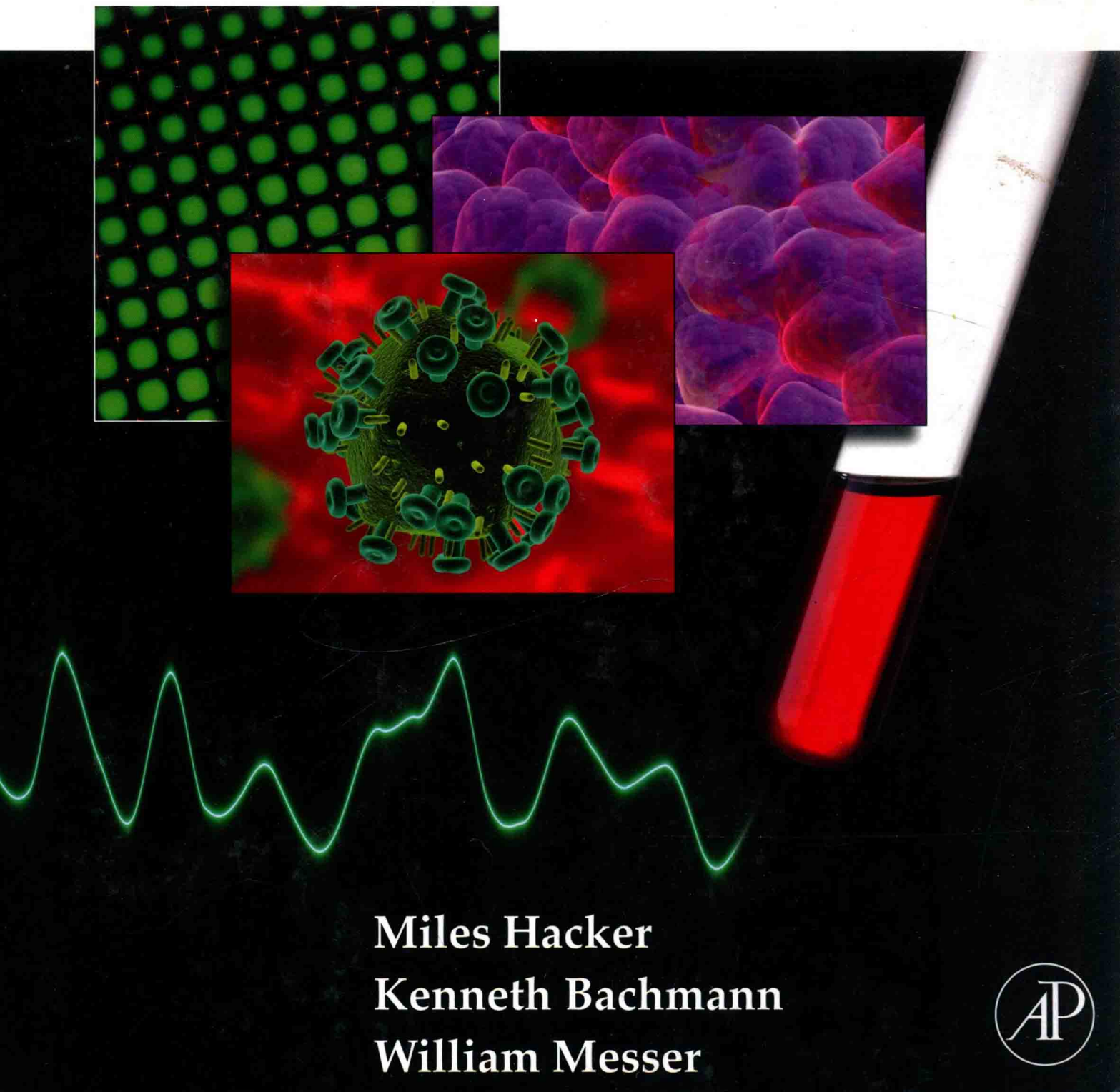
Pharmacology

Principles and Practice



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Pharmacology: Principles and Practice

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

Library of Congress Cataloging-in-Publication Data
APPLICATION SUBMITTED

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

ISBN: 978-0-12-369521-5

For information on all Academic Press publications
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Printed in China
09 10 9 8 7 6 5 4 3 2 1

Pharmacology

This textbook is dedicated to the memory of three of our close colleagues and friends, Gerald Sherman, Timothy Sullivan, and James Byers, and their efforts to help students understand and appreciate pharmacology and pharmacokinetics.

