THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE

A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine

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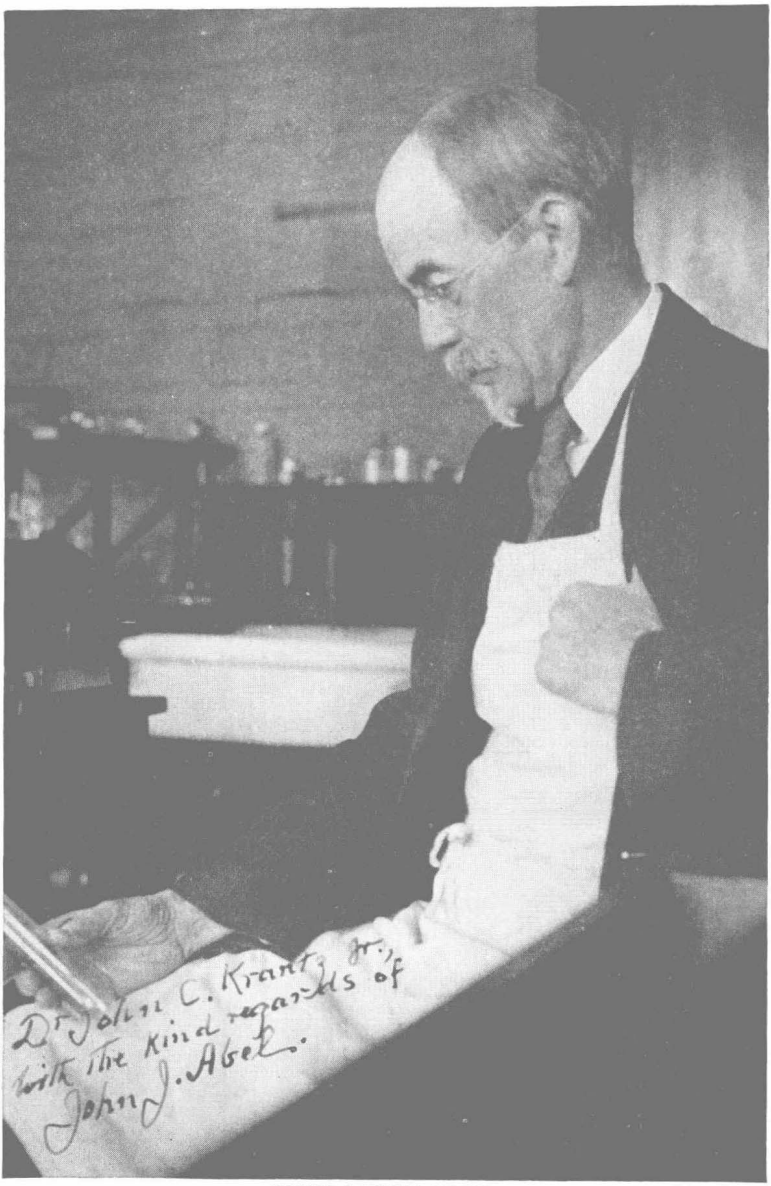

JOHN JACOB ABEL
1857–1938
The Dean of American Pharmacologists

"This substance, as we now know, is an amino alcohol of a relatively simple constitution, characterized by the chemical name dihydroxymethylaminoethylol-benzene (epinephrine)".

Preface to the Fourth Edition

The principal aim of the fourth edition of this treatise is the same as that established in the previous editions. It is expressed in the title. "Principles" embraces what to do and why; "practice" is how to do it and when. We have retained essentially the same general arrangement of the subject matter.

Several changes of considerable magnitude have been made. These are the removal of the chapter on the antihistaminics from the section on the autonomic nervous system to Part IX to become a part of a new chapter on "Pharmacologic Agents in Allergic Diseases." Two new chapters have been included; namely, "Use of Drugs in the Treatment of Mental Illness" and "The Local Use of Drugs in the Ear, Eye, Nose, and Throat." The chapter on epilepsy has been enlarged to include other hyperkinetic states.

