MEDICINAL CHEMISTRY

SECOND EDITION

EDITED BY
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CHARLOTTESVILLE

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Preface

The great expansion of research in medicinal chemistry all over the world during the last three decades has contributed much to the unparalleled progress of medicine during that period. Interest in medicinal chemistry has been stimulated by improved methods of biological test procedures and of clinical diagnosis, and the ensuing demands for new corrective and curative agents. Perhaps the greatest incentives have been provided by the introduction of deeper biochemical insight into experimental biology, the resulting greater stature of pharmacological theories, and the unprecedented expansion of the pharmaceutical industry. The elucidation of the structure of many complex natural products including many metabolites has also made possible a more intensive study of their mode of action and therapeutic applications. The investigation of medicinal chemicals and their testing and manufacture have become so productive and intellectually rewarding that more and more scientists are choosing one of the many facets of these fields as their occupation and avocation.

Since the publication of the first edition of this treatise, all aspects of medicinal chemistry and related fields have advanced so rapidly that a revision of the book became imperative. A reasonably rapid preparation of a comprehensive text in such a diversified field could no longer be attempted by one author. Therefore, the help of thirty-four contributors was enlisted. Without their specialized knowledge, cooperation, and devotion to the task this book could not have been written. The expansion of medicinal chemistry is reflected in an increase of twelve chapters over the first edition. Even those chapters which could have been brought up to date by additions and deletions have been rewritten completely for the most part and present a new approach to their subject matter. Because so much more is known about the mechanisms of action of drugs with overlapping activities, the topics in many chapters have been rearranged to conform with modern views.

The list of references in each chapter has also been expanded greatly. In most chapters, the literature up to early 1957 has been covered, but many significant advances to the end of 1957 have been recorded wherever possible.

The book is addressed principally to the more advanced reader. It hopes to familiarize him with past achievements and current thoughts and hypotheses, and to point the direction of research needed in medicinal chemistry. An effort has been made to unify the text and to subordinate the varied approaches of different contributors to a medicinally oriented picture of the whole field. In a few instances, the purely chemical background of the nutritional and therapeutic agents had not yet been collected in up-to-date monographs, and has therefore been assigned a prominent place in this book, especially in the chapters on vitamins and antibiotics.

The preparation of the manuscripts for this volume would not have been possible without aid from several sources. We have been fortunate to have had at our disposal the library and literature services of several universities, pharmaceutical companies, and the National Institutes of Health. The abstracting services of Parke, Davis & Company, and of Smith Kline & French Laboratories have been especially helpful. Several sections of the book have been read critically by friends of the contributors. Chapter 13 has been read in this way by Drs. N. B. Eddy and C. I. Wright of the National Institutes of Health, and Chapter 18 by Drs. Leonard Cook and G. E. Ullyot of Smith Kline & French Laboratories. Chapter 38 has been surveyed by Drs. E. Heftmann, R. Hertz, and E. Mosettig of the National Institutes of Health, by Dr. R. M. Wilder of the Mayo Clinic, and by Dr. E. C. Kendall of Princeton University. Dr. R. Baltzly of the Wellcome Research Laboratories has gone over Chapter 42, and Drs. D. B. Capps, L. M. Long, P. E. Thompson, Miss M. J. Morelock, and Messrs. F. H. Tendick and D. F. Worth of Parke, Davis & Company have read Chapter 43. Dr. R. Pitillo of the same laboratories has reviewed parts on microbiology of Chapter 44. Dr. E. W. Hurst of Imperial Chemical Industries, and Drs. H. R. Cox, S. Davis, George Sharpless, J. Vaughan, and C. Waller of the American Cyanamid Company have given helpful reviews on Chapter 51. Mr. E. Swindell of the University of Maryland has helped in drawing figures for Chapter 7.

