# A TEXTBOOK OF PHARMACOLOGY

*ILLUSTRATED*

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*Principles and Application of Pharmacology to the Practice of Medicine*

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# PREFACE

This is a personal book, recording the experiences and reflecting the choices of one who has spent many hours at the bedside of clinical patients as well as long nights in the laboratory. To one who always has in mind the course of human disease and the hope that it may be ameliorated, the vast accumulation of fundamental fact and theory in pharmacology must necessarily be confusing. There are so many side issues, blind alleys and petty experiments which seem to lead nowhere that the medical student and the physician alike are frequently amused and often annoyed with the frustration of pinning the pharmacologist down to concrete cases. In fact the world never knows quite what to expect from a self-styled pharmacologist because the range of that science is so broad. Such remote subjects as pest control, industrial hazards and murder are included in this one science.

Accordingly the author has selected those things which he believes the medical student and the up-to-date practitioner should understand. This does not mean that the presentation cannot be scientific or rigorous. It means simply that the examples which are cited in evidence of fundamental statements are selected from material which has a clinical bearing.

Another very confusing thing about pharmacology is the overwhelming number of facts embraced within its fences. Even today the science bristles with unrelated facts and data. Most of us need some undercurrent philosophy to hold our understanding together. In this spirit the medical pharmacology presented here has been construed in terms of pathologic physiology. It is assumed boldly that disease has a rational and mechanistic explanation in most instances, and that by the same token the remedy of the disease deserves to be expounded in mechanistic terms.

In this narrow sense of pharmacology, therefore, a drug is a remedy for human ills. In some cases we still have little more understanding of our herbs than did the primitive medicine man. In many other instances, however, the mechanism of action has been expounded in careful and logical terms, and new drugs related to some prototype have been developed to improve upon Nature's original dispensation. The ultimate goal of the modern physician must ever be towards rational and well controlled therapeutic and preventive agents. Only under such circumstances can the art and science of medicine blossom into fullest vigor.

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WILLIAM T. SALTER

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# PART I

## GENERAL PRINCIPLES OF PHARMACOLOGY

CHAPTER 1

# *The Heritage of Pharmacology*

Anything green that grew out of the mould
Was an excellent herb to our fathers of Old.
KIPLING: *Rewards and Fairies*

Reading never made a physician. Medicine
is an art and requires practical experience.
PARACELSUS

## THE DEVELOPMENT OF PHARMACOLOGY

**Early Pharmacology.** Stretching back into the dim obscurity of prehistoric times are traces of the medical folklore of primitive peoples.[30] Much of this consisted of chance observations on the effects of food on the skin or isolated organs. Medicine was mingled with magic, and in the witches' cauldron were mixed various materials of animal, vegetable[41] and mineral origin. The medicine man antedated the medical man, but no sharp delineation has ever existed.[63]

Such lore is often held in contempt, notwithstanding the fact that our most potent alkaloids were discovered by primitive peoples.[23] As civilization advanced and a learned priesthood developed, systematic records were kept of these empirical discoveries. The early Egyptian papyri of Ebers (1550 B.C.)[54] and Smith (1700 B.C.) refer to liver as a remedy for anemia. Ultimately the Egyptians[46] developed a codified and conventionalized form of therapy, as exemplified in the Edwin Smith papyrus. They recognized clinical syndromes which could be treated successfully and others which could not. They described in detail procedures for the preparation and administration of remedies. Many of their prescriptions contained combinations of therapeutic materials (polypharmacy).[56] The exact placement of the patient and the dosage of the medicament were prescribed with religious precision.

After *Theophrastus* (370-286 B.C.)[13] had presented his systematic description of the botany of classical times, his work was applied medically about 57 A.D. by *Dioscorides*, the surgeon of Nero.[32] Unlike the Egyptian priests, Dioscorides classified his materia medica[11] by substance rather than by disease. Ultimately this precedent led to the development of modern pharmacopeias. He not only described carefully the individual crude materials in each medicament, but also gave the method of preparation and administration.[8]

One century later *Galen* (131-201 A.D.) extended the work of Dioscorides by developing an elaborate system of polypharmacy which was destined to influence medicine profoundly for some fifteen hundred years.[15] Born at Pergamus, the son of an architect, he began the practice of medicine at Rome in 164 A.D. He became a most skilled practitioner and wrote thirty books on pharmacy embodying his therapeutic endeavors. He initiated the use of the vegetable simples which are still known as "galenicals." He prescribed hyoscyamus, hellebore and colocynth, as well as wine, honey, turpentine and hartshorn.[25] In his eagerness to learn more about therapy he travelled far and wide about the ancient Mediterranean world to investigate native remedies. In his time the "terra sigillata" of Lemnos was a much advertised nostrum, and to be certain that his own skepticism was justified Galen made two journeys to that island.