Many other changes in the text have become necessary owing to the rapid advances which have been made in the medical sciences. New concepts of the nature of disease and its treatment with drugs acting at an enzyme level have been included. Most of the chapters have been expanded, such as those on the *antibiotics*, *hypertension*, the *arthritides*, and *diabetes*. To conserve space many drugs no longer generally used have been deleted. The fourth edition has been brought abreast of the United States Pharmacopeia XV and the National Formulary X. Approximately 140 new drugs not mentioned in the third edition are included in the fourth edition. No effort has been made to include all dosage forms and drug mixtures. For this information the reader is referred to the numerous drug encyclopedias. Generally-used drugs representing types of therapeutic agents are included, which illustrate pharmacologic principles. From a knowledge of these the reader can evaluate the efficacy of similar drugs.

We have adhered to our previous policy of using the name for a drug by which it is most generally known to the medical profession. Thus in some instances the official name is employed, whereas in others when only one trade name is extant we have for convenience used it in preference to the less commonly used official name.

Many new charts and figures have been included. The chemical formulas have been made to conform with those in The Merck Index, Pharmacopeia of the United States, and New and Nonofficial Drugs.

The authors are grateful for the many friendly, critical, and constructive suggestions which have come to them from teachers of pharmacology in schools of medicine, dentistry, pharmacy, and veterinary medicine. We welcome further comments.

In the revision of the text, which involves many areas of clinical med-

icine, we employed the same policy used in preparing the original manuscript, i.e., sending sections of the text for criticism and review to various specialists. This help has been of inestimable value. To the following specialists who have served in this capacity we are greatly indebted:

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Part I

THE HISTORY OF PHARMACOLOGY, PHARMACOLOGIC PRINCIPLES, AND AN INTRODUCTION TO DRUGS

CHAPTER 1

The Scope of Pharmacology

Pharmacology is the science that deals with drugs. In its broadest sense it includes all of the knowledge that has been accumulated regarding medicinal agents. The word pharmacology is derived from the Greek words *pharmakon* (drug) and *logos* (a discourse or treatise), and hence includes such allied fields as *pharmacy*, *pharmacognosy*, *toxicology*, *posology*, *chemotherapy*, *therapeutics*, and *materia medica*. Each of these subdivisions of pharmacology is a highly specialized field of endeavor and makes its contribution to our composite knowledge of drugs. The word drug is derived from the French word *drogue* which means a dry herb. The Federal Food, Drug and Cosmetic Act defines a drug as follows: The term *drug* means (1) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals.

Pharmacy is concerned with the collection, preparation, and standardization of drugs. Its scope includes the cultivation of plants which serve as drugs, the synthesis of chemical compounds of medicinal value, and the chemical analysis and testing of the agents used for medicinal purposes. The pharmacist is responsible for the manufacture of *dosage forms* of drugs, such as tablets, capsules, and sterile solutions for injection. He compounds prescriptions for drugs.

Pharmacognosy is the science of identification of drugs. The scope of the pharmacognosist is confined to drugs of vegetable and animal origin.

He is concerned with the characteristics of various species of plants, their gross and cellular structures, and also characteristics which serve as means of identification. The present-day pharmacognosist is concerned with the biochemistry of plants (biosynthesis), molds, fungi, sera, and vaccines.

Toxicology is the science of poisons. It is concerned with the mechanism of action of poisonous substances on living organisms. Further, the symptoms produced by the ingestion of poisons frequently shed light upon the mechanism of the action of the poison if it is administered in smaller doses as a drug. The toxicologist as a medico-legal officer is interested in the chemical detection of poisons where criminal intent is suspected. Also from the point of view of environmental hygiene the toxicologist is called upon to determine the toxicity of industrial dusts and vapors in order to protect the health of individuals exposed to these hazards.