A number of books were consulted frequently, and we wish to take this opportunity to express our indebtedness to the following sources: A. Allen, *Sex and Internal Secretions*, The Williams and Wilkins Co., Baltimore, 1934; H. H. Anderson, W. L. Bostick, and H. G. Johnstone, *Ame-*

biasis: Pathology, Diagnosis and Chemotherapy, Charles C. Thomas, Springfield, Ill., 1953; G. W. Corner, *The Hormones in Human Reproduction*, Princeton University Press, Princeton, N. J., 1947; R. I. Dorfman and R. A. Shipley, *Androgens*, John Wiley and Sons, Inc., New York, 1956; H. F. Dowling, W. E. Herrill, and I. H. Jukes, Selected Articles in *Antibiotics Monographs*, Nos. 1, 3, 4, Medical Encyclopedia, Inc., 1955; V. A. Drill, editor, *Pharmacology in Medicine*, McGraw-Hill Book Co., Inc., New York, 1954; E. C. Faust, *Amebiasis*, Charles C. Thomas, Springfield, Ill., 1954; L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, 1949; G. M. Findlay, *Recent Advances in Chemotherapy*, Vol. I, 3rd ed., Blakiston, Philadelphia, 1950; H. W. Florey, E. Chain, N. G. Heatley, M. A. Jennings, A. G. Sanders, E. P. Abraham, and M. E. Florey, *Antibiotics*, Vols. I, II, Oxford University Press, 1949; S. H. Hutner and A. Lwoff, editors, *Biochemistry and Physiology of Protozoa*, Vol. II, Academic Press, Inc., New York, 1955; R. S. Harris, G. F. Marrian, and K. V. Thimann, editors, *Vitamins and Hormones*, Academic Press, Inc., New York; H. R. Ing, in H. Gilman, editor, *Organic Chemistry*, Vol. III, John Wiley and Sons, Inc., New York, 1953; G. J. Martin, *Biological Antagonism*, The Blakiston Co., New York, 1951; H. Most, editor, *Parasitic Infections in Man*, Columbia University Press, New York, 1951 (pp. 163–186, by H. H. Anderson); G. Pincus and K. V. Thimann, editors, *The Hormones*, Vols. I, II, III, Academic Press, Inc., New York, 1948, 1950, 1955; H. Welch, *Principles and Practice of Antibiotic Therapy*, Medical Encyclopedia, Inc., 1954; F. Y. Wiselogle, *Survey of Antimalarial Drugs*, 1941–1945, Edwards Brothers, Ann Arbor, Mich., 1946.

The subject index was alphabetized by electronic sorting devices through the courtesy of Dr. Maxwell Gordon and Mr. Paul Ackley of Smith Kline & French Laboratories.

We shall be grateful for comments from the readers of this book pointing out any errors in fact or interpretation.

Charlottesville, Virginia
May, 1960

Alfred Burger

Contents

1. Introduction

ALFRED BURGER

Medicinal chemistry is a science whose fundamental roots lie in all branches of chemistry and biology. The term "pharmaceutical chemistry" has been used for "medicinal chemistry," particularly in its industrial ramifications where attention is focussed on materials useful in pharmacy and therapy.

Among the purposes of medicinal chemistry are the isolation, characterization, elucidation of the structure, and the synthesis of compounds which can be used in medicine for the cure or the treatment of disease. Moreover, medicinal chemistry is concerned with the understanding of the chemical and biological mechanisms by which the action of drugs can be explained. It also tries to establish relations between chemical structure and biological activity and to link the latter to the physical properties of the drugs.

The medicinal chemist must be well versed in the sciences that contribute to his own specialty. Because he works in a borderline field, he must understand many phases of the sciences which funnel information into his own. A medicinal chemist must be experienced in organic chemistry, physical chemistry, and biochemistry, pharmacology, microbiology, and many phases of medicine pertinent to his work. Even though he may be expert in only one or two of these sciences, his acquaintance with the others will enable him to bridge gaps of knowledge and to paint a composite picture of a situation which the specialist in one field could barely achieve.

On the other hand, half-measures are not enough to attain scientific results, and even a fairly close acquaintance with a field is insufficient to work out details. Therefore, the medicinal chemist is necessarily a member of a research team which usually consists of him, the biochemists who determine the fate of the drug in the body as an explanation of its mode of action, pharmacologists who test the drugs, physicians who transpose animal experiments into clinical trials, and chemical engineers who manufacture the tested and proved drug for general therapeutic use. Many great results of recent medicinal researches have been obtained by research teams rather than by individual scientists.

