Introduction to Pharmaceutical Dosage Forms

HOWARD C. ANSEL

SECOND EDITION

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I am a Pharmacist

I am a specialist in medications

I supply medicines and pharmaceuticals to those who need them.
I prepare and compound special dosage forms.
I control the storage and preservation of all medications in my care.

I am a custodian of medical information

My library is a ready source of drug knowledge.
My files contain thousands of specific drug names and tens of thousands of facts about them.
My records include the medication and health history of entire families.
My journals and meetings report advances in pharmacy from around the world.

I am a companion of the physician

I am a partner in the case of every patient who takes any kind of medication.
I am a consultant on the merits of different therapeutic agents.
I am the connecting link between physician and patient and the final check on the safety of medicines.

I am a counselor to the patient

I help the patient understand the proper use of prescription medication.
I assist in the patient's choice of nonprescription drugs or in the decision to consult a physician.
I advise the patient on matters of prescription storage and potency.

I am a guardian of the public health

My pharmacy is a center for health-care information.
I encourage and promote sound personal health practices.
My services are available to all at all times.

This is my calling · This is my pride

Author Unknown

SECOND EDITION

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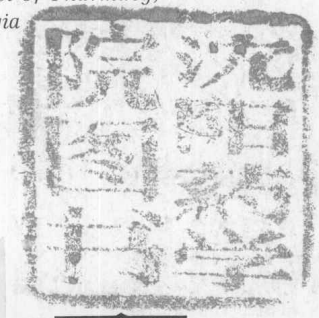
Howard C. Ansel, Ph.D.
Head, Department of Pharmacy and Professor of Pharmacy, School of Pharmacy, University of Georgia



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Preface

THE SECOND edition of *Introduction to Pharmaceutical Dosage Forms* represents a major revision of the first edition, both in content and organization, although the purpose of the text remains the same—to present to the beginning pharmacy student introductory concepts of dosage form design, manufacture, and utilization.

In contrast to the traditional organization of the first edition, based solely on the physical characteristics of the various dosage forms, the second edition is arranged according to routes of administration. For instance, the various dosage forms applied topically to the skin, including those which are solutions, suspensions, powders, or semisolids, are all discussed in the chapter covering dermatological preparations.

It is felt that this new organizational approach will enable the student to better relate the basic information on drugs and dosage forms to their actual use in drug therapy. It also provides the student with the concept of dosage form alternatives in patient care. It is intended that the new structure and content of the text will contribute to the beginning pharmacy student's understanding of the role of the pharmacist as both the provider of medication and the source of information to other health professionals on the selection and use of pharmaceuticals.

As in the first edition, appropriate consideration is given in the beginning chapters to such topics as drug action, drug dosage, drug standards, dosage form design, bioavailability and good manufacturing practice. The official compendia again serve as the foundation for the drugs and dosage forms discussed in the text, although a number of nonofficial preparations are also included, as rectal and vaginal foams, ophthalmic inserts, and otic preparations. Continued from the first edition is the practice of identifying commercial counterpart products for the official preparations discussed.

An appendix chapter dealing with pharmaceutical measurement has been added

and includes discussion of the systems of weight and measure, and the equipment and techniques used to measure liquids and to weigh on the pharmaceutical balance.

My sincere appreciation is extended to a number of my colleagues who have shared their thoughts with me pertaining to the revision of this text. I would particularly like to thank H. Douglas Johnson, Ph.D. for preparing the definitions of the official drug categories as they appear in the Appendix; to Larry A. Sternson, Ph.D. for his contributions to the discussion of drug solubility; to William F. Pillow, Jr. of Eli Lilly and Company and to John S. Ruggiero, Ph.D. of the Pharmaceutical Manufacturers Association, for their generous contributions to the text. I would also like to thank my secretary, Mrs. Kay Oliver, for her patience and help in the preparation of the manuscript, and to Mr. Martin C. Dallago and Mr. John F. Spahr of Lea & Febiger for their editorial assistance.