Another important phase of toxicology is the selection of antidotes for poisons. This phase of the science is of great importance to the physician for he is frequently called upon to treat an individual who has accidentally or purposefully ingested a poison.

Posology is the study of dosage. It is an important division of pharmacology. A knowledge of the dose of commonly-used drugs is an essential factor in acquiring confidence in prescribing. Doses vary with individual tolerance and susceptibility. Generally speaking, a dose of a drug may be considered that quantity which is required to elicit the desired therapeutic response in the individual. In brief, it is "*enough*".

Chemotherapy is the use of chemical agents in the treatment of infectious diseases. Substances so employed are referred to as *chemotherapeutic agents*. These agents are designed to kill the invading organisms without harmful effects upon the host.

Therapeutics in its broadest sense may be considered as any measure which is taken in the treatment of disease. The word in Greek means the *art of medicine*. The pharmacologist is primarily concerned with one branch of therapeutics, namely, pharmacotherapy, i.e., the administration of drugs to the sick. This is in contradistinction to physiotherapy and psychotherapy, which are measures not involving the use of drugs. Naturally the physician is fundamentally interested in pharmacotherapy and it is this phase of pharmacology which makes the greatest contribution to medicine.

Materia medica is the division of pharmacology that treats of the sources, description, and preparations of drugs. It is an older term and its use in medicine appears to be diminishing. Years ago as a didactic, descriptive body of knowledge concerning drugs, materia medica had a prominent place in the medical curriculum. It has now been replaced by the experimental science of pharmacology.

FRANÇOIS MAGENDIE
1783–1855
The First Pharmacologist

"Facts and facts alone are the foundation of science. . . . When one devotes one's self to experimental research it is in order to augment the sum of known facts, or to discover their mutual relations."

Pharmacology in a more restricted sense has come to mean the study of *the response of living organisms to chemical stimuli*. One may further divide the subject in this restricted sense into *pharmacodynamics* and *pharmacotherapy*. The former division of the science is concerned with the response of living organisms to chemical stimuli in the absence of disease. The latter branch of pharmacology, namely, pharmacotherapy, deals with the response of the organism in a pathologic state to chemical stimuli. This is the phase of pharmacology which is of special interest to the physician. It includes the treatment of the sick with drugs and therefore is of prime importance in the practice of medicine. It is fundamental in the health economy of any people.

The foregoing definition of the science of pharmacology is a comprehensive one and it is of interest to view the scope of this science. The action of insecticides on plant and animal cells and the health hazards involved in their use comes within the purview of the science. The response of bacteria and animal parasites such as intestinal worms and amoeba to chemical stimuli comes within the scope of this subject. The treatment of diseases of poultry and cattle has definite pharmacologic features. Chronic intoxication that might be caused by the ingestion of chemical agents added to food products is a problem of concern to the pharmacologist. Although these and other ramifications of the science have a broad public health implication, the primary concern of the physician in this science lies in pharmacotherapy.

One might well inquire as to the interest of the physician in pharmacodynamics, i.e., the response of tissues to chemical stimuli in the absence of disease. The response of non-pathologic tissues to chemical stimuli is a necessary study in order to understand the mechanism of the action of drugs. A knowledge of pharmacodynamics is essential often as a basis of pharmacotherapy. Besides, it is frequently impossible to produce in animals pathologic conditions identical with diseases which occur in man. Therefore the pharmacologist is called upon to study the pharmacodynamic activity of a chemical compound and through his skill and experience offer a prognosis as to its possible use as a therapeutic agent in the treatment of disease in man. Indeed the study of the response of normal tissues to the action of chemical substances has done much to shed light on physiologic mechanisms and also to elucidate the action of drugs which have been used empirically in the treatment of disease.

Pharmacology and the Basic Medical Sciences

Although pharmacology is the youngest of the basic medical sciences, its scope is constantly enlarging and its contribution to therapy has made its position in medicine an important one. Its relationship to the other

medical sciences is interesting and enables one to understand better the position of this science in the training of a student in medicine.

