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ESSENTIALS OF MEDICINAL CHEMISTRY

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PREFACE

The nature of a textbook should be determined by the demands of a curriculum which, in turn, should fill the needs of the student. During the early part of the century, subject matter which now is under the heading of medicinal chemistry was included in a course in materia medica to fulfill the needs of the practicing pharmacist who prepared many of the medicaments in his shop. Consideration of the pharmacist as a chemist in control of his domain—the repository of drugs—was reflected in the nature of textbooks emerging in the 1940's and bearing the words *pharmaceutical* and *medicinal chemistry* in their titles. These texts, employing a chemical classification of drugs, were essentially classical textbooks in organic chemistry with inclusion of brief descriptions of pharmacological actions and clinical uses. However, in view of the preempting of certain functions of the practicing pharmacist by the pharmaceutical houses which provided virtually all drugs in final dosage form, these texts were slow to admit changing needs and only gradually and partially did they adopt the pharmacological classification of drugs. The late Professor F. F. Blicke of the University of Michigan recognized as early as 1926 the need for a change when he organized his lectures to pharmacy students using a pharmacological classification. The trend has continued until today. In some institutions, courses in medicinal chemistry have been combined with pharmacology with less and less chemistry remaining in the courses.

With the usurping of a principal function of the pharmacist by the manufacturers of drugs, the modern pharmacist with his excellent educational curriculum needed greater professional fulfillment. While for years students were told that they should become consultants to physicians, they were reluctant except in isolated instances to assume that role. Now courses in clinical pharmacy constitute a large part of the pharmaceutical curriculum.

New curricula in general are directing students toward the patient and away from medicaments as chemicals. Similarly, new curricula of the physician involving abbreviated courses in basic medical science are removing the physician still further away from drugs as chemicals. If the trend continues away from

emphasis on drugs as chemicals and toward emphasis on the patient, who will fill the void as chemical and pharmacological authority? Thus, despite the trend away from chemistry because of a new concern for the patient, we believe that the pharmacist should not relinquish his historical role as custodian and master of the repository of chemicals.

The aim of this text is to conduct the student of pharmacy from basic chemistry over a bridge of medicinal chemistry to pharmacology. Medicinal chemistry, together with basic chemistry and biological science, is essential to an understanding of bioavailability—the requirement that a drug reach the active site in adequate concentration to be effective. Pharmaceutical subjects such as biopharmaceutics and pharmacokinetics are covered in other texts. Succinctly stated facts and theories are presented in this text in a form which hopefully will be palatable and yet provide information useful to the student in his future mission of helpfulness to the physician and patient, whether his location will be in the community, hospital, or laboratory.

The absence of preparative chemical methods and historical sketches constitutes concessions to limitations of space. The average contemporary student of pharmacy will not regret these omissions. To the student who wishes to know more of chemical methods relating to drugs, *Merck Index* is recommended as an example of an excellent source. Detailed historical and other aspects of the medicinal chemistry of drugs may be found under References in this text.

Monographs of drugs listed in The United States Pharmacopeia XIX (1975) and The National Formulary XIV (1975), as well as the First Supplements to these compendia, were taken into consideration in the preparation of this text.

We trust that this book also will prove to be helpful to chemists and biologists who are interested in facts and theories relating to drugs which are in actual use.

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PART 1

INTRODUCTION

CHAPTER 1

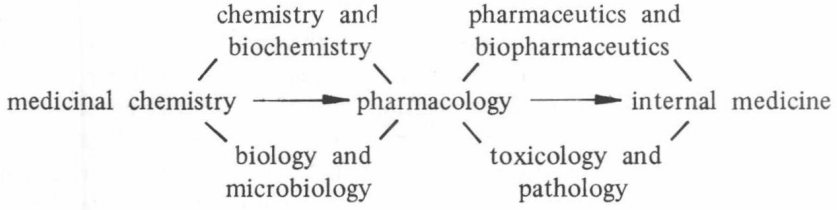
BASIC CONSIDERATIONS

I. MEDICINAL CHEMISTRY

A. Definition

Medicinal chemistry has been aptly defined by Dr. Glenn Ullyot as a field which applies the principles of chemistry and biology to the creation of knowledge leading to the introduction of new therapeutic agents. Thus, the medicinal chemist must not only be a competent organic chemist but he must have a basic background in the biological sciences, particularly biochemistry and pharmacology.