HOWARD C. ANSEL

Athens, Georgia

Contents

Chapter 1

Introduction to Drugs and Pharmacy

A DRUG may be defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in man or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body. Drugs categorized as ecbolics or oxytocics stimulate the activity of the uterine muscle, but other drugs act as uterine muscle relaxants. Some drugs selectively stimulate the cardiac muscle, the smooth muscles, or the skeletal muscles; other drugs have the opposite effect. Mydriatic drugs dilate the pupil of the eye; miotics constrict or diminish pupillary size. Drugs can render blood more coagulable or less coagulable; they can increase the hemoglobin content of the erythrocytes or expand blood volume.

Drugs termed emetics induce vomiting, whereas antiemetic drugs have the opposite effect. Diuretic drugs increase the flow of urine, sudorific drugs promote sweating, expectorant drugs increase respiratory tract fluid, and cathartics or laxatives promote the evacuation of the bowel. Other drugs may decrease the flow of urine, diminish body secretions, or induce constipation.

Drugs can be employed to reduce headache, pain, fever, thyroid activity, sneezing, rhinitis, insomnia, gastric acidity, motion sickness, and mental depression. Drugs can elevate the mood, the blood pressure, or the activity of the endocrine glands. Drugs can combat infectious disease, destroy intestinal worms, or act as antidotes against the poisoning effects of still other drugs. Antineoplastic drugs provide one means of attacking the cancerous process; radioactive pharmaceuticals provide another.

Drugs may be used to diagnose diabetes, liver malfunction, tuberculosis, or pregnancy, or they may be employed to replenish a body deficient in antibodies, vitamins, hormones, electrolytes, protein, enzymes, or blood. Drugs may be used to prevent measles, poliomyelitis, or pregnancy or to assist the maintenance of pregnancy or to extend life itself.

Certainly the vast array of effective medicinal agents available today represents one of man's greatest scientific accomplishments. It would be frightening to perceive of our civilization devoid of these remarkable and beneficial agents. Through their use, many of the diseases which have plagued mankind throughout history, as smallpox and poliomyelitis, are now facing extinction. Illnesses such as diabetes, hypertension, and mental depression are now effectively controlled with modern drugs. Today's surgical procedures would be virtually impossible without the benefit of general anesthetics, analgesics, antibiotics, blood transfusions, and intravenous fluids and nutrients.

The process of drug discovery and development is no simple task. It involves the collective contributions of many scientific specialists including organic, physical, and analytical chemists, biochemists, bacteriologists, physiologists, pharmacologists, toxicologists, hematologists, immunologists, endocrinologists, pathologists, biostatisticians, pharmaceutical scientists, clinical physicians and many others.

After a potential new drug substance is discovered and has undergone definitive chemical and physical characterization, a great deal of biological information must be gathered. The basic *pharmacology* or the nature and mechanism of action of the drug on the biological system must be determined including toxicologic features. A study must be made of the drug's site and rate of absorption, its pattern of distribution and concentration within the body, its duration of action, and the method and rate of its elimination or excretion. Information must be obtained on the drug's metabolic degradation and the activity of any of its metabolites.

A comprehensive study must be made of the drug's short term and long term effects on various body cells, tissues, and organs. Highly specific information may be obtained, as the effect of the drug on the fetus of a pregnant animal or its ability to pass to a nursing baby through the breast milk of its mother. Many a promising new drug has been abandoned because of its potential to cause excessive or hazardous adverse effects.

A new drug's most effective routes of administration (e.g., oral, rectal, parenteral) must be determined and guidelines established concerning the dosage recommended for persons of varying ages, weights, and states of illness. To facilitate administration of the drug by the selected routes, appropriate *dosage forms* as tablets, capsules, injections, suppositories, ointments, aerosols, and others are formulated and prepared. These dosage forms are highly sophisticated pharmaceutical drug delivery systems. Their design, development, production, and use are a prime example of the application of the pharmaceutical sciences—the blending of the basic, applied, and clinical sciences with pharmaceutical technology.