In return for the aid the contributing sciences render medicinal chemistry, the latter has given chemical, biological, and engineering sciences a new impetus in fields which had been dormant because of lack of interest in a given application. The discovery of the medicinal usefulness of an obscure compound has always stimulated inquiry into the reactions and improved methods of preparation of similar substances, and almost in every instance has led to purely theoretical developments no longer directly connected with medicinal applications. Likewise, methods of pharmacology and biology have had to be improved and revised to meet the peculiarities of new drugs, and the experiments performed in these studies have inevitably clarified underlying biological mechanisms. Finally, the manufacture of an unusual drug necessitates new designs in equipment and new methods which inevitably solve the problems of other industrial procedures.

One of the prime motives of medicinal chemistry is service to medicine. Some of the proudest and most spectacular achievements of medicine have been made possible by chemists and chemical engineers who, in turn, have shared in the satisfaction of the service they have rendered.

Many medicinal chemists are so engrossed in preparing, analyzing, testing, and applying drugs that they overlook one fundamental aspect of their science—and of all science. Medicinal chemistry may have been stimulated by the need of the sick for drugs, or even by the commercial rewards of their manufacture, but what the science of medicinal chemistry has achieved is the product of the ideas of thousands of persons whose driving motive has been scientific curiosity and an urge to explore relations between fundamental sciences. The great advances of the past have come from the keen interpretation of often accidental and unforeseen observations, and research organizers should keep this in mind for attaining future decisive results.

I. THE SCOPE OF THIS BOOK

This book makes an attempt to present to the reader the wide and ramified field of medicinal chemistry as it has been pictured above. It hopes to go beyond the scope of many other compendia on drugs which have been concerned with the structural analysis and the synthesis of important medicinal chemicals. These subjects will be treated carefully but not to the exclusion of other aspects of drugs. On the whole, the derivation of the structure of a naturally occurring drug will be discussed only if the particular case has not been reviewed in a readily accessible book or journal. Important modes of synthesis will be given for representative drugs only, and the reactions involved should be understood readily by any chemist with some graduate training.

In the case of the vitamins and steroid hormones, where structural proof and efficient syntheses have been essential in making these compounds available economically, considerable space will be allotted to these instructive chemical phases of study. This holds similarly for the antibiotics and polypeptides.

The methods of biological testing will be reviewed briefly for each class of drugs. In every chapter, the therapeutic usefulness and drawbacks of a given class of drugs will be pointed out, but an effort has been made not to encroach upon the realm of the physician. It is often difficult to draw a line between chemical pharmacology and medicinal chemistry, and only differences in emphasis and point of view separate these fields. Throughout this book emphasis has been placed on chemical aspects, and it is not anticipated that a physician will be able to construct a prescription from the facts stated in the text. However, this book will acquaint the physician with the background and with newer developments of drugs and give him an appreciation of the scientific work in other fields that has made his therapeutic tools possible.

The greatest progress in medicinal chemistry has come from the application of modern biochemistry to its problems. This has furnished an explanation of the mechanism of action of a number of drugs and has raised medicinal chemistry from an empirical art to a science. An attempt has been made in this book to point out the advantages of this approach, and it is hoped that the stature of medicinal chemistry among other sciences will be heightened by this mode of presentation. Although the biochemical approach is proving more and more valuable for the development of medicinal chemistry, it has actually raised more questions than it has answered. In this book speculations about biochemical mechanisms of drug action have been admitted where they appear to further the subject constructively. Even if this procedure may break the lines of scientific conservativism in some instances, it should serve to stimulate new questions in the mind of the reader who would like to see rational approaches to drug structure expanded.

The text has been documented extensively but no attempt has been made to furnish complete bibliographies. Likewise a selection of subjects has been imperative. Additional information on details omitted here may be obtained from pertinent monographs and review articles.

There is no space in one book for a complete account of the thousands of compounds that have been tested biologically and found inactive. Knowledge of such "negative experiments" is important if it teaches us that an approach which might have been expected to be successful has been eliminated from consideration by experimental findings. However, the random inclusion of chemicals that have been screened for every kind of physiological activity because they were handy in a given laboratory could only be expected within the framework of a review article. Emphasis has therefore been placed on positive results, with proper reference to exceptions to "rules" and other experiments which permit a critical evaluation of the therapeutic achievements of medicinal chemistry.