Accompanying Web site with additional materials available at
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Preface

Several years ago we noted a paucity of textbooks that dealt with the principles of pharmacology as a science, rather than pharmacology as a therapeutic entity. In an attempt to remedy this, we organized a textbook designed to meet the needs of students interested in pharmacology at the advanced undergraduate and early graduate level. This text addresses the many facets that form the foundation of pharmacology.

Students will find extensive discussions by leaders in the field are written in clear and straightforward manner. Illustrations are included to help further the reader's understanding of the material covered in each chapter. The editors and authors have focused on the science of pharmacology and use drugs for illustrative purposes only.

As pharmacology is a field of science that encompasses science from various arrays, we have included chapters dealing with each level of biological organization, both biology and chemistry which has been included in discussion of each chapter and how they related to one another. The material in this textbook will provide the student and the practicing pharmacology scientist excellent education and reference materials. Each chapter is written in a matter similar to Scientific American, where the text is not interrupted by referencing, but an extensive bibliography is provided for the reader at the end of each chapter.

The editors are grateful for the dedication and cooperation of the authors and recognize the efforts put forth by each to create a textbook that is not only first rate, but also a useful resource to students and researchers alike. The editors are also deeply grateful for the assistance that we received from the highly talented and professional staff of the publisher, Elsevier.

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Chapter

1

History of Pharmacology—From Antiquity to the Twentieth Century

Miles Hacker

OUTLINE

1.1 WHAT IS PHARMACOLOGY?

Obviously, a discussion of all the ancient remedies would require more space than possibly could be allotted for one chapter in a textbook. In this chapter we will discuss a few of the more fascinating examples of how ancient civilization was able to treat disease with available natural products. We will then discuss the progression of pharmacology from the science of testing crude extracts of plants, animals, and minerals for their medicinal properties, to the science it is today, in which isolated chemicals are examined for their effects on live tissue. This begs the question, what is a good working definition for modern pharmacology? On the surface, this seems like an easy task, but as we peruse the textbooks and articles pertaining to pharmacology we rapidly realize that the definition of pharmacology varies greatly, depending on who is defining the discipline.

A dictionary defines pharmacology as:

> **1. Study of drugs**: the science or study of drugs, especially of the ways in which they react biologically at receptor sites in the body
>
> **2. Drug's effects**: the effects that a drug has when taken by somebody, especially as a medical treatment

Yet another source defines pharmacology in this way:

> Branch of **medicine** dealing with the actions of **drugs** in the body—both therapeutic and toxic effects—and development and testing of new drugs and new uses of existing ones.

Though the first Western pharmacological treatise (a listing of herbal plants) was compiled in the first century AD, scientific pharmacology was possible only from the eighteenth century on, when drugs could be purified and standardized. Pharmacologists develop drugs from plant and animal sources and create synthetic versions of these, along with new drugs based on them or their chemical structure. They also test drugs, first *in vitro* for biochemical activity and then *in vivo* for safety, effectiveness, side effects, and interactions with other drugs and to find the best dose, timing, and route.

When reading textbooks, we find such definitions as:

> Pharmacology is the science of drugs, their chemical composition, their biological action and their therapeutic application to man and animal. It includes toxicology, which encompasses the harmful effects of chemicals, whether it is used therapeutically or not.
>
> Pharmacology is the study of the interaction of chemicals with biological entities.
>
> Pharmacology is the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and thereby activate or inhibit biological activities in the body.

There are as many definitions of pharmacology as there are those defining the science. Given the breadth and scope of the discipline it is hardly surprising that there is such a variance in definitions. For the purposes of this chapter we will define the field in as simple yet inclusive terms as possible:

Pharmacology is the study of the effects of chemicals and the mechanism of these effects on living organisms (pharmacodynamics), and the effects of the living organisms on the chemicals including absorption, distribution, metabolism, and excretion (pharmacokinetics).

1.2 WHAT IS THE POSITION OF PHARMACOLOGY IN THE FIELD OF THERAPEUTICS?

Briefly, the medicinal chemist works in concert with the pharmacologist in determining the efficacy of the chosen target molecule. The lead molecule then is identified following a series of chemical modifications of the target molecule (structure activity relationship, or SAR). The analytical chemist works with both the medicinal chemist and the pharmacologist to assure the chemical structure and purity of the chemical product. The pharmacodynamics group works closely with pharmacology while performing the SAR studies. The pharmacokinetics group works with pharmacology and analytical chemistry to assess how the body affects a chemical once administered. The pharmaceutics group works with the pharmacokinetics/pharmacodynamics groups and the pharmacologist to determine how best to formulate the drug for maximum efficacy. Once the lead compound, formulation, and route(s) of administration have been selected, the toxicology group works with the pharmacologist to determine potential sites of toxicity in experimental animals.