Each particular pharmaceutical product is a formulation unique unto itself. In addition to the active therapeutic ingredients, a pharmaceutical formulation also contains a number of nontherapeutic agents. These agents are generally referred to as *pharmaceutical adjuncts, excipients* or *necessities*, and it is through their use that a formulation achieves its unique composition and characteristic physical appearance. Included are such things as fillers, thickeners, vehicles, suspending agents, tablet disintegrants, stabilizing agents, preservatives, flavors, colorants, and sweeteners. *Dosage units*, as capsules, tablets, or "unit-dose" packages of liquid medications, are designed to contain a specified quantity of medication for ease and accuracy of dosage administration.

In order to assure the stability of a drug in a formulation and the continued effectiveness of the drug product throughout its usual shelf life,[1] the principles of chemistry, physical pharmacy, microbiology, and pharmaceutical technology must be applied. The formulation must be such that all components are physically and chemically compatible, including the active therapeutic agents, the pharmaceutical necessities, and the packaging materials. The formulation must be preserved against decomposition due to chemical degradation and protected from microbial contamination and the destructive influences of excessive heat, light, and moisture. The therapeutic ingredients must be released from the dosage form in the proper amount and in such a manner that the onset and duration of the drug's action is that which is desired. The pharmaceutical product must lend itself to efficient administration and must possess attractive features of flavor, odor, color, and texture that enhance patient acceptance. Finally, the product must be effectively packaged and clearly and completely labeled according to existing legal regulations.

Once prepared, the pharmaceutical product must be properly administered if the patient is to receive maximum benefit. The medication must be taken in sufficient quantity, at specified intervals, and for an indicated duration of time. The effectiveness of the medication in achieving the prescriber's objectives should be reevaluated at regular intervals and necessary adjustments made in the dosage, *dosage regimen* or dosage schedule, dosage form, or indeed, in the choice of the drug administered. Patient expressions of disappointment in his rate of progress or complaints of side effects to the prescribed drug should be evaluated upon report and decisions made as to the continuance, minor adjustment, or major change in drug therapy. Prior to initially taking a medication, a patient should be warned of any expected minor side effects, and of foods, beverages, and/or other drugs which may interfere with the effectiveness of the medication or with the course of therapy.

Through professional interaction and communication with other health professionals the pharmacist is able to contribute greatly to patient care. His intimate knowledge of drug ac-

[1]The term "shelf life" refers to the length of time a drug product may remain on the (pharmacist's) shelf, in the original package and under usual environmental conditions, and retain an acceptable level of its original potency and overall quality. In most instances solid dosage forms, as tablets and capsules, have a shelf life of 5 years from the date of manufacture. Usually liquid dosage forms, disperse systems as aerosols and emulsions, and semisolid forms as ointments and suppositories have shorter shelf lives. However, a great deal depends upon the individual chemical and physical characteristics of the active ingredients, the formulative materials, and the packaging employed. Poor storage conditions, with extremes of temperature, humidity, and light can adversely affect the stability of pharmaceutical products.

tions, drug therapy, dosage form design and utilization, available pharmaceutical products, and drug information sources makes him a vital member of the health care team. He is entrusted with the legal responsibility for the procurement, storage, control and distribution of effective pharmaceutical products and for the compounding and filling of prescription orders. Utilizing his extensive training and knowledge, the pharmacist serves the patient as an advisor on drugs and encourages their safe and proper utilization. The pharmacist delivers pharmaceutical services in a variety of community and institutional health care environments and effectively utilizes record-keeping and monitoring techniques in safeguarding the public health.

To appreciate the progress that has been made in drug discovery and development in recent years and to provide some background for the study of modern drugs and pharmaceutical dosage forms, it is important to examine pharmacy's heritage.

The Heritage of Pharmacy

Drugs, in the form of vegetation and minerals, have existed longer than man himself. Human disease and man's instinct to survive have, through the ages, led to their discovery. The use of drugs, crude though they may have been, undoubtedly dates back long prior to recorded history, for the instinct of primitive man to relieve the pain of a wound by bathing it in cool water or by soothing it with a fresh leaf or protecting it with mud is within the realm of belief. From experience primitive man would learn that certain therapy was more effective than others, and from these beginnings the practice of drug therapy began.

Among many early races, disease was believed to be caused by the entrance of demons or evil spirits into the body. The treatment quite naturally involved ridding the body of the supernatural intruders. From the earliest records of history it is evident that the primary methods of doing so were through the use of spiritual incantations, the application of noisome materials, and the administration of specific herbs or plants.