Fig. 1. Squill plant as it appeared in a sixth century manuscript of Dioscorides (early copy).

Probably his greatest single contribution to therapeutics was the tincture of opium, later named laudanum by Paracelsus.

During the Dark Ages the continuum of medical knowledge, much distorted by armchair philosophy, was preserved by the Persians[26] and by the Arabs.[57, 64] Notable among the Arabs was *Avicenna* or ibn Sina (980-1037), "the Prince of Physicians." As physician-in-chief at Bagdad he enjoyed a lucrative court practice and became vizier to several caliphs. He wrote a hundred works and became known as the father of geology. His orderly mind arranged facts and pseudofacts derived from scholastic ratiocination together in extensive systems. His "Canon," which codified the whole system of medical knowledge, is a miracle of syllogism and was characterized by Haller as "methodic inanity." Nevertheless listed among the complex combinations of drugs which he employed are descriptions of sulfuric acid and of alcohol, with an account of their preparation and properties. Furthermore he and the medieval compilers, like Mesuë who succeeded him, condensed and passed on the vast accumulation of medical recipes derived from the ancient Egyptians and the later Coptic literature and Greco-Roman writers. For example, the use of mercury in skin ointments by the Arabs led directly to its exhibition in lues late in the fifteenth century.

The Middle Ages were the days of polypharmacy, as exemplified by the classical

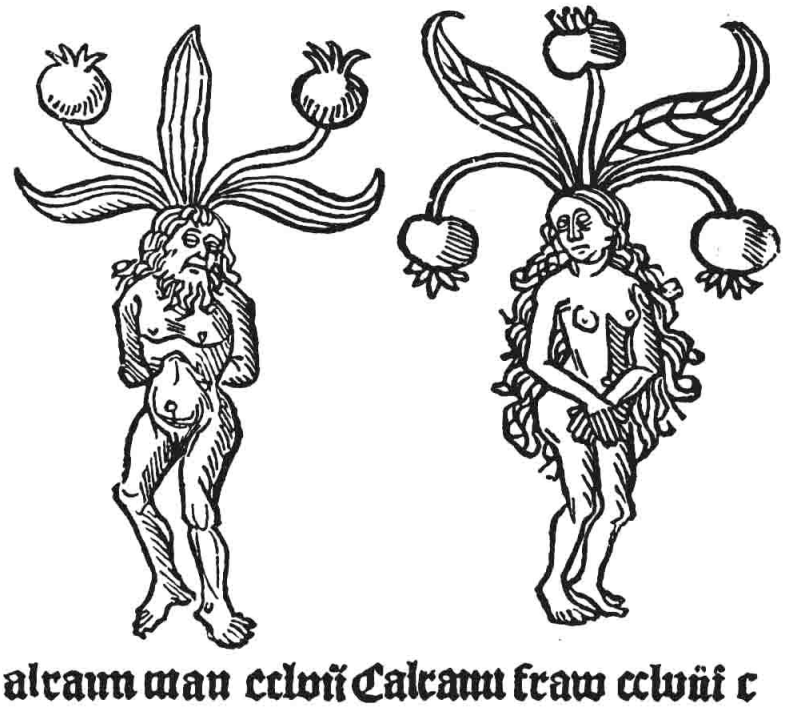


Fig. 2. This excerpt from a medieval herbal illustrates the perpetuation for over a thousand years of the supposed sex difference between the mandrake roots. The originals of this combined plate appeared in the Gart der Gesundheit (Hortus Sanitatis), Joh. Schönsperger, Augsburg, 1485.

Triaca or Theriaca.[7] This preparation contained the flesh of vipers and was supposed to have cured Mithridates, King of Pontus, of snake-bite.[16] In the lifetime of Dioscorides, the "Mithridaticum" had grown to have 57 constituents. By the fifteenth century it had become the Theriaca, with 110 items, and was certified by physicians, pharmacists and potentates in public ceremonies.


Fig. 3. Digitalis lutea as pictured in Fuchs's Hortus. (Fuchs: De Historia Stirpium, Leyden, 1549.)