The relationship of medicinal chemistry to other disciplines is indicated by the following diagram:



B. Historical Evolution

The beginning of effective therapy by chemicals is lost in antiquity, since it preceded recorded medical history. Early successes in the quest for chemicals effective against disease were predominantly found among antiinfective diseases rather than against those usually accompanying the aging process, such as hypertension or cancer. Also, because chemical processes were largely undeveloped, nature initially provided the more sophisticated and promising agents. Emperor Sheng Nung in 3000 B.C. listed the crude drug ch'ang shan for malaria. Pliny in A.D. 50 introduced aspidium for helminthiasis.

The last several centuries are replete with ironies and paradoxes. Galen is revered today, but his worthless procedures of using small quantities of natural

products to treat diseases, introduced during the second century, prevailed for about 1500 years. On the other hand, Theophrastus Paracelsus, originally named Bombastus von Hohenheim, was ironically frustrated by unsuccessful attempts during his lifetime to introduce the useful laudanum (morphine tincture) for relief of pain and tartar emetic, still a useful antimonial, for the dread schistosomiasis. Paracelsus was the first physician or scientist to state the paradox that medicines can be both helpful and harmful. It is ironic that the most visible tribute to Paracelsus in Salzburg, Austria, where he died in 1493, is a painting of him below the apartment where he lived and above the Paracelsus Droggerie, a shop which dispenses only nonprescription drugs.

Another medical irony is that Lord Lister, responsible for the historic use of phenol in aseptic surgery, is remembered chiefly through a proprietary product which bears his name but which has questionable efficacy.

During the seventeenth century, ipecacuanha for amebiasis and cinchona for malaria were introduced. Later simple synthetics, such as ether, chloral, and acetanilid, became available. Just before the turn of the century, Emil Fischer's lock-and-key theory of drug action and, after just the turn of the century, Ehrlich's arsphenamine introduced the rational approach to the search for therapeutic agents. The rational approach has already provided a relatively large number of valuable drugs, as seen in Chapters 2 and 3. However, methods which were largely empirical produced the sulfonamides by Domagk in 1935 and the antibiotics beginning with Fleming in 1929 and revived by Chain and Florey in 1939.

Recent years have seen the creation of new therapeutic agents by medicinal chemists working usually as part of interdisciplinary teams. All their names and contributions are too numerous to mention here. However, two are selected for special recognition. The late Oliver Kamm, Scientific Director of Parke, Davis and Company, left the University of Illinois, where he had been a young instructor in organic chemistry. While there he wrote the first textbook in qualitative organic analysis and helped initiate the valued series entitled *Organic Syntheses*. Kamm, forced to become a pharmacologist as well as chemist, initiated or encouraged the initiation of a remarkable number of successful medicinal agents.

As an illustration of one from the universities who provided leadership in medicinal chemistry, the late Professor F. F. Blicke, of the University of Michigan, founded the first Ph.D. program in the field in the United States, which emphasized a specific curriculum in synthesis. Seventy-eight students received the Ph.D. under his direct supervision. He became the first person in whose name the Division of Medicinal Chemistry of the American Chemical Society held a symposium.

II. CLASSIFICATION OF DRUGS

Drugs can be classified according to various criteria. Usually they are classified according to (*a*) chemical structure or (*b*) pharmacological action.

The first classification was extensively used some years ago and it is still used by some authors. Following this classification, drugs fall in one or more of these categories: acetals, acids, alcohols, amides, amidines, amines, amino acids, amino alcohols, amino ethers, amino ketones, ammonium compounds, azo compounds, enols, esters, ethers, glycosides, guanidines, halogenated compounds, hydrocarbons, ketones, lactams, lactones, mustards, nitro compounds, nitroso compounds, organominerals, phenols, quinones, semicarbazides, semicarbazones, stilbenes, sulfonamides, sulfones, thiols, thioamides, thioureas, ureas, ureides, urethans.

Presently, the second classification is the one preferred by most medicinal chemists. Following this classification, drugs can be divided into these main groups: (*a*) pharmacodynamic agents, used in noninfectious diseases to correct abnormal functions; (*b*) chemotherapeutic agents, used to cure infectious diseases; (*c*) vitamins; (*d*) hormones; and (*e*) miscellaneous agents. Each group can be subdivided. For instance, among pharmacodynamic agents we have (1) drugs acting on the central nervous system; (2) drugs stimulating or blocking the peripheral nervous system; (3) drugs acting primarily on the cardiovascular and renal systems.

In this textbook, drugs are classified mainly according to their pharmacological action. Each one of these many classes is then subdivided according to the chemical structure of the several drugs which comprise it.

III. NOMENCLATURE OF DRUGS

A. Names of Drugs

Drugs have three or more names. These names are the following: code number or code designation; chemical name; proprietary, trivial, brand or trade name, or trademark; nonproprietary, generic, official, or common name; synonym and other names.