Physiology is concerned with the function of the systems of the living organism. *Biological chemistry* deals with the changes in composition of matter which occur in the processes of life. *Pathology* treats of morphologic, functional or chemical changes and imbalances which may occur to the normal organism. Pharmacology uses chemical stimuli to produce changes in function and sometimes in the morphology of living systems. This is pharmacodynamics. When a living system is in imbalance through distortion of normal bodily processes a pathologic condition is present; it is then that the chemical stimulus, the pharmacologic agent, the drug, is administered to attempt to reestablish the organism to a normal physiologic and chemical balance. In the parlance of the clinic, a drug is administered to alleviate symptoms and possibly cure the diseased condition. Examples will serve further to show this relationship between the sciences.

Let us consider the trihydric alcohol glycerin $C_3H_5(OH)_3$. As a product of digestion from edible fats the biological chemist is concerned with its fate in the body. He is interested in the fact that it can serve as a precursor of glycogen. The steps of its catabolism in the body from glyceric aldehyde to carbon dioxide and water constitute an important metabolic pattern of the fate of this substance in the animal organism. Substances of this character which serve essentially as foods are not the primary concern of the pharmacologist. If, however, one replaces the 3 hydroxyl groups in the glycerin molecule with 3 nitrate radicals, producing glyceryl trinitrate ($C_3H_5(NO_3)_3$, the compound serves no longer as a food. The oily glyceryl trinitrate, in exceedingly small doses, dilates the blood vessels, causing a fall in blood pressure. The coronary arteries share in this dilatation and hence glyceryl trinitrate serves both as a drug and a therapeutic agent, and has been thoroughly studied by the pharmacologist. It is used in the treatment of coronary artery disease.

The effect of ethyl alcohol C_2H_5OH on the animal organism is intriguing and illustrates the divisions of interest among the basic medical sciences. When ingested in small quantities alcohol produces no symptoms. It is metabolized, producing carbon dioxide and water, and each gram gives rise to 7 calories. Hence in small quantities alcohol serves merely as a food and its fate in the body is mainly a biochemical problem. In larger amounts alcohol profoundly affects the central nervous system, causing a depression of the inhibitory centers in the brain, and produces the pharmacologic syndrome of inebriety. This phase of the action of alcohol brings it immediately within the scope of pharmacology, and as a drug it has been extensively investigated.

As a product of a gland of internal secretion the physiologist studies the

effect of cortisone on the living organism. The action of cortisone on the organism under stress and its effect on metabolism are of prime physiologic importance. As a product from the adrenal glands, available as a therapeutic agent, the pharmacologist has interest in this compound. It is a potent drug, useful in the treatment of arthritis and certain other diseases.

Indeed one can readily judge from the examples cited that there are no sharp lines of demarcation between the basic medical sciences. The overlapping is frequent and far reaching. In fact the student must view the basic medical sciences as a specialized study of biology. These sciences are the study of the human body in health and in disease, structurally, functionally, and chemically. When outside chemical stimuli are introduced we designate the study as *pharmacology*. It is clear that these divisions of the sciences are man made. They are useful for the systematizing of knowledge only. The ultimate purpose of each is the same, i.e., *understanding of life processes and the utilization of this knowledge for the health of mankind.*

CHAPTER 2

The Historical Development of Pharmacology

Introduction. Fighting disease with drugs is a timeless struggle. Its beginnings echoed out of the primeval jungle. Man's survival on this planet has depended upon its success. Today the conflict continues unabated in laboratory and clinic. The scientific approach to this struggle is pharmacology.

Paracelsus. There are several significant events in the history of science which led to the development of pharmacology as a separate and distinct medical discipline. One of the first of these was the life and work of the Swiss physician-chemist Paracelsus. Paracelsus appeared upon the European scene at the beginning of the Renaissance. He was a contemporary of Columbus, Martin Luther, and Michelangelo.