The First Apothecary

Before the days of the priestcraft, the wise man or woman of the tribe, whose knowledge of the healing qualities of plants had been gathered through experience or handed down by word of mouth, was called upon to attend to the sick or wounded and prepare the remedy. It was in the preparation of the medicinal materials that the art of the apothecary originated.

The art of the apothecary has always been associated with the mysterious, and its practitioners were believed to have connection with the world of spirits and thus performed as intermediaries between the seen and the unseen. The belief that a drug had magical associations meant that its action, for good or for evil, did not depend upon its natural qualities alone. The compassion of a god, the observance of ceremonies, the absence of evil spirits, and the healing intent of the dispenser were individually and collectively needed to make the drug therapeutically effective. Because of this, the tribal apothecary was one to be feared, respected, trusted, sometimes mistrusted, worshipped, and revered, for it was through his potions that spiritual contact was made and upon which the cures or failures depended. Throughout history the knowledge of drugs and their application to disease has always meant power. In the Homeric epics, the term *pharmakon* (Gr.) from which our word *pharmacy* was derived connotes a charm or a drug that can be used for good or for evil purposes. Many of the tribal apothecary's failures were doubtless due to impotent medicines, inappropriate medicines, underdosage, overdosage, and even poisoning. His successes may be attributed to an appropriate drug based on his experience, coincidence of proper therapy, inconsequential effect of the therapy for an individual with a nonfatal illness, or *placebo effects*, that is, successful treatment due to psychologic rather than therapeutic effects. Even today, placebo therapy with nonpotent or inconsequential chemicals is successfully employed in the treatment of individual patients and is a routine practice in the clinical evaluation of new drugs where group response to the effects of the actual drug and the placebo are compared and evaluated.

As time passed, the art of the apothecary became combined with priestly functions, and among the early civilizations the priest-magician or priest-physician became the healer of the body as well as of the soul. Pharmacy and medicine are indistinguishable in their early history, since their practice was generally the function of the tribal religious leaders.

Early Drugs

Due to the patience and intellect of the archeologist, the types and the specific drugs employed in the early history of drug therapy are not as indefinable as one might suspect. Numerous ancient tablets, scrolls, and other relics dating as far back as 3000 B.C. have been uncovered and deciphered by archeological scholars to the delight of historians of both medicine and pharmacy, for contained in these ancient documents are specific associations with our common heritage.

Perhaps the most famous of these surviving memorials is the *Papyrus Ebers*, a continuous scroll some 60 feet long and a foot wide dating back to the sixteenth century before Christ. This document, which is now preserved at the University of Leipzig, is named for the noted German Egyptologist, Georg Ebers, who discovered it in the tomb of a mummy and partly translated it during the last half of the nineteenth century. Since that time, many scholars have participated in the translation of the document's challenging hieroglyphics, and although they are not unanimous in their interpretations there is little doubt that by 1550 B.C. the Egyptians were using many of the same drugs and dosage forms still employed today.

The text of the Ebers Papyrus is dominated by drug formulas, with more than 800 formulas or prescriptions being described and over 700 different drugs being mentioned. The drugs referred to are chiefly botanic, although mineral and animal drugs are also noted. Such currently used botanic drugs as acacia, castor bean (from which we express castor oil), and fennel are mentioned along with apparent references to such minerals as iron oxide, sodium carbonate, sodium chloride, and sulfur. Animal excrements were also employed in drug therapy.

The formulative vehicles of the day were beer, wine, milk, and honey. Many of the pharmaceutical formulas employed two dozen or more different medicinal agents, a type of preparation later referred to as a "polypharmacal." Mortars, hand mills, sieves, and balances were commonly used by the Egyptians in their compounding of suppositories, gargles, pills, inhalations, troches, lotions, ointments, plasters, and enemas.

Introduction of the Scientific Viewpoint

Throughout history many individuals have contributed to the advancement of the health sciences. Notable among those whose genius and creativeness had a revolutionary influence on the development of pharmacy and medicine were Hippocrates (ca. 460–377 B.C.), Dioscorides (1st century A.D.), Galen (ca. 130–200 A.D.), and Paracelsus (1493–1541 A.D.).

