also accumulate by mechanisms unrelated to solubility—eg, cobalamin (vitamin B_{12}) in the liver or norepinephrine in the specific granules of adrenergic nerve. The concentration of the antimalarial drug quinacrine in parenchymal tissues is several thousand times that in plasma.

2. To sites of metabolism or excretion–The drug and its more water-soluble metabolites will accumulate at the sites of metabolism and excretion: in the liver if that is the site of biotransformation; in the intestinal contents if secretion is into the bile; or in the kidney if the metabolites are concentrated in tubular urine.

3. To fetal tissues–The distribution of drugs across the placenta is dependent primarily upon passive diffusion. The fetal tissues covering the villi are in contact with maternal blood. Some substances move back and forth across this membrane as if it were conforming to the lipid barrier model. The general anesthetic agents, the narcotic analgesics, and the barbiturates reach and depress the fetal central nervous system as expected, but quaternary ammonium compounds such as succinylcholine do not. However, the fetal barrier is at times permeable to particles as large as red cells.

4. To milk–In animal studies, the appearance of drugs in milk appears to be predictable by reference to the lipid barrier model. Since milk is slightly more acidic than plasma, basic compounds may be concentrated in milk. Small neutral molecules (alcohol) appear in milk in the same concentration as in plasma. Acidic drugs such as penicillin appear in milk (pH 6.6)

in concentrations less than in plasma, and bases (erythromycin) are more concentrated in milk.

Verified reports of toxic reactions in nursing infants due to drugs ingested by the mother are few. Drugs that have bad demonstrable effects include the nicotine in cigarettes, bromides, cascara and purified anthraquinones, antithyroid drugs, and phenindione (but not the other anticoagulants). Heroin—but not morphine or codeine—is said to act on the infant. Many drugs—eg, radioactive agents and antimetabolites—are almost certainly dangerous.

TERMINATION OF DRUG ACTION

The processes that terminate drug action determine the duration of effect of a drug. If they are altered by disease or concurrent administration of other drugs, the intensity and duration of drug effect may be altered.

ELIMINATION OF UNCHANGED DRUG OR METABOLITE

Elimination by the Lungs

The gases and volatile liquids used as general anesthetics are absorbed and excreted across the pulmonary alveolar membrane. Many other volatile drugs—eg, alcohol or paraldehyde—appear in the expired air but have other more important routes of excretion or metabolism. However, the content of alcohol and certain industrial solvents in alveolar air reflects plasma levels in a consistent way and can be used to quantify the degree of intoxication.

Elimination by the Kidneys

Drugs and their metabolites or conjugates appear in the urine as a result of 2 processes: (1) They appear in the glomerular filtrate, and (2) an additional fraction is then secreted or reabsorbed through the renal tubular cell. The reabsorptive process is also an example of passive diffusion. The more lipid-soluble the material, the greater the degree of reabsorption. The more water-soluble the material, the greater the fraction that remains in the urine. The excretion of the unmetabolized, lipid-soluble drug can be altered by acidification or alkalinization of the urine. (Fig 2–2.) For example, intoxication with salicylates or barbiturates (both weak acids) is treated by maintaining a high volume of alkaline urine. The weak acids then exist largely in the salt form or the ionized, water-soluble form, and reabsorption is greatly decreased.

The renal tubule is also able to actively transport or secrete organic anions and cations through separate channels.

Other Routes of Elimination

Drug and drug conjugate may appear in the feces subsequent to excretion in the bile or secretion by the colon. Specific drugs may also appear in saliva or sweat in significant amounts.

TERMINATION OF DRUG ACTION BY PROCESSES NOT INVOLVING ELIMINATION OF DRUG

The action of a drug may terminate even though a major portion of the drug is still present in the body. Conversely, if the change caused by the drug requires a long period for compensation, the effect may persist long after the drug has been eliminated from the body.

Redistribution

The differential distribution of a drug (see above) may be a mechanism for terminating its activity. For example, when the anesthetic thiopental is injected intravenously, a high plasma level is immediately achieved. The subsequent distribution of thiopental depends upon its high lipid solubility and the blood flow to the various tissues. An effective amount of thiopental is immediately carried to the central nervous system and other vessel-rich tissues. However, over the subsequent 10–120 minutes, the less well perfused tissues, eg, muscle and adipose tissue, take up enough thiopental to bring about its withdrawal from the central nervous system and the termination of its anesthetic action. In somewhat the same manner, the action of injected epinephrine or norepinephrine is terminated mostly because the amine enters sympathetic nerve and can no longer act on smooth muscle.

Repair of Drug-Induced Changes

Some drugs that disappear from the body after a few hours cause changes that may take many days for correction. For example, after prothrombin synthesis is inhibited by a coumarin anticoagulant, the effect persists until new protein is synthesized.