Early in the sixteenth century appeared the Renaissance herbarium (hortus siccus), as important for art as for pharmacy. Many of these literary gardens have been preserved for present-day inspection and admiration. Line drawings of the best of these were published at Basel in 1542 from a collection compiled by Leonhard Fuchs, an adherent of Luther, who held the chair of medicine at Tübingen (1535-66). A busy practitioner, interested in improving the materia medica of his times, he employed artists to illustrate useful plants in over 500 plates (Fig. 3). From these early efforts stem the complex pharmacopeias of the eighteenth century.

## RISE OF MODERN PHARMACOLOGY

From these beginnings came the pharmacology of today. To its development three chief movements contributed: the development of pharmacopeias, the elaboration of experimental gross toxicology and the rise of chemistry. A brief glance at each of these achievements must suffice to orient subsequent consideration of modern trends.

**Development of Pharmacopeias.** From the early hortus were derived during the sixteenth century reference books of standardized medicinal preparations endowed with legal sanction. In their development the various modifications current among the guilds of the apothecaries were reviewed and made uniform. The relation of dosage to effect was early recognized and many poisonous substances were listed. In the formulation of standard prescriptions, various procedures for preparation were publicized. During this time too the art of distillation which the alchemists had learned from the Arabs was directed toward the production of "elixirs"; and the quest for eternal youth indirectly helped produce drugs conducive to better health.

Fig. 4. A medieval apothecary shop. (Gart der Gesundheit, Peter Schöffer, Mainz, 1485, as modified in Peters: Ancient Pharmacy and Medicine, published by G. P. Engelhard & Co., Chicago.)

Many of the simpler "pure" substances prepared by the alchemists were diverted to medical use. Johann Rudolph Glauber (1604-1688) used sodium sulfate (a modern horse purgative) to cleanse the human intestinal canal. Likewise, Paracelsus (1493-1541) pop-

ularized "tinctures," salts like potassium sulfate, and simple preparations of sulfur, iron and arsenic which were chemical entities.[61] This Paracelsus deserves special mention because he has been called the father of pharmacology—or at least its grandfather.

*Paracelsus,* whose real name was Aureolus Theophrastus Bombastus von Hohenheim,[59] was born in Einsiedeln, near Zurich, the son of a scholarly physician. The son, although endowed with a brilliant mind, was also endowed with a "coarseness of fiber"[55] which made him notorious in his day as a truculent, independent mountaineer. He became a doctor of medicine and a teacher who advanced his science by bullying, browbeating and quarreling. His humor, as George Moore remarked, drifted "from the obscene into the incomprehensible." Nevertheless, his major and minor surgeries and his treatise on industrial diseases contain some remarkably successful guesses at the truth. He had an unusual knowledge of alchemy, mining and astrology.

At first glance Paracelsus' bombastic writings and high-flown verbiage are misleading. When this apparent nonsense is sifted carefully, however, some extraordinary nuggets of sound knowledge appear. Paracelsus discarded Galen's theory of the four humors. He attacked witchcraft. He evolved chemical therapeutic agents from the alchemist's collection. He recognized and treated successfully certain occupational diseases. He taught asepsis! In his journeyings he recognized both the geographical and physiological relationship between cretinism and endemic goiter. The doctrine of signatures, as expanded by Paracelsus and his disciples, heralded the school of homeopathy. Among the various tinctures and alcoholic extracts which he popularized was laudanum, which he prepared from crude opium.

Fig. 5. Woodcut from title page of the Grete Herball. Even as late as 1527 the Grete Herball published in English perpetuated the mythical sex difference in the roots of the May-apple. The Grete Herball, Peter Treveris, 1526.

By 1546 the need for standards and official regulation of drugs had become recognized. Indeed, in that year, Andreas Vesalius wrote a long letter on Smilax (the China root) to that effect. In that year, too, appeared the early genuine pharmacopeia (Dispensatorium), published by authority of the Senate of the City of Nuremberg. It was the work of the brilliant youth *Valerius Cordus,*[68] who had died two years earlier. This gifted young Prussian, the son of a physician and botanist, was the inventor of ether *(oleum dulce vitrioli).* His posthumous commentary on Dioscorides, couched in modern terminology, described some five hundred new species. The Dispensatorium contains the complicated

preparations of that day, but each complex formula was carefully listed to ensure a uniform product and each preparation was given a simple name for easy recognition.

*Mandragora.*

Fig. 6. In Fuchs's herbal the mandrake myth was abandoned. Compare with Figure 2. (Fuchs: De Historia Stirpium, Leyden, 1549.)