Hippocrates was a Greek physician who is credited with the introduction of scientific pharmacy and medicine. He rationalized medicine, systematized medical knowledge, and put the practice of medicine on a high ethical plane. His thinking on the ethics and science of medicine dominated the medical writings of his and successive generations, and his concepts and precepts are embodied into the now renowned Hippocratic oath of ethical behavior for the healing professions. His works included the descriptions of hundreds of drugs, and it was during this period that the term *pharmakon* came to mean a purifying remedy for good only, transcending the previous connotation of a charm or drug for good or for evil purposes. Because of his pioneering work in medical science and his inspirational teachings and advanced philosophies that have become a part of modern medicine, Hippocrates is honored by being called the "Father of Medicine."

Dioscorides, a Greek physician and botanist, was the first to deal with botany as an applied science of pharmacy. His work, *De Materia Medica*, is considered a milestone in the development of pharmaceutical botany and in the studies of naturally occurring medicinal materials. This area of study is today known as pharmacognosy, a term formed from two Greek words, *pharmakon*, drug, and *gnōsis*, knowledge. Many of the drugs described by Dioscorides, as aspidium, opium, ergot, hyoscyamus, and cinnamon, are also used in medicine today. His descriptions of the art of identifying and collecting natural drug products, the methods of their proper storage, and the means of detecting adulterants or contaminants were the standards of the period and established the need for additional work and the guidelines for future investigators.

Claudius Galen, a Greek pharmacist-physician who attained Roman citizenship, aimed to create a perfect system of physiology, pathology, and treatment and formulated doctrines that were followed for 1500 years. He was one of the most prolific authors of his or any other era, having been credited with 500 treatises on medicine and some 250 others on subjects of philosophy, law, and grammar. His medical writings include descriptions of numerous drugs of natu-

ral origin with a profusion of drug formulas and methods of compounding. He originated so many preparations of vegetable drugs by mixing or melting the individual ingredients that the area of pharmaceutical preparations has been commonly referred to as "Galenic pharmacy." Perhaps the most famous of his formulas is one for a cold cream, called Galen's Cerate, which is remarkably similar in formulation to some in use today.

Pharmacy remained a function of medicine until the increasing variety of drugs and the growing complexity of compounding demanded specialists who could devote full attention to the art. Pharmacy was officially separated from medicine for the first time in 1240 when a decree of the German Emperor Frederick II regulated the practice of pharmacy within that part of his kingdom called the Two Sicilies. His edict separating the two professions acknowledged that pharmacy required special knowledge, skill, initiative, and responsibility if adequate care to the medical needs of the people was to be guaranteed. Pharmacists were obligated by oath to prepare reliable drugs of uniform quality according to their art. Any exploitation of the patient through business relations between the pharmacist and the physician was strictly forbidden. Between that time and the evolution of chemistry as an exact science, pharmacy and chemistry became united somewhat as pharmacy and medicine had been.

Perhaps no man in history exercised such a revolutionary influence on pharmacy and medicine as did Aureolus Philippus Theophrastus Bombastus von Hohenheim, a Swiss physician and chemist who called himself Paracelsus. He influenced tremendously the transformation of pharmacy from a profession based primarily on botanic science to one based on chemical science. Some of his chemical observations were astounding for his time and for their anticipation of later discoveries. He believed that it was possible to prepare a specific medicinal agent for use in combating each specific disease and introduced a host of chemical substances to internal therapy. Some of the formulas he devised, some of the names he coined, and some of the theories he advanced have become a part of our daily practice of pharmacy.

Early Research

As the knowledge of the basic sciences increased, so did their application to pharmacy. The opportunity was presented for the investigation of medicinal materials on a firm scientific basis, and the challenge was accepted by numerous pharmacists who conducted their research in the backrooms and basements of their pharmacies. Noteworthy among them was Karl Wilhelm Scheele (1742–1786), a Swedish pharmacist who is perhaps the most famous of all pharmacists because of his scientific genius and dramatic discoveries. Among his discoveries were the chemicals lactic acid, citric acid, oxalic acid, tartaric acid, and arsenic acid. He identified glycerin, invented new methods of preparing calomel and benzoic acid, and discovered oxygen a year prior to Priestley.