Once preclinical toxicology studies have been completed, an application is submitted to the FDA for approval to perform clinical trials for efficacy and toxicity in human subjects. Finally, if efficacy and toxicology warrant it, another application is submitted to the FDA for drug marketing approval. As we can see from the brief description, the pharmacologist plays a pivotal role in every aspect of the drug discovery and development process. A thorough discussion of this process can be found in Chapter 15 of this textbook.

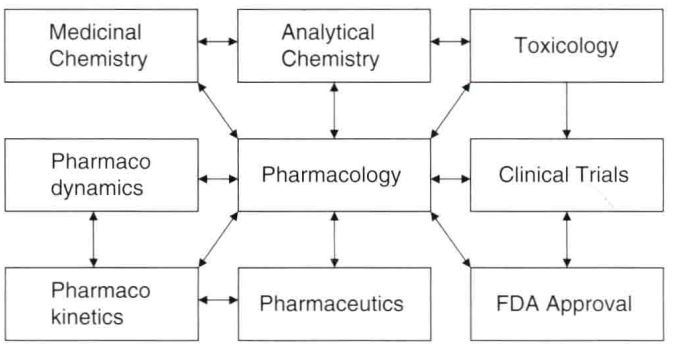

Figure 1.1 Pharmacology: A multifacted discipline.

1.3 THE BEGINNINGS OF PHARMACOLOGY

Pharmacology is both an ancient science and a relatively new science. Since the beginning of mankind there has been a search for ways to alleviate the pain and suffering associated with life. To the ancient pharmacologist this meant painstaking observations and experimentation with natural products such as plants, animals, and minerals. Substances like fruits, leaves, bark, roots, dirt, and animal parts were rubbed on to the human body, boiled in hot water and drunk, smelled, or consumed in the physical state that they were gathered. The effects of these preparations on the human were noted and discussed and thus tribal folklore evolved. Slowly a knowledge base developed regarding what to use for a given malady.

As different tribes comingled, exchange of tribal folklore more than likely occurred and an ever-increasing compendium of useful, not so useful, and even horribly dangerous remedies developed. A good example of how these ideas and concepts grew into understanding the need of specific items in our diet and health was common salt. Long before recorded time, salt trade routes were established between the hot dry climates near the sea where salt deposits flourished, and the areas where salt was scarce. Why did salt become an essential ingredient in the lives of the ancients? Perhaps by ancients observing animal behavior and dietary activities in and around natural salt flats. The practice of mimicking animal behavior aided in the evolution of both foodstuffs and potential remedies for disease.

Diet was then and remains today a vital component of maintaining good health and battling disease. Various foods were scrutinized for their possible health values and were passed from culture to culture and generation to generation. Those who were charged with maintaining the health of a given tribe or population were expected to know the values of different foods, medicinal plants, minerals, and even such esoteric things as the healing properties of smoke and chants. Equally importantly these individuals had to know how and when to administer these healing agents. Records from ancient China, India, Sumeria, Egypt, and Greece are full of suggestions, often in great detail, of the health benefits of every known fruit, grain, tuber, berry, or vegetable. Other records describe different soil and mineral preparations, as well as animal parts, for medicinal properties. In certain cultures, many of these preparations remain in vogue and are still used.

Consider one example and how important it may have been in maintaining the health of early hunter/gatherer societies, especially nomadic tribes constantly moving into new uncharted territories. Having no extensive knowledge of the new area these people relied heavily on trial and error when it came to gathering plants for food. Using observational information obtained by watching what the indigenous animal ate helped somewhat. Given what we now know about species variation

among animals, plants that are edible for a given animal could prove to be a devastating poison to the humans who recently moved into the new region. From careful observations the ancients also knew that certain plants or parts of plants could induce vomiting. If the consumption of an unknown foreign plant resulted in unpleasant sensations in the GI tract they knew to consume a medicinal plant to rid themselves of the new plant. In fact, one of the most widely described medicinal purposes of plants was that of a purgative.

One of the oldest medicinal preparations made by man was alcohol. Here again careful observations provided the basis for the development of this ancient and important drug. Recipes for beer, wine, and mead are found in the oldest of recorded literature from cultures worldwide. Not only were these liquids used in ceremonial practices, their medicinal properties of decreasing pain sensation and the ability to induce sleep were greatly appreciated. As the cultures became more sophisticated these alcoholic beverages were used as tinctures of herbs to enhance the medicinal effectiveness of herbs and plants.