II. ARRANGEMENT OF DRUGS ON THE BASIS OF THEIR MEDICINAL USE

The uncertainties of the relations of chemical structure and biological activity make it appear unwise to arrange all drugs from a purely structural point of view. Alcohols are known to exert hypnotic, analgesic, and antibiotic properties. Amines are found in the series of analgesics, vasopressors, antihistaminics, bacteriostatics, and antimalarials. Phenolic groups are present in antiseptics, autonomic drugs, trypanocidal agents, estrogenic hormones, and certain vitamins. Lactones are encountered among cardiotonic and anthelmintic drugs. This enumeration could be extended to almost every other kind of structural unit and biological action. It has therefore been deemed advantageous to arrange drugs according to their medicinal uses. Drugs acting on various functions of the body (functional or pharmacodynamic drugs) have been grouped together, as have those used in combatting pathogenic parasites (chemotherapeutics, antiseptics, antibiotics, etc.). Nutritional factors

such as vitamins and catalytic endocrine materials (hormones) will be discussed at appropriate places.

The theory of the mode of biochemical action of drugs has progressed to a point where it can be placed ahead of detailed descriptive chapters. This serves the useful purpose of eliminating repeated references to the same basic phenomena in these chapters. Likewise, a general pharmacological review of humoral and neurohormonal agents will aid in introducing the reader to those overlapping fields of pharmacodynamic phenomena which are primarily governed by changes in nervous transmission.

III. THE LITERATURE OF MEDICINAL CHEMISTRY

Articles dealing with subjects of interest to medicinal chemists may be found in all major chemical, pharmaceutical, and medical journals and books. Monographs and review articles on specific fields have appeared in considerable numbers and may be found in chemical, biological, and medical abstracts journals under the respective headings. Specific pathological conditions, or specific drugs tested in such conditions, are also indexed in such abstracts periodicals.

Much valuable information concerning the synthesis, reactions, and biological transformation of drugs is contained in chemical journals. Treatises on pharmacology and biochemistry, even though addressed primarily to medical students, deal with many biological aspects of the major useful drugs. The compounds are listed by their nonproprietary and proprietary names and occasionally by rational chemical nomenclature.

It is much more complicated to obtain information on drugs which have not gone beyond the experimental stages. One may have to resort to abstracts of papers presented before scientific meetings in order to follow the development of such studies. The Proceedings of the Society for Experimental Biology and Medicine may serve as a typical example for such source material. The abstracts of papers given before the Divisions of Biological or of Medicinal Chemistry of the American Chemical Society, and before the annual Gordon Research Conferences, the Ciba Symposia, etc., contain much preliminary information which often is not published for years after.

It would be impossible to give a complete list of journals in which medicinal chemical publications may be found. Instead, a few of the most important abstract journals and periodicals presenting medicinal articles are listed below, together with a selection of review journals containing lengthy bibliographies.

Acta Medica Scandinavica
Advances in Enzymology
American Pharmacist
Angewandte Chemie
Annual Review of Biochemistry
Annual Review of Physiology
Antibiotics & Chemotherapy
Archiv der Pharmazie
Archives internationales de pharmacodynamie et de thérapie
Arzneimittel-Forschung
Bacteriological Reviews
Biological Abstracts
British Journal of Pharmacology and Chemotherapy
Chemical Abstracts
Chemical and Engineering News
Chemical Reviews
Chemisches Zentralblatt
Ciba Symposia
Cold Spring Harbor Symposia on Quantitative Biology
Deutsche medizinische Wochenschrift
Farmaco (Pavia)
Fortschritte der Vitamin-und Hormonforschung
Harvey Lectures
Journal of the American Medical Association
Journal of the American Pharmaceutical Association
Journal of Medicinal and Pharmaceutical Chemistry
Journal of Pharmacology and Experimental Therapeutics
Journal of Pharmacy and Pharmacology
Lancet
Medicinal Chemistry (sponsored by the American Chemical Society)
Medizin und Chemie
The Pharmacist
Pharmacological Reviews
Physiological Reviews
The Practitioner
Presse médicale (Paris)
Proceedings of the Society for Experimental Biology and Medicine
Quarterly Journal of Medicine
Quarterly Reviews (London)
Quarterly Review of Biology
Research Today
Review of Immunology