Antagonism

The effect of a drug may be terminated by giving its competitive or physiologic antagonist—eg, the sedative and analgesic effects of morphine can be antagonized by nalorphine, while the physiologic effect of histamine can be partially antagonized by epinephrine.

Physiologic Compensations

Some adaptations or compensations by the organism may decrease or completely abolish the effects of a drug. Other compensations may modify only certain prominent responses such as pulse rate or blood

pressure but give the impression of a decreased overall response to the drug.

The familiar compensatory reflexes originating from a change in pressure within the carotid baroreceptor areas are activated whenever a pressor or depressor drug is given. These reflexes may not modify a drug-induced rise in pressure but can cause a reflex bradycardia that obscures the drug's primary effect. Vasoconstrictor drugs (norepinephrine, ephedrine, angiotensin) can reduce cardiac output by increasing the amount of work needed to move the same volume of blood. A long-acting vasoconstrictor such as ephedrine may limit cardiac output enough to limit the rise in blood pressure that it causes. Such a state of reduced response of the blood pressure when the vasoconstricting and other actions are maximal is called tachyphylaxis.

Limited tolerance to the effects of other drugs arises from other compensatory mechanisms. Administration of the potent antihypertensive agents—eg, guanethidine, hydralazine, or methyldopa—results in an expanded plasma volume, and the dose of the drug may have to be increased to maintain the effect unless other supplemental drugs are used.

Tolerance of a qualitatively different kind follows the administration of organic nitrates or the narcotic analgesics. In this case, larger and larger doses must be given to maintain the effect, and tolerance can be made absolute—ie, many previously lethal doses can be given without danger or even much effect.

BIOTRANSFORMATION; ENZYMATIC ALTERATION

Many pharmacologists feel that it is impossible to overemphasize the importance of drug metabolism; others feel that this has already been achieved. In a few cases—eg, the study of cholinesterase or of monoamine metabolism—important information about the mechanism of drug actions and drug interactions has developed. Usually, however, the action of enzymes on drugs, unlike the study of the action of drugs on enzymes, does not often provide information about the mechanism of action of drugs. The process of biotransformation usually reduces or destroys the activity of the drug and hastens its excretion (reduces renal tubular reabsorption) by converting it to a more water-soluble form. More often than not, the process will consist of conjugation or of hydroxylation followed by conjugation. The process of biotransformation of drugs is often called detoxification.

Biotransformation can modify the effects of the drug administered in several ways:

(1) By forming an inactive metabolite from an active drug: This is the most common mechanism of drug inactivation. The metabolite may itself be further transformed and a mixture of metabolites and conjugates excreted, or the fragments may be lost in the metabolic pool.

(2) By forming an active metabolite from an initially inactive drug: For example, the cholinesterase inhibitor parathion must have a sulfur atom replaced by an oxygen atom before it is active; and the antimalarial chlorguanide and the alpha-adrenergic blocking agent phenoxybenzamine must cyclize before they can become active. (See Fig 11–1 for the reaction that converts phenoxybenzamine to a cyclic compound.)

(3) By forming an active metabolite from an initially active drug: Enzymatic transformation of a drug does not always terminate its action—eg, heroin is converted to morphine, and phenacetin is metabolized to an equally potent analgesic, acetaminophen (Fig 27–2).

(4) By forming a toxic metabolite from an initially less toxic drug: An example is isoniazid, which is acetylated to produce an intermediate compound that is the likely cause of hepatic necrosis, particularly in those in whom acetylation is rapid. The metabolism of phenacetin yields small quantities of ethoxyaniline, which is capable of converting hemoglobin to methemoglobin and occasionally produces methemoglobinemia of clinical importance.

CLASSES & EXAMPLES OF METABOLIC REACTIONS

The metabolism of specific drugs will be discussed in subsequent chapters. In the following paragraphs, the general classes of metabolic reactions will be described briefly and some of the many specific reactions will be cited as examples. Because the conjugation reactions apply to so many drug groups and because the oxidative enzymes of liver microsomes are important in drug interactions, they should be especially noted.

Conjugation Reactions

The conjugation reactions (also often called syntheses or transfer reactions) will be discussed first to emphasize their dual function. They can modify not only the original drug but also common metabolites formed by the reactions listed below. In the latter case, the polarization or increase in water solubility begun by one reaction is intensified by conjugation.

A. Glucuronide Formation: Each of the conjugation or synthetic reactions can be represented by the following reaction:

$$Ab + CD \xrightarrow{\text{Transferase}} AC + bD$$

where Ab is a drug or drug metabolite with functional group b, and C is the donor molecule activated by