MODERN PHARMACOGNOSY

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Library of Congress Catalog Card Number: **58-10003**

THE MAPLE PRESS COMPANY, YORK, PA.

PREFACE

The drugs of biological origin continue to remain the backbone of drug therapy; in fact, they have increased in significance. The enormous development of structural and dynamic biochemistry in the last decades, however, has created a need for an up-to-date text considering the natural drugs from a biochemical standpoint. *Modern Pharmacognosy* places greater emphasis on the biochemical relationships of drug materials, attempting to create a better understanding of the participation of drug components in cell metabolism, their significance in the drug producing organisms, and their relationship to the fundamental conversions of amino acids, carbohydrates, and fats.

Intended primarily as a text for the pharmacy student, this work gives him biochemical insight that is indispensable for the understanding of the natural drugs themselves and is an invaluable asset when the student undertakes his subsequent studies in pharmacology. Because of its approach, it will also be of interest to pharmacologists, physiologists, manufacturing pharmacists, and pharmaceutical chemists.

To provide better integration of the individual drugs and a clearer understanding of the relationships between them, a biogenetic classification is most suitable and has been adopted; a chapter on biogenesis has been included for the same reason. Also included are chapters on the variability of natural drug products, microbiological fermentation methods, the commercial aspects of drug production, and the analysis and storage of crude drugs. Understanding largely replaces the need for details, and therefore principles, rather than details, have been stressed. A general discussion at the beginning of each chapter applies to the whole group of drugs under discussion, and particulars are included under the individual drugs. Structural formulas of drug constituents have been used to illustrate biochemical relationships. To relieve the text of cumbersome details, certain information has been tabulated, especially information not found in pharmacopeias and other common reference works. References to recent literature are given at the ends of chapters to serve as a source for further and more detailed information. According to the wishes of the editor, epithets of botanical binominals have been written consistently in the lower case to bring them into harmony with bacteriological and zoological nomenclature practice.

With regard to the drugs included in the book, only those drugs which are of great importance in contemporary medicine and cosmetics have been considered, while drugs that are used rarely, or the use of which is not based upon scientific rationale, have been omitted. But even by severe use of the pruning knife, the remaining number may still seem high for the student.

Most of the material for the chapter on Commercial Aspects of Drug Production was furnished by S. B. Penick and Company. Frank O'Connell wrote with me the chapter on Variability in Drug Activity, and Roger Smith contributed to the section on Alkaloid Biogenesis. I am obliged to Edward Woodward of S. B. Penick and Company, to Frank O'Connell, and to Al Goodeve, who have read most of the manuscript, corrected errors, and given valuable suggestions. George Yim gave me valuable criticism on pharmacological statements. Goodeve also helped me in preparing several illustrations, Elmore Taylor has prepared the index, and Mrs. Theodore Andrews checked the literature references.

Over the years I have discussed with colleagues many problems having to do with the writing of this textbook, and they have given freely of their advice. Governmental agencies, industrial firms, scientific journals, and many scientists at home and abroad have been very helpful in providing up-to-date illustrations. I am deeply indebted to them all for their help.

Egil Ramstad

CONTENTS

Table of Measures

Metric Unit	International Symbol	U.S.P. XV Designation	Metric Equivalent	Approximate U.S. Equivalent
*kilo*meter	km		10^3 m	0.62 mile
*hecto*meter	hm		10^2 m	
*deka*meter	dkm		10 m	
meter	m	M.	International prototype	3.28 feet
*deci*meter	dm	dm.	10^{-1} m	
*centi*meter	cm	cm.	10^{-2} m	
*milli*meter	mm	mm.	10^{-3} m	0.039 inch
micron	μ	μ	10^{-6} m	
millimicron	mμ		10^{-9} m	
ångström	Å	A	10^{-10} m	
hectare	ha		hm^2 ($=10^4$ m^2)	2.47 acres
liter	l	L.	Volume of 1 kg of water at 4° and 760 mm Hg (approx. 1 dm^3)	1.06 quarts
milliliter	ml	ml.	10^{-3} l (approx. 1 cm^3)	16.23 minims
microliter	μl (or λ)	μl.	10^{-6} l (approx. 1 mm^3)	
ton	tonne		10^3 kg	1.10 short tons 0.98 long ton
kilogram	kg	Kg.	International prototype (approx. mass of 1 liter of water at 4°)	2.20 pounds avoir. 2.68 pounds apoth.
gram	g	Gm.	10^{-3} kg	0.77 scruple 0.257 dram apoth.
milligram	mg	mg.	10^{-6} kg	0.0154 grain
microgram	μg (or γ)	μg.	10^{-9} kg	

Temperature (T) is given in Celsius (centigrade) degrees (°C).