The isolation of morphine from opium by the German pharmacist Friedrich Sertürner (1783–1841) in 1805 prompted a series of isolations of other active materials from medicinal plants by a score of French pharmacists. Joseph Caventou (1795–1877) and Joseph Pelletier (1788–1842) combined their talents and isolated quinine and cinchonine from cinchona, and strychnine and brucine from nux vomica. Pelletier together with Pierre Robiquet (1780–1840) isolated caffeine, and Robiquet independently separated codeine from opium. Methodically one chemical after another was isolated from plant drugs and identified as an agent responsible for the plants' medicinal activity. Today we are still engaged in this fascinating activity as we probe nature for more useful and more specific therapeutic agents.

Throughout Europe during the late 18th century and the beginning of the 19th century, pharmacists like Pelletier and Sertürner were held in great esteem by their communities because of their intellect and technical abilities. They applied the art and the science of pharmacy to the preparation of drug products that were of the highest standards of purity, uniformity, and efficacy possible at that time. The extraction and isolation of various active constituents from crude or unprocessed drugs were a major breakthrough in the development of concentrated dosage forms of uniform strength containing singly effective therapeutic agents of natural origin. Many pharmacists of the period began to manufacture quality pharmaceutical products on a small but steadily increasing scale to meet the growing drug needs of their communities. Some of today's gigantic pharmaceutical manufacturing companies developed from these progressive prescription laboratories of over a century and a half ago.

Although many of the drugs indigenous to America and first used by the American Indian

were adopted by the settlers, the vast majority of drugs needed in this country before the 19th century were imported from Europe, either as the raw materials or as finished pharmaceutical products. With the Revolutionary War, however, it became more difficult to import drugs, and the American pharmacist was stimulated to acquire the scientific and technologic expertise of his European contemporary. From this period until the Civil War, pharmaceutical manufacture as we know it today was in its infancy in this country, but some of the pharmaceutical firms established during that period are still preparing drugs. Three firms are known to have been established before 1826, with 22 additional ones having their origin in the subsequent half century. In 1821, the first American school of pharmacy was established in Philadelphia.

The United States Pharmacopeia

The term *pharmacopeia* comes from the Greek, *pharmakon,* meaning "drug," and *poiein,* meaning "make," and the combination indicates any recipe or formula or other standards required to make or prepare a drug. The term was first used in 1580 in connection with a local book of drug standards in Bergamo, Italy. From that time on there were countless city, state, and national pharmacopeias published by various European pharmaceutical societies. As time passed, the value of a uniform set of drug standards within a nation became apparent. In England, for example, three city pharmacopeias—the London, the Edinburgh, and the Dublin—were official throughout the kingdom until 1864, when they were replaced by the British Pharmacopoeia (BP).

In the United States drug standards were first provided on a national basis in 1820, when the first *United States Pharmacopeia* (USP) was published. The need for drug standards was recognized, however, in this country long before the first USP was published. For convenience and because of their familiarity with them, colonial physicians and apothecaries used the pharmacopeias and other references of their various homelands. The first American pharmacopeia was the so-called "Lititz Pharmacopeia," published in 1778 at Lititz, Pennsylvania, for use by the Military Hospital of the United States Army. It was a 32-page booklet containing information on 84 internal and 16 external drugs and preparations.

During the last decade of the 18th century, several attempts were made by various local medical societies to collate drug information, set appropriate standards, and prepare an extensive American pharmacopeia of the drugs in use at that time. In 1808 the Massachusetts Medical Society published a 272-page pharmacopeia containing information or monographs on 536 drugs and pharmaceutical preparations. Included were monographs on many drugs indigenous to America, which were not described in the European pharmacopeias of the day.