The code number usually is formed with the initials of the laboratory or the chemist or the research team that prepared or tested the drug the first time, followed by a number. It does not identify the chemical nature or structure of the drug. It is discontinued as soon as an adequate name is chosen.

The chemical name should describe unambiguously the chemical structure of a drug. It is given according to rules of nomenclature of chemical compounds.

Since the chemical name is sometimes very elaborate, it is not suitable for routine usage.

The proprietary name is the individual name selected and used by manufacturers. If a drug is manufactured by more than one company, as frequently happens, each firm assigns its own proprietary name. *It should be written with capitalization of the first letter of each word of the name.*

The nonproprietary name refers to the common, established name by which a drug is known as an isolated substance, irrespective of its manufacturer. It should be simple, concise, and meaningful but often it is not. The first letter is not capitalized. It is chosen by official agencies, such as the U.S. Adopted Names (USAN) Council, sponsored by the American Medical Association (AMA), the American Pharmaceutical Association (APhA), the U.S. Pharmacopeial (USP) Convention, and the U.S. Food and Drug Administration (FDA). In the *Journal of American Medical Association,* volume 213, page 608, July 27, 1970, appeared guiding principles for coining U.S. adopted names. On a worldwide scale, however, the World Health Organization is the official agency to select, approve, and disseminate the generic names of drugs.

Synonyms are names given by different manufacturers to the same drug or old nonproprietary names. Some drugs may have several names. For instance, diphenhydramine has 13 different names; chlorpromazine, 16; phenobarbital, 22; pethidine, 26; prednisone, 29; chloramphenicol, 45; sulfanilamide, 60; meprobamate, 64; vitamin B_{12}, 82.

B. Generic and Brand Names Not Always Equivalent

It is usually assumed that a drug bearing a generic name is equivalent to the same drug with a brand name. However, this is not always true. Although chemically equivalent, drugs having the same nonproprietary name but different proprietary names, because they are manufactured by different laboratories, can markedly differ in their pharmacological action. Several factors, such as those pointed out by Sadove, account for this difference: size of crystal or particle, its forms, and isomers; form of the agent–solution vs. salt and type of salt; vehicle (primary and secondary), excipient, or binder; coatings, number, and types; degree of hydration of crystal or addition of dehydrating substances to package, or hydration of diluents, vehicles, and the like; diluent; purity–type and number of impurities; viscosity; pH; sustained-release forms; enteric coating; solubility; vehicle, base, or suspending agents; container–stopper, type of glass, whether or not glass is preheated or impervious; package, dating, type, literature enclosed, dehydration of cotton in package–amount of cotton; quality of active ingredient: relative and absolute; contaminants; allergenic substances (primary and secondary) in product; irritation; melting point; ionization of ingredients; surface tension–surface-active agents; storage factors: time, heat, light, vibration; flavoring and

coloring agents; dose or quantity of drug, its distribution, and size of tablet or surface-to-tablet ratio; type and characteristics of gelatin capsules; antioxidant included in preparation; dissolution and disintegration rate; buffer type and amount; air, mold, or bacterial contamination of product; antibacterial preservative; metallic contamination in process of manufacture or in packaging.

The following among certainly many other drugs have been found to differ in pharmacological action when supplied by different manufacturers: chloramphenicol, prednisone, *p*-aminosalicylic acid, phenylbutazone, acetylsalicylic acid, sulfisoxazole, diphenylhydantoin, meprobamate, secobarbital, digitoxin, penicillin G, dextroamphetamine, chloral hydrate, heparin, dicumarol, diethylstilbestrol, digoxin, oxytetracycline, tetracycline, acetaminophen, ampicillin, chlordiazepoxide, erythromycin, nitrofurantoin, riboflavin, sulfadiazine, warfarin.

IV. METABOLISM OF DRUGS

Drugs and other foreign compounds which enter a living organism are stored in the body or removed from it after a period of time. While inside the body, they may remain intact or undergo chemical transformation, giving compounds (*a*) less active, or (*b*) more active, or (*c*) having similar or different activity. This process of chemical alteration of drugs inside the living organism is called *drug metabolism.*

Drugs such as analogues of biogenic amines, steroids, purines, pyrimidines, and amino acids resemble closely substances normally present in animals, including man. For this reason, they may undergo the same specific interactions with enzymes, carrier proteins, and transport systems as their endogenous counterparts.

Most drugs, however, have no relationship whatsoever with normal body substrates. Hence, their metabolism involves nonspecific enzymes, and their movement across membranes and barriers is carried out by either passive diffusion or nonspecific transport systems.