2. Historical Development of Medicinal Chemistry

ALFRED BURGER

The history of a science is composed of the ideas and facts which have advanced the borders of contemporary knowledge. It is an account of feats of imagination and careful correlation, high-lighted by those rare sparks of scientific insight which draw novel conclusions from a few significant observations. The great advances of medicinal chemistry have been achieved by two types of investigators: those with the genius of prophetic logic who have opened a new field by interpreting correctly a few well-planned experiments, and those who have varied patiently the chemical structures of physiologically active but toxic compounds until a useful drug could be evolved as a service to medicine.

More than in any other branch of science, empiricism has been employed in medicinal chemical research, and the formulation of basically sound ideas has taken place hesitantly only during the last 50 or 60 years. This may appear as a long period in comparison with still younger sciences, such as biochemistry, nuclear physics, etc., but the bulk of defendable theories of medicinal chemistry has actually been developed only during the past 30 years.

I. DRUGS OF ANTIQUITY

The comparatively short period of serious scientific growth of medicinal chemistry opens the question as to when the history of this field really started. Some ancient Chinese emperors and Roman philosophers have been credited with having been the forerunners of modern pharmacy and pharmaceutical science since their empirical methods of collection and therapeutic administration of herbs and herbal concoctions evoke an echo in the present-day selection and medical study of botanical drug mixtures, but they surely were not medicinal chemists. The oldest records of therapeutic plants and minerals stem from the ancient civilizations of the Chinese, the Hindus, the South American Mayas, and the Mediterranean peoples of antiquity. The scholar-Emperor Shen Nung (2735 B.C.) compiled a book of herbs and is credited with observing the antifebrile effects of Ch'ang Shang, which has now been shown to contain antimalarial alkaloids. He also noticed the diaphoretic and stimulatory effect of the drug Ma Huang, from which, almost 5000 years later, Nagai isolated the active alkaloid ephedrine.

Other oriental civilizations have also left records of their uses of medicinal plants. The antileprotic action of the chaulmoogra fruit was known to the ancient Indians, and the ipecacuanha root was used in Brazil and the Far East for the treatment of dysentery and diarrhea. Its main alkaloid, emetine, still constitutes an important drug for amebiasis. The plant which contains the anthelmintic ascaridol was prescribed under different names by the medicine men of the Hebrews (Jerusalem Oak), Mexicans (Mexican Tea), and the Romans (*Chenopodium anthelminticum*). The early explorers found the South American Indians in possession of the cinchona bark from which Pelletier and Caventou extracted the antimalarial alkaloid quinine only 300 years later (1820). These Indians also chewed coca leaves as a stimulant and euphoric.

Metallic salts were recommended by Hippocrates in the 4th century B.C., and the influence of his teachings was felt for 2000 years in occidental medicine.

The most retarding influence in progressive medicinal thought was exerted by the Roman naturalist Galenus (131–200 A.D.). His contention that herbal mixtures could provide all the essential elements of health and that proper herb mixtures could thus be used for all conceivable health defects dominated the middle ages and was fostered by the ecclesiastical monopoly on medical progress which promoted ignorance and superstition among the laiety. The four humors of ancient Greece—heat, cold, moisture, and dryness—were fused with early metallurgical views into a mystical legend which grew as the tendency towards irrationalism rose throughout the first 15 centuries of Christian civilization. Nevertheless, the history-minded scholar could discern beginnings of a *materia medica* even in those times. In Galenus' apothecary shop (αποθήκη, storeroom) herbs and some metallic drugs (copper and zinc ores, iron sulfate,

cadmium oxide) were found in abundance, and a semblance of assaying was maintained by insistence on "pure" drugs, that is, the right variety and age of the botanical specimens. Opium, squill, hyoscyamus, and viper toxin were part of Galenus' armamentarium, and an intimation of dosage levels can be seen in his contention that powerful narcotics relieve pain but may also cause death.