$\frac{9}{5}\, T°C + 32 = T°F$(ahrenheit)

- - - - → reaction not proved
——→ reaction known to occur
—⫲—→ reaction in several steps

Part One

1

INTRODUCTION

The science of drugs is divided into three branches: (1) *pharmacy* (φάρμακον = poison or drug), which treats of drugs: their procurement, testing, storage, and conversion into suitable medicinal forms; (2) *pharmacodynamics* (δύναμις = force), a branch of physiology, which is concerned with the action of drugs upon the animal organism; and (3) *pharmacotherapy* (θεραπέια = treatment), the science of the use of drugs in the treatment of diseases. The latter two branches are generally designated as *pharmacology* (λογος = word, knowledge).

Drugs are agents used in the treatment of diseases. They may be *organic* or *inorganic*. Organic drugs are essentially of two types: (1) purely synthetic, the product of man's creation of new chemical entities, nonexistent before the era of synthetic chemistry; and (2) drugs of biological origin, produced in the living cell, biogenic drugs.

Pharmacognosy is the science of drugs of biological origin (γνώσις = knowledge). The designation pharmacognosy, as coined by Seydler in 1815, originally included the knowledge of *all* drugs, whether inorganic or of animal or vegetable origin. The term *physiopharmacognosy* (φύσις = nature), proposed by Wasicky, is a more appropriate name than pharmacognosy but has not won general acceptance.

Pharmacognosy has been the subject of great development during the twentieth century. A century ago, the objective of pharmacognosy was limited primarily to the recognition of crude plant and animal drugs and their sources. The pharmacist then was personally concerned both with the procuring of drugs and the manufacturing of galenical preparations from them.

With the discovery by Jakob Schleiden in 1857 that various types of sarsaparilla root can be distinguished by means of their endodermal cells, drug histology was recognized as an important means of detecting impurities and adulterants in crude drugs. Commerce made more foreign drugs available and adulterations became more common; and with the rise of drug houses, drugs became available not only in whole form but also in cut and powdered form. The powders could not be identified with certainty by visual inspection only, and, as a result, the identification of some drugs and the testing of their purity became much more complex.

The rapid development of organic and inorganic chemistry during the nineteenth century had a strong impact upon pharmacy, and it became

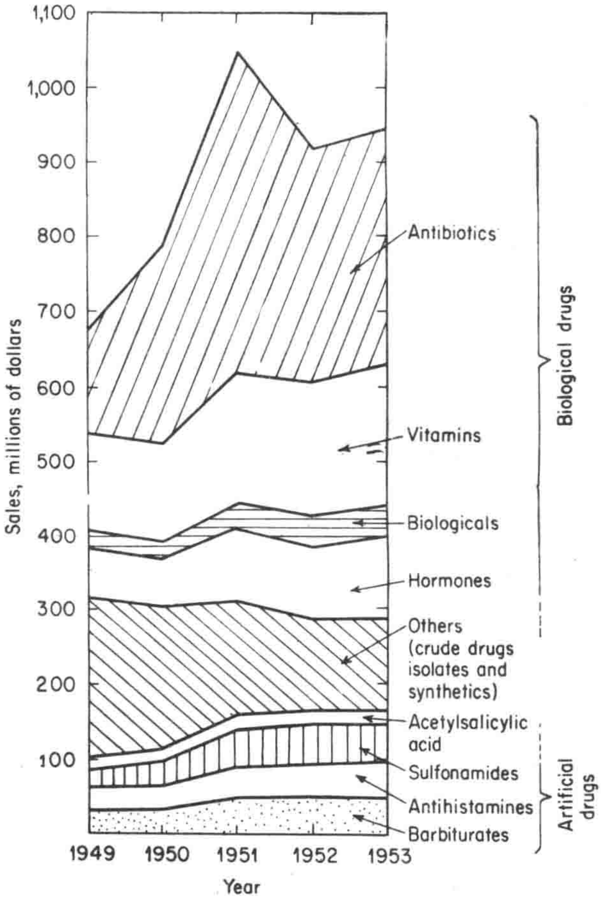

FIG. 1.1 **Sales of ethical drugs at manufacturers' level.** (*Adapted from R. F. Larsen et al.: Chem. Week,* **74(2)**: 24, 1954.)

necessary for the pharmacist to understand chemistry. Indeed, pharmacists pioneered in the progress of this science. In the latter half of the nineteenth century, substances entirely synthetic found their way into therapy (ether, chloroform, sulfones, and barbiturates). Thus, knowledge of synthetic chemistry also became a necessity, and qualitative and quantitative analysis became indispensable for controlling the quality of pharmaceuticals.