Prior to the time of Paracelsus the purpose of chemistry had been to search for the philosopher's stone, a fictional charm which would confer perpetual youth and convert the baser metals into gold. Paracelsus appeared upon the stage of science and medicine, not as a careful experimenter, but as a timely iconoclast. He thundered his stirring message through the ranks of the medical and chemical practitioners of his time. "The purpose of chemistry is not to make gold but to study the fundamental sciences and turn them against disease." "Not gold but medicine is the purpose of chemistry" declared Paracelsus. The message of Paracelsus penetrated deeply the fabric of chemistry and enlisted this dynamic science as a handmaiden of medicine. It portended the synthesis of thousands of compounds for pharmacologic testing and possible medical application.

Cinchona and malaria. In 1630 the use of Peruvian bark in the treatment of malarial fever was discovered. It became known as the cinchona bark. From this bark 2 centuries later the French pharmaceutical chemists Caventou and Pelletier isolated the alkaloid *quinine*, the first *specific drug* to be used in an infectious disease. The use of quinine in the treatment of malaria, as medicine became more enlightened, required pharmacologic study to place the therapy on a rational basis. Besides, other compounds related to quinine demanded study and the necessity for the skills of the pharmacologist became obvious.

Arsenic linked to carbon. In 1760 Louis Cadet, apothecary to the French army, made cacodyl oxide $(CH_3)_2As—O—As(CH_3)_2$ by heating

together potassium acetate and arsenious oxide. This was the first time that man had succeeded in attaching an arsenic atom to a carbon atom. The experiment portended the synthesis of the organic arsenicals. It meant that the toxicity of this potent element arsenic could be modified by combining it in a multiplicity of organic molecules. Pharmacologic studies would be necessary. They followed, but nearly 2 centuries elapsed before Paul Ehrlich made the organic arsenical, arsphenamine, and used it successfully in the treatment of syphilis.

The purple foxglove. In 1783 the English physician William Withering published his epoch-making monograph on the use of digitalis entitled, "An Account of the Purple Foxglove and its Medicinal Use". Withering had used digitalis in the treatment of dropsy and believed that he was dealing with a drug which had a direct action upon the kidney. How the drug acted was a puzzling question. To explore its many possibilities in therapy became a problem of pressing medical importance. The answer to questions of this character strongly suggested the necessity for the birth of a new science. Later, pharmacology supplied many of the data to answer these questions.

Morphine and other alkaloids. The German apothecary Sertürner isolated from opium the alkaloid morphine in 1807. He showed by experiments on dogs that much of the narcotic activity of opium was dependent upon morphine. This was the *first alkaloid* that was isolated from a plant. It was a forerunner of the rapid series of discoveries which were to follow in this field. For shortly thereafter strychnine, caffeine, emetine, atropine, and quinine were to be separated as pure crystalline alkaloids. Morphine elicited intriguing actions on the living organisms which required pharmacologic study. Later, in the nineteenth century the first pharmacologist *François Magendie* was to study the pharmacologic action of these compounds. But a distinct medical science of pharmacology appeared to be warranted.

Wöhler and urea. One of the most significant events in the history of mankind was the synthesis of urea by Wöhler in 1828. It ranks with the great discoveries of the ages. Wöhler made urea from ammonium cyanate $NH_4OCN \rightarrow (NH_2)_2CO$ by the evaporation of an aqueous solution of the latter. He had made urea without a kidney. But what is more, he had synthesized an *organic* chemical compound without the intervention of the mysterious *vital force*. He had begun an era in chemistry and he had laid the basis for the changing of the character of civilization. Organic chemistry, carbon chemistry, was to rise from this experiment. The chemist was to become a creator. More than a half million new chemical entities were to appear. These are produced at the prodigious rate of about 30 thousand a year. New dyes, new plastics and new perfumes were made. But what about new drugs? A science was needed that had for one of its