II. THE MIDDLE AGES

The groundwork of chemistry and physics shifted from the Greco-Roman to the Arabian scene during the next centuries, and in the writings of Arabian alchemists was born the idea of the philosopher's stone. The monk Albertus Magnus (1193(?)–1280), and his successor Roger Bacon (1214–ca. 1294), amplified this phantom thought and expressed the belief that the philosopher's stone, if ever discovered, would prove to be a universal remedy or elixir of life. The medical alchemist (iatrochemist) Paracelsus (1493–1541) adopted the glorification of antimony and its salts in elixirs as cure-alls as they had first been recommended by Basilius Valentinus 50 years earlier. He was so successful in this undertaking that he relegated herbs to a secondary place and raised antimony to an important though highly controversial drug.

The 16th century counted a long list of figures in many lands who swindled the public with worthless "sympathetic powders," mercury, and the laying on of hands. The latter procedure, an ancestor of psychosomatic medicine, was probably more effective than all the drugs of that era.

III. THE TRANSITION PERIOD

One great herbal drug of the 17th century has survived the test of time, the cinchona bark from which quinine was extracted later. It was brought to Europe from South America by missionaries (hence the name Jesuit bark or powder), and, after being rejected initially by unconvinced medical faculties, it became the prize medicine for fevers, chills, and malarias, its weight being matched in gold at various times.

The 16th and 17th centuries saw an improvement of the practices of pharmacists, and the influx of many new drugs of botanical and mineral origin from the New World necessitated a revision and enlargement of older compendia on *materia medica*. The first pharmacopoeias were edited in Florence (1498), Nürenberg (1535), Basel (1561), Augsburg (1564), and London (1618). These reference works also tried to bring order and reason into the ever-widening gulf between advocates of medicines of herbal and of metallic origin. The latter were to win the uneven battle because the now rapid progress of inorganic chemistry focussed attention on many new substances and made available to the medical profession chemically pure compounds for the first time. It is reasonable therefore to choose the late part of the 17th or the early years of the 18th century as the beginnings of what we call medicinal chemistry today (*6*).

In 1646, the French physician Guy Patin (1602–1672) suggested to a medical student: "Above all flee books on chemistry, *in quorum lectione oleum et perdes*" (*8*). This attitude changed as exact laws of chemistry were formulated, as the physiological action of well-defined compounds became amenable to quantitative study, and as the active principles of ancient herbal drugs were extracted, purified, and fitted into stoichiometric laws. The transition period was characterized by more precise classifications of botanical drugs and their biological effects, patterned upon the schemes of Linnaeus (1707–1778) and his followers. In the *Lectures on Materia Medica* by the Scotch physician William Cullen (1712–1790), the terms antispasmodic, antiseptic, cathartic, and emetic can be found (*4*). But, since the action of a drug upon functional organs in the body was not yet understood, the ancient theory of the four humors was unearthed again. Cullen expressed the belief that the neural system was primarily affected by drugs, but that the latter acted differently on persons of different temperaments, the choleric and melancholic, the temperaments of youth and age. He may not have been so wrong in this opinion, as every pediatrician or geriatrician can attest. We also know today that even the most innocuous drug is not tolerated well by some individuals, and this fact has been a justification for the many parallel searches for compounds which might exhibit not a better, but only the same medicinal activity.

Another view of that time was that some drugs acted on fluids, whereas others acted on moving and on static solids in the body. This idea again had its roots in the interpretation of the iatrochemists who had assumed that drugs diluted body fluids or changed its acidity or alkalinity, the change being measured by syrup of violets, which (due to its content of anthocyanins as we now know) turns red in acid and green in alkaline solution. These contradictory and fluctuating ideas were not aided by the suspicion that chemicals might behave one way in the laboratory and another way in the body, perhaps obeying different laws. This is a forerunner of the observations of many differences of *in vitro* and *in vivo* activi-

ties, the explanation of which is still lacking today. No wonder that 18th century medical scientists to whom organic chemistry still was the result of supernatural vital forces should have turned back to mysticism and Greco-Roman philosophical ideas to explain the action of their drugs.