At the turn of the twentieth century, drugs in crude form still played a dominant role in medicine as compared with chemically pure compounds. Technical development flourished and the growth of science progressed rapidly. Industrialization prospered and the invention of improved means of transportation changed concepts of distances, leading to widespread commercial expansion. Pharmacists could no longer collect drugs themselves and, more and more, reliable pharmaceutical manufacturers took over the procuring and extraction of crude drugs as well as the synthesis of pharmaceutical chemicals. Many of the constituents to which crude drugs owe their activity now became available in pure form. The crude drugs, which continued to serve as the source of a majority of the more important drugs, were procured and processed by the chemical and pharmaceutical industries, while a smaller portion of the unprocessed materials went to the retail pharmacies. A tendency to specialization within pharmacy had occurred, and this development has continued to this date.

The branching off of pharmaceutical chemistry as a specialty from pharmacognosy gradually led to some confusion in definition and delineation between the two fields. The chemical aspects of crude drugs, the very reason for their use, often became subordinated in the teaching of pharmacognosy and emphasis was placed, instead, on taxonomy, morphology, and the anatomy of crude drugs. However, during this century pharmacognosy has undergone a development from taxonomic studies of source materials, methods of processing, and morphologic, anatomic, and chemical studies to include such areas as biochemical, physiological, and genetic investigations of the drug sources. Pharmacognosy also sees as its objective the study of the use of microbes, plants, and other natural products not yet investigated or not yet developed into practically useful drugs or chemicals.

Alexander Tschirch (1856–1939), one of the founders of modern pharmacognosy, defines pharmacognosy in the following way: "By the term Pharmacognosy is meant the science whose object it is to study scientifically the drugs of plant and animal origin[1] from every viewpoint, with exception of their physiological action, to describe them correctly and correlate them under certain general viewpoints."

Pharmacognosy, to meet this definition, must of necessity be of very broad scope, making use of a great variety of supporting sciences from which it draws for its own purposes. Like most applied sciences, pharmacognosy unites a variety of disciplines, yet is different from any of them. Also, like other biological sciences, pharmacognosy has utilized related fields to bridge the transition from a descriptive science to a functional science.

[1] Microbes played an insignificant role in drug production when he wrote this.

Thus, the science of pharmacognosy is now concerned also with such problems as the biogenesis of drug products, drug resistance, mutation and adaptation, and the effect of environment on drug-producing organisms. It shares ground with chemistry, biochemistry, physiology, enzymology, food technology, bacteriology, and a number of other fields of specialization. As a result of the wide scope of pharmacognosy, research pharmacognosists specialize in definite areas, although they must be familiar with all areas in a general sense. The fields of specialization which pharmacognosists may choose include taxonomy, anatomy, morphology, plant physiology, genetics, biochemistry, phytochemistry, drug-plant cultivation, microbiology, and several others.

Of prime importance to all pharmacists is the understanding of the active principles of drugs as chemicals. Pharmacognosy can and does supply the general information needed by all pharmacists and the specific information needed by specialists. The practicing pharmacist will be interested in solubilities (dispensing), reactivity (incompatibilities), stability (storage), toxicity, and dosage. The manufacturers, upon whom the retail pharmacist must rely to a large extent, are concerned with availability (procurement), purity and yield (cost and analysis), and ease of extraction and purification (production). The scientist, and the manufacturer too, being interested in the search for new materials and improvement of the old, will concern themselves with problems of isolation and identification, breeding and cultivation of drug plants and microbes, biogenesis of active principles, and other methods which lead to improvement.

A general understanding of all of these phases of pharmacognosy is necessary background for all members of the pharmaceutical profession. For this reason, pharmacognosy, the science of drugs of biological origin, has become a discipline of increased significance in the curriculum of pharmaceutical education.

Classification of Natural Drugs. In any organized treatment of drugs, the drugs must be grouped into a system so as to facilitate discussion and to bring about a better understanding by correlating them. Several different systems of classification have been used with different purposes in mind: (1) alphabetic system, which is used only in lexicographic books including pharmacopeias; (2) taxonomic system, significant for the identification of drug-furnishing organisms and investigation of new sources of supply and of related species; (3) morphologic system, valuable in the identification of crude drugs; (4) therapeutic system, useful to physicians; and (5) chemical system, important for storage, identification, evaluation, extraction and purification, for pharmaceutical operations, and also for work on quality improvement, biogenesis, and understanding of pharmacological behavior. The chemical system is used in this book.

A chemical classification may be based upon functional groups in the molecule or upon general structural features of the whole molecule. According to the first method, such widely divergent compounds as ethanol, ascorbic acid, menthol, and morphine could all be placed in the same group, all being alcohols; while the second method might place them in aliphatic, heterocyclic, hydroaromatic, and aromatic groups respectively. A "natural" chemical system of classification, however, can be based upon the natural kinship between various chemical compounds based upon the source of their origin, i.e., a biogenetic system. Such a classification is simplest, least ambiguous, and gives a better understanding of the material. It should be stated, however, that while the biogenesis of primary metabolites has been investigated and clarified quite extensively, the final proofs of the biogenesis of secondary constituents often are still to be produced.