On January 6, 1817, Dr. Lyman Spalding, a physician from New York City, submitted a plan to the Medical Society of the County of New York for the creation of a national pharmacopeia. Dr. Spalding's efforts were later to result in his being recognized as the "Father of the United States Pharmacopeia." He proposed dividing the United States as then known into four geographical districts—the Northern, Middle, Southern, and Western. The plan provided for calling a convention in each of these districts, to be composed of delegates from all medical societies and medical schools within them. Where there was as yet no incorporated medical society or medical school, voluntary associations of physicians and surgeons were invited to assist in the undertaking. Each district's convention was to draft a pharmacopeia and appoint delegates to a general convention to be held later in Washington, D.C. At the general convention, the four district pharmacopeias were to be compiled into a single national pharmacopeia.

Draft pharmacopeias were submitted to the convention by only the Northern and Middle districts. These were reviewed, consolidated, and adopted by the first United States Pharmacopeial Convention assembled in Washington, D.C., on January 1, 1820. The first *United States Pharmacopeia* was published on December 15, 1820, in English and also in Latin, then the international language of medicine, to render the book more intelligible to physicians and pharmacists of any nationality. Within its 272 pages were listed 217 drugs considered worthy of recognition, many of them taken from the Massachusetts Pharmacopeia, which is considered by some to be the precursor to the USP. The objective of the first USP was clearly stated in its preface and still serves as the guideline for drug admissions. It reads in part:

> "It is the objective of a Pharmacopeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries."

Before adjourning, the Convention adopted a Constitution and Bylaws, with provisions for subsequent meetings of the Convention leading to a revised *United States Pharmacopeia* every 10 years. As many new drugs entered into drug therapy, the need for more frequent issuance of standards became increasingly apparent. In 1900, the Pharmacopeial Convention granted authority to issue supplements to the currently official USP whenever necessary to maintain satisfactory standards. At the 1940 meeting of the Convention, it was decided to revise the Pharmacopeia every 5 years while maintaining the use of periodic supplements. The *United States Pharmacopeia* was last revised on September 1, 1975, with the issuance of the USP XIX, the 19th revision of the compendium.

The first United States Pharmacopeial Convention was composed exclusively of physicians. In 1830, and again in 1840, prominent pharmacists were invited to assist in the revision, and in recognition of their contributions pharmacists were awarded full membership in the Convention of 1850 and have participated regularly ever since. Indeed, by 1870 the *Pharmacopeia* was so nearly in the hands of pharmacists that vigorous efforts were required to revive interest in it among physicians. The present Bylaws provide that a minimum of one-third of the members of the Board of Trustees and of the Committee of Revision shall represent the medical profession.

After the appearance of the first USP, the art and science of both pharmacy and medicine changed remarkably. Prior to 1820, the drugs employed in the treatment of disease had been much the same for centuries. The *Pharmacopeia* of 1820 reflected the fact that the apothecary of that day was competent at collecting and identifying botanic drugs and preparing from them the mixtures and preparations required by the physician. The individual pharmacist seemed quite fulfilled as he applied his total art to the creation of elegant pharmaceutical preparations from crude botanic materials. It was a time that would never be seen again because of the impending upsurge in technologic capabilities and the steady development of the basic sciences, particularly synthetic organic chemistry.

The second half of the 19th century brought great and far-reaching changes. The United States was now under the full impact of the industrial revolution. The steam engine, which used water power to turn mills that powdered crude botanic drugs, was replaced by the gas, diesel, or electric motor. New machinery was substituted for the old whenever and wherever possible, and often machinery from other industries was adapted to the special needs of pharmaceutical manufacturing. Mixers from the baking industry, centrifugal machines from the laundry industry, and sugarcoating pans from the candy industry were a few examples of the type of improvisations made. Production increased rapidly, but the new industry had to wait for the scientific revolution before it could claim newer and better drugs for mankind. A symbiosis was needed between science and the advancing technology.