In the meantime, new medicines were discovered and old ones improved. Withering (1741–1799) introduced digitalis (purple foxglove) as a therapeutic agent for dropsy, and almost the same material is used in the treatment of cardiac edema today. Van Swieten (1700–1772) taught the advantages of corrosive sublimate (mercuric chloride) over older mercurial preparations in "fevers." Ether made its first legitimate appearance in Hoffmann's drops or anodyne (Friedrich Hoffmann, 1660–1742), and opium was dispensed and studied by de Quincy (1785–1859) "to tranquilize all irritations of the nervous system, to stimulate the capacity of enjoyment and...to sustain the else drooping animal energies" (*4*).

Van Swieten is generally credited as the founder of the Viennese school of therapeutic nihilism which was more clearly expressed by Hahnemann (1755–1843) and dominated the development of pharmacology and medicinal chemistry until about 1870. Hahnemann believed that "*similia similibus curantur*," that both drugs and spiritual healing powers must be the opposite of the disease, and that only symptoms could be treated, not the cause of the disease. The treatment should consist of diluting drug solutions to the point of practically omitting their content of active components, because high concentrations of drugs produced toxic reactions, *i.e.*, symptoms similar to those of disease. This idea had already been expressed by William Shakespeare in *Hamlet*, Act IV:

> Diseases, desperate grown,
> By desperate appliance are relieved
> Or not at all.

These concepts led to the system of homeopathy which tended to abolish drugs altogether (therapeutic nihilism). It ran its due course and was finally completely reversed by Louis Pasteur (1822–1895), who regarded disease as caused by pathogenic parasites; this led to the age of healing with chemicals (chemotherapy).

Another theory was proposed by Samuel Thomson (1769–1843) in this country, who stated that "all diseases are the effect of one general cause and may be removed by one general remedy" (*8*). Echoes of this statement are found in Ehrlich's life-long ambition to find the *materia magna sterilans*, a cure-all for all infectious diseases, and in Hans Selye's stress theory in functional disorders. The nearest approach to this description of a drug may be found in modern broad-spectrum antibiotics.

IV. THE AGE OF MEDICINE

On the occasion of the centenary celebration of American independence, Edward H. Clarke of Harvard University surveyed the progress of medicine (*3*). He said:

> When Boerhaave, the most accomplished and celebrated physician of the 18th century, died, he left behind him a volume, the title page of which declared that it contained all the secrets of medicine. But this page like all others, except one, was blank, and on that one was written: Keep the head cool, the feet warm, and the bowels open. This legacy of Boerhaave to suffering humanity typified, not inaptly or injustly, the acquirements, not of medical science, but of medical art at the close of the 18th century.... To quiet the nervous system, to equalize the circulation, to provide for the normal action of the intestinal canal, and to leave all the rest to the *vis medicatrix naturae* was sound medical treatment.... The blank pages of the book were prophetic of the work which medical science was destined to accomplish. The science of his age could inscribe only a single sentence upon a single page. The 19th century has filled two or three additional pages with the secrets it has discovered, calling them vaccination, anesthesia and preventive medicine. It now transmits the volume to the coming ages, confident that each succeeding century will make new discoveries, till all of Nature's secrets are discovered, and then the title of the book shall be the just index of its contents.

Perhaps the most beneficial medicinal innovation of the 19th century was the discovery of general anesthesia. Davy (1778–1829) introduced nitrous oxide (laughing gas) as an inhalation anesthetic, and this was followed by the first clinical experiments with ether in the surgical amphitheater. Crawford W. Long (1815–1878) of Georgia employed ether as an anesthetic in 1842, and William T. G. Morton (1819–1868) of Boston showed its use in the "ether dome" operating room at Massachusetts General Hospital in 1846. The British anesthetist Simpson (1811–1870) employed chloroform the following year, and surgery was put on a scientific basis by these agents.

The first important pure drugs were alkaloids, several of which were extracted from long-known sources in the first 75 years of the 19th century. Morphine was isolated by the pharmacist Sertüner in 1806, the mydriatic base atropine by Mein, Geiger, and Hesse in 1833, and quinine by Pelletier and Dumas in 1823. Early synthetics included acetanilide, salicylic acid (Kolbe, 1818–1884), antipyrine (Knorr, 1883), aspirin (Dreser,