**Experimental Gross Toxicology.** Until the seventeenth century gross toxicology had not been studied systematically, although the Medici and their associates doubtless had some vague philosophy regarding poisons. In 1676, however, Johannes Wepfer studied the tetanus produced in dogs by large doses of nux vomica. These observations were followed by those of Anton Störck (1731-1803) upon the effects of hemlock, stramonium, aconite and hyoscyamus. Finally in 1765 Felice Fontana presented a toxicological survey based upon more than six hundred experiments. From his work stems directly our present concept of "localization of site of action" which will be discussed presently.

**The Rise of Chemistry.** The subject matter of pharmacology is a blending of biology and chemistry. In the late eighteenth and early nineteenth century began the stupendous advances in organic chemical synthesis which have revolutionized our civilization.[39] With these advances pharmacology moved forward rapidly. Pure and invariable drugs of known constitution became available. New isolation procedures were developed and methods of chemical synthesis were invented which led to the production of congeners of natural products. The isolation (1806) by Friedrich W. Sertürner from opium of the white crystalline substance named morphine after Morpheus (the god of sleep) led to the search for other essential principles in the various crude remedies then available. The theoretical importance of such advances was championed by the French scientists Gay-Lussac (1778-1850) and François Magendie (1783-1855).[18]

Consequently in 1821, at Paris, Magendie was able to publish a medical formulary made up entirely of pure chemical agents. This compendium included the discoveries of new therapeutic agents such as the following: the emetine of Joseph Pelletier (1788-1842) obtained from the root of ipecacuanha; the quinine of J. B. Caventou (1795-1877) from cinchona[35] and the strychnine of Magendie, himself, from nux vomica beans.[10] After its publication, other alkaloids were progressively isolated: for example, cocaine from coca leaf by Wöhler in 1856, a drug which Carl Köller in 1884 employed in local anesthesia.

From this time on, synthetic chemists have been constantly at work attempting to develop new drugs or to improve on natural products. The high price of quinine, for example, led to the manufacture of synthetic antipyretics and analgesics. Likewise, after Willstätter had deciphered the chemical structure of cocaine, a host of less toxic and more efficient local anesthetics were developed. Thus modern biochemorphology arose, but it is still largely an empirical trial-and-error process in which by laborious testing the more desirable chemical derivatives are selected from a large family of congeners.

### The Academic Family of Schmiedeberg

Oswald Schmiedeberg (1838-1921), the pupil of Buchheim, transformed the old-fashioned materia medica[6] into modern pharmacology—an independent science.[2, 38] In 1872 he became Professor of Pharmacology at Strasbourg, and thereafter students flocked to him from all over the world. He founded, with Naunyn and Klebs, the "Archiv für experimentelle Pathologie und Pharmakologie," the first modern journal of pharmacology; and published a classic textbook, the "Grundriss der Arzneimittellehre."[62] Among his eminent pupils are listed Abel,

Cushny, Sollmann, Hans Horst Meyer[48, 49, 50, 51] and Heubner.[3]

*John Jacob Abel*[15, 67, 27] brought to America the traditions of the Schmiedeberg school[47] and became the Father of American Pharmacology.[29, 1] He occupied the first full-time professorship of pharmacology in the United States at the University of Michigan in 1891 and later taught at Johns Hopkins (1893); he influenced many students profoundly. His studies on epinephrine,[34] insulin and vividiffusion are classic.

by *Arthur Robertson Cushny* (1868-1926), another pupil of Schmiedeberg. For thirty years Cushny specialized in drugs affecting the heart and circulatory apparatus, although many other topics interested him. In 1905 he became Professor at University College in London, and in 1918 at Edinburgh. Together with the enthusiastic Dale and Dixon[31] he exerted a world-wide influence[52] on the development of professional pharmacology. Cushny's textbook[44] perpetuated the inspiration of Schmiedeberg and served as an out-

Fig. 7. John Jacob Abel, the Father of American Pharmacology.

"The fact that Dr. Abel had subjected himself to a long and thorough training in the fundamental biomedical disciplines at a time when few medical men did so, indicates that he understood and realized the real nature and purpose of scientific medicine. He spent about seven years (1884-1891) in intensive study in Europe and attended the universities of Leipzig, Strassburg, Heidelberg, Berne, and Vienna, with vacation studies in Wurzburg, Berlin, and Paris. He chose to study under such great leaders as Carl Ludwig, Schmiedeberg, Hoppe-Seyler, Drechsel, von Nencki and Wislicenus in the fields of physiology, pharmacology, biochemistry and chemistry" (Geiling[28]).