A. Factors Influencing Metabolism

Dearborn has pointed out several factors which affect the metabolism of drugs:

1. Internal environmental factors: sex, age, weight, nutritional state, activity, body temperature, flora and fauna of intestinal tract, pregnancy, emotional state, other chemicals present, hydration, genetic composition, enzyme activity states.

2. Drug administration factors: route of administration, site of administration, rate of administration, volume administered, vehicle composition,

number of doses – duration of therapy, frequency of dosing, physicochemical state of drug.

3. External environmental factors: temperature, humidity, barometric pressure, ambient atmospheric composition, light, other radiation, sound, season, time of day, presence of other animals, habitat, chemicals, handling.

B. Site of Metabolism

Most drugs are metabolized in the liver through the action of microsomal enzymes. The intestines, brain, kidneys, and lungs are other sites of drug metabolism.

C. Phases of Metabolism

According to Williams, drugs which are foreign to the body are generally transformed to metabolites of ever increasing polarity, until they can be easily excreted by the kidneys. Figure 1.1 represents this process, which is

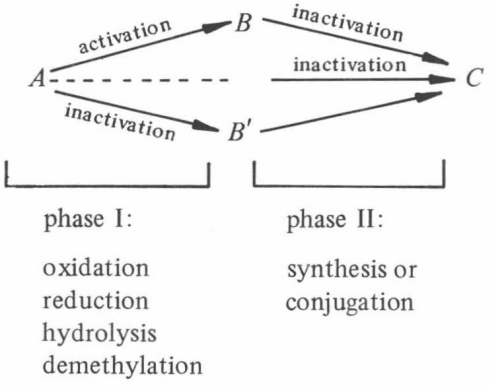


Figure 1.1 Routes of drug metabolism, according to R. T. Williams, *Detoxication Mechanisms*, 2nd ed., Wiley, New York, 1959, p. 735.

usually biphasic. In the first phase, nonpolar drugs are either inactivated, in general, or activated, in some cases, by the introduction of polar groups through oxidation, reduction, and hydrolysis or by the removal of nonpolar (alkyl) groups in order to uncover potential polar groups. In the second phase, the polar compounds are inactivated by a process of synthesis or conjugation, such as methylation, acylation, thiocyanate formation, mercapturic acid formation, glucuronic acid conjugation, amino acid conjugation, and sulfate conjugation. Therefore, the drug administered may be excreted (*a*) unchanged, (*b*) oxidized, reduced, or hydrolyzed, (*c*) conjugated. Some examples of drug metabolism are given in Table 1.1.

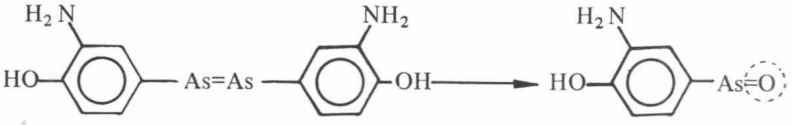
Table 1.1 Metabolism of Some Drugs

parathion
(inactive)

paraoxon
(active)

chloral hydrate
(active)

trichloroethanol
(more active)

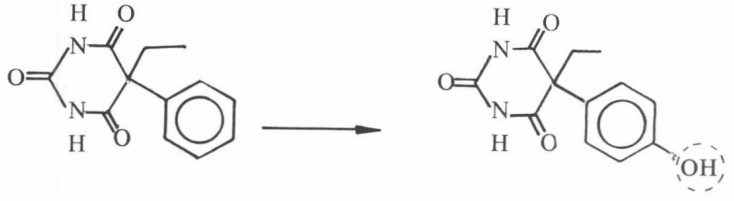


arsphenamine
(active)

oxophenarsine
(more active)

amphetamine
(active)

hydroxyamphetamine
(less active)



phenobarbital
(active)

p-hydroxyphenobarbital
(inactive)

D. Stimulation or Inhibition of Metabolism

Compounds are known which either stimulate or inhibit drug metabolism. Stimulants shorten the duration of action of a drug by inducing liver microsomal enzymes. More than 200 different compounds have this property; examples are barbiturates, polycyclic hydrocarbons, imipramine, glutethimide, phenylbutazone, nikethamide, glucocorticoids, DDT, chlordane, anabolic steroids, tolbutamide, spironolactone. Inhibitors impair drug metabolism by prolonging the duration of drug action; examples are SKF 525-A (diethylaminoethyl diphenylpropylacetate), Lilly 18947 (2,4-dichloro-6-phenylphenoxyethyl diethylamine), monoamine oxidase inhibitors, thyroxine, alloxan, morphine, DPEA (2,4-dichloro-6-phenylphenoxyethylamine), SKF 26754-A (aminoethyl diphenylpropylacetate), carbon tetrachloride.

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