Chemotherapy

By 1880, the industrial manufacture of chemicals and pharmaceutical products had become well established in this country, and the pharmacist was relying heavily upon commercial sources for his drug supply. Synthetic organic chemistry began to have its influence on drug therapy. The isolations of some active constituents of plant drugs had led to knowledge of their chemical structure. From this arose methods of synthetically duplicating the same structures, as well as manipulating molecular structure to produce organic chemicals yet undiscovered in nature. In 1872 the synthesis of salicylic acid from phenol inaugurated the synthesis of a group of analgesic compounds. Other new chemicals synthesized for the first time were phenolphthalein, a laxative, and sleep-producing derivatives of barbituric acid called "barbiturates." A new source of drugs, synthetic organic chemistry, welcomed the turn into the 20th century.

Until this time, drugs created through the genius of the synthetic organic chemist relieved

a host of maladies, but none had been found to be curative—none, that is, until 1910, when arsphenamine, a specific agent against syphilis, was introduced to medical science. This was the start of an era of chemotherapy, an era in which the diseases of mankind became curable through the use of specific chemical agents. The concepts, discoveries, and inspirational work that led mankind to this glorious period are credited to Paul Ehrlich, the German bacteriologist who together with a Japanese colleague, Sahachiro Hata, discovered arsphenamine. Today most of our new drugs, whether they be curative or palliative, originate in the flask of the synthetic organic chemist.

Federal Regulation

The advancement of science, both basic and applied, led to drugs of a more complex nature and to more of them. The drug standards advanced by the USP were more than ever needed to protect the public by insuring the purity and uniformity of the drugs administered. The authority of the *United States Pharmacopeia* in setting these standards was recognized fairly early in the statutes of some states, but federal recognition did not come about until June 30, 1906, when President Theodore Roosevelt signed into law the first federal Pure Food and Drug Act. This law designated the USP as establishing the standard of strength, quality, and purity of medicinal agents recognized within it, when sold in interstate commerce for medicinal use. The *National Formulary* (NF), a publication of the American Pharmaceutical Association, was given the same legal standing by the law. Thus, the USP and the NF of current revision are called "official compendia." Among other things, the law of 1906 requires that whenever the designations "USP" or "NF" are used or implied on drug labeling with respect to official drugs or preparations, the products must conform to the physical and chemical standards as set forth for the drug in the compendium monograph. With the passage of the law of 1906, the USP and the NF became indispensable to the entire American drug trade.

The National Formulary

When the American Pharmaceutical Association was organized in 1852, the only authoritative and generally recognized book of drug standards available was the third revision of the *United States Pharmacopeia*. In order to serve as a therapeutic guide to the medical profession, its scope, then as now, was restricted to drugs of established therapeutic merit. Because of this policy of strict selectivity, many drugs and formulas that were widely accepted and used by the medical profession were not granted admission to early revisions of the *Pharmacopeia*. As a type of a protest, and in keeping with the original objectives of the American Pharmaceutical Association to establish standardization of drugs and formulas, certain pharmacists, with the sanction of their national organization, prepared a formulary containing many of the popular drugs and formulas denied admission to the *Pharmacopeia*. The first edition was published in 1888 under the title *National Formulary of Unofficial Preparations*. The designation *Unofficial Preparations* reflected the protest mood of the authors, since the *Pharmacopeia* had earlier adopted the term "official" as applying to the drugs for which it provided standards. The title was changed to *National Formulary* when the Pure Food and Drug Act of 1906 made it an *official* compendium. The early editions of the *National Formulary* served mainly as a convenience to practicing pharmacists by providing uniform names of drugs and preparations and working directions for the small-scale manufacture of popular pharmaceutical preparations prescribed by physicians. Today the drugs and formulas included in each new edition of the *National Formulary* are selected on the basis of therapeutic or pharmaceutic merit, not because of popularity or extent of use. However, they are still selected from among those drugs and preparations not voted admission to the concurrent revision of the *Pharmacopeia*. The determination of the drugs and preparations to be admitted, along with their chemical and physical standards, is entrusted to the chairman and ten members of the National Formulary Board, appointed by the Board of Trustees of the American Pharmaceutical Association. Like the *Pharmacopeia*, the *National Formulary* was originally revised every 10 years, but since 1940 a new edition has appeared every 5 years. Between editions, revision announcements or supplements are issued as required. The currently official *National Formulary*, the 14th edition (NF XIV), replaced the previous edition on September 1, 1975.

On January 2, 1975, the United States