Abel was succeeded at Michigan in 1893

standing guide to students for at least one generation.

## FUNDAMENTAL PHARMACOLOGY

Many an important pharmacological advance has been made by a combine of chemists and drug-testers operating together in a program of frank empiricism. The academic mind, however, balks at compilations of unrelated facts and tries to evolve general principles from disjointed data. From such efforts a science is born. It must be confessed, at present, that most endeavors to conceive of pharmacology as a unified science have aborted. Nevertheless, three main trends of philosophical approach have slowly gathered strength and bid fair to unite in a scientific

trinity which will distinguish pharmacology as an orderly science in its own right. These involve, respectively, emphasis upon site of action, chemical constitution and physiological mechanism.

**Localization of Site of Action.** From studies of crude drugs, Felice Fontana had suggested that each active principle exerted its characteristic effect preferentially upon one or more specific tissues. Subsequently E. Purkinje (1787-1869) extended Fontana's animal experiments to observations upon himself. When numerous pure principles became available, Magendie continued this work on the localization of the site of action in the complex mammalian organism. His brilliant pupil, Claude Bernard (1813-78),[19] extended these studies by focusing attention upon the specific mechanism of the action of individual drugs.[22] For many years his correct interpretation of the mechanism of carbon monoxide poisoning was the only clear example of a successful solution of this all-important problem. In 1844 he began his classic studies on the action of curare, and showed that it involved the myoneural junction.

**Chemical Constitution and Biologic Action.** Long before Mendelejeff, James Blake (1815-93) stated that various salts exhibit an increasing biolc gic effect with increase in the atomic weight of their constituent isomorphous elements. In 1841 Blake had begun to wonder, in chemical terms, how drugs acted. He established the fact that they were effective only after reaching a responsive tissue. He noted that how readily the drug reached its effector depended upon the rate of absorption and distribution of the material administered to an animal. In the case of many inorganic salts, the action was more closely related to the anion than to the cation.

Comparable studies of organic compounds, such as the alkaloids, were made by A. Crum Brown (1838-1923) and T. R. Fraser (1841-1920). Proceeding on this vague but broad hypothesis of biochemorphology, Paul E. Ehrlich (1854-1915) developed his six hundred and sixth and nine hundred and fourteenth compounds for the treatment of syphilis. Likewise, A. R. Cushny (1866-1926) and A. S. Loevenhart (1878-1929) made systematic comparisons of the actions of large families of congeners. In recent times Fieser[20] has collated the action of phenanthrenes in similar fashion. Moreover, Jacques Loeb (1859-1924) demonstrated that biological action could be expressed in physicochemical terms.

**Mechanisms and the Physiological Approach.** Much attention has been focused upon the "localization" of drug action since the time of Felice Fontana about 1765. At times this emphasis has led to the erroneous assumption that a gross fixation of the drug occurs in these centers. Apart from specific storehouses like the thyroid, however, this assumption seems not to be generally valid. The tissue in question is merely more sensitive than other tissues to the prevailing concentration in the *milieu intérieur.*

Recognition of this fact allows the investigator in certain cases, at least, to study the animal's reaction to drugs in terms of steady states and circulating concentrations. The term "steady state" must be emphasized, because immediately after the administration of a drug there will usually be a period of adjustment in which blood concentration[53] may be high and not in equilibrium with the responsive tissue. This methodological approach can be used whether the drug acts on cell surfaces or enters into conjunction with catalytic systems within cell protoplasm.

In order to exploit this concept successfully it is necessary to understand two chief problems: first, which are the tissues most prone to respond to the drug in question; and secondly, what factors increase the concentration of circulating drug and what factors decrease it?

*Gross Mechanisms of Particular Drug Action.* In describing the mechanism of action for any given drug, it is desirable to know both which tissues are primarily involved and what particular functions of those tissues are affected. For decades the emphasis was laid upon gross physiological phenomena.[9, 17] Thus, in the field of anesthesia,[24] Long, Morton and Simpson noted the progressive loss of sensation and of various reflexes. Such gross observations are important but are mainly descriptive.[12] More fundamental are the studies in quantitative pharmacology which relate loss of function to concentration of circulating drug.

*Detoxication and Excretion.* At best, most drugs enjoy a precarious existence in the organism. As the dose administered is pro-