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2

THE DEVELOPMENT OF MATERIA MEDICA

It is difficult for man to visualize today the hardships his ancestors faced in days gone by. Life was hard, cruel, merciless, and short, and only the most fit were able to survive. The life span of the neolithic man is as yet unknown, but the average life span about A.D. 1600 in the city of Genoa, computed from records of the city, was an unusually low eight years. Since then years have been added gradually to man's life span. During the last part of the nineteenth century life expectancy in Western Europe and North America climbed to approximately thirty-five years. In the last half-century the average life span in these parts of the world has almost doubled, being now about 40 per cent higher than in 1900. Recent progress is illustrated by the fact that the death rates for ages 1 to 4 decreased in the United States from 20 per 1,000 in 1900 to 1.7 per 1,000 in 1952. This conspicuous change is attributed to sanitary, hygienic, nutritional, medical, and social developments.

It is true that in the field of therapeutics more progress has been achieved during the last century than from the Neolithic age up until 1850. In fact, in the last century man was in a less favorable situation with regard to health than were the neolithic tribes. The agglomeration of populations into industrial cities, which lacked adequate sanitation facilities, created conditions that were favorable for ravaging epidemics. Such a lack of sanitary provisions was of no concern to the scattered neolithic tribes. Furthermore, the ever-increasing use of preserved food led to the appearance of vitamin-deficiency diseases, which, there are reasons to believe, were rare or nonexistent in prehistoric times.

The extremely rapid development of therapeutic and prophylactic medicine in recent years, however, should not lead us to think that the knowledge of drugs in past ages was insignificant. Ancient man, having no accumulated knowledge or precedent to draw upon, made discoveries only by accident or by time-consuming trial and error. Consequently, progress in medical knowledge was extremely slow at first but it was carried on through the course of thousands of years during man's endeavors to control nature. Past generations, through their work, struggles, failures, and successes, laboriously laid the foundations upon which the material and intellectual structure of modern societies could be erected.

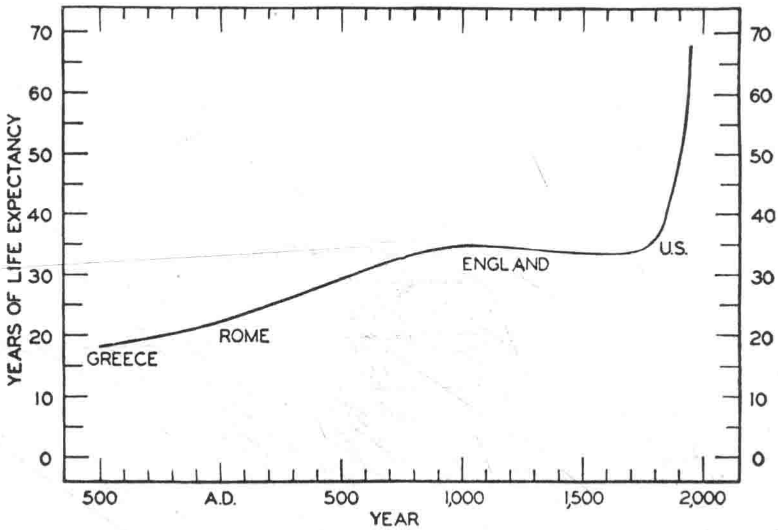

FIG. 2.1 Average life expectancy of man during past centuries. (*Reprinted from N. W. Shock: Trends in Gerontology, 2d ed., with the permission of the publishers, Stanford University Press. Copyright* 1951/1957 *by the Board of Trustees of Leland Stanford Junior University.*)

Man appears to be afflicted with more diseases than any other animal species. There can be little doubt that he very early sought to alleviate his sufferings from injury or disease, taking advantage of the plants growing in his environment. Our ideas about the medicine of prehistoric times is largely guesswork since only few relics of an organic nature remain from those remote times. Some of the oldest drugs known were found in the pileworks of the lake dwellers of Switzerland (5000 to 6000 B.C.). More than 200 different plants found among these remains have been identified. Some of them are still being used in medicine. The purveying and storing of drugs seem to have been the job of women at first. Only later, when drugs also could serve the purpose of imparting power and influence to the individuals who knew how to handle them, did drugs become the field of elevated men or priests.

The medical knowledge of prehistoric man was essentially empirical. The principle of cause and effect must have been understood at a very early stage, and the effects of the various products that served him as food certainly gave him considerable knowledge about the plants and their virtues. Both curiosity and the continuous search for food made him a