1.4 PHARMACOLOGY OF THE GRECO-ROMAN ERA

Probably the best recognized of all the ancient Greek physicians is Hippocrates. It is likely that much of the writings attributed to this man came from a group of health professionals of whom Hippocrates was the most prominent member. During this time rationality was introduced in the healing process as they began to understand the importance of careful descriptions of diseases, symptoms, and geographical locations. In spite of the importance of this group in the field of medicine they really had little to do with drugs. Rather, Hippocrates and his followers relied much more on the healing power of nature, known as *Vis medicatrix naturae*. It is of interest that even today there is evidence of the placebo effect in which the patient cures him- or herself though the belief in the curing effects of the drug even though no drug is present in their medicine. Is this not an example of the healing power of nature?

The evolution of the healing practices was transferred to the Roman empire as Greek doctors came to Rome, many times as slaves. It is here where interest in medicines grew rapidly. Celsus wrote eight books on disease, containing significant references to the use of drugs in the treatment of disease. As in Greece, the health professionals of Rome felt it necessary to maintain excellent records and perform careful observations. One of the most important records of that time was kept by Dioscorides, a Roman surgeon, who traveled with Nero's armies compiling all the information on drugs that he could. This compendium, entitled *Materia Medica*, included some 600 plants, also including illustrations, how to find the plant, where to find the plant, and how and when to use the plant.

With the growth of knowledge of the medicinal properties associated with plants came the fear of accidental or intentional poisoning. Rulers of Rome were especially fearful as it was clearly established that ascension along the political ranks was best accomplished by assassination of those above you. An interesting undertaking was that of Mithridates, King of Pontus, in which he described a "universal antidote" called mithridatium, a concoction of 35 different ingredients. An interesting myth associated with this universal antidote is that a ruler taking mithridatium was given the opportunity to kill himself rather than suffer the embarrassment of being killed by his captors. To do this he had to use his sword because none of the available poisons were effective against mithridatium.

An important physician during the second century AD was Galen, who solidified the concept of the four humors first championed by Hippocrates into the workings of the healthcare providers. These humors were blood, phlegm, yellow bile, and black bile. So powerful was the influence of Galen, that Galenic principles of medicine were practiced to the eighteenth century, much to the detriment of medical evolution. It must be noted however that Galen was an excellent experimentalist and observationalist. Galen first described that blood occupied the arterial system, that the heart provided the power to move blood, and that the heart isolated from the body continued to beat.

As time progressed, the Byzantine and Muslim worlds added to the base of knowledge concerning drugs. Most of the information gained during this period was a continuation of the efforts started in Greece and Rome, that being the production of further compendia of medicinal plants. The Muslims provided such contributions as the development of syrups for respiratory ailments, the use of mercurial formulations for skin diseases and the process of distillation to obtain concentrates of beer and wine. In addition, important refinements were made in the record keeping and organization of medical plants. However during this time the alchemists came into fashion and worked diligently on such projects as turning lead into gold and the search for the universal "elixir of life" to cure all diseases and prolong a healthy life. The concept behind the elixir arose from the observations that wine made the ill feel better, brought on a feeling of euphoria, and made the elders feel young again. Thus, it was believed that with proper distillation techniques the important elixir or spirit could be isolated and used. Unfortunately for all, this was never accomplished.

1.5 PHARMACOLOGY AND THE MIDDLE AGES

The middle ages of Europe (*ca* 10–15 centuries AD) were a time of feudalism, authoritarianism, and dogmatic religious leaders. During this period intellectual thought and discovery were hampered terribly by the intellectual complexity of the times. The Roman era

of peace and security was gone and was replaced by epidemics, squalor, poverty, and ignorance throughout Europe. All teachings revolved around salvation through the church. The health professional virtually disappeared and the use and understanding of drugs fell back to pre-Greco-Roman times. Civilization and learning were almost the exclusive provenance of the monasteries, monks skillfully copying manuscripts for dispersal to other monasteries. Monks maintained drug-herbal gardens to assure at least a semblance of plant drug supply.

If one city can be highlighted as the most important in bringing Greco-Roman medicine back to Europe it must be Salerno, an important trading center on the southwest coast of Italy. Here traders from all over the world came to trade their goods and bring information and knowledge back to Europe. It is here where a hospital not under the thumb of the church sprang up. The caretakers of the sick sought reference works from the foreign traders and back came the drug information that had been all but lost during the middle ages. The task of converting these compendia from their native languages of Greek and Arabic to Latin fell onto the shoulders of a few, with one of the most notable being Constantinus Africanus. Born in Carthage and widely traveled, Constantinus took on the onerous responsibility of manuscript translation including a major compendium on Greco-Roman and Muslim plant- and animal-based drugs. So influential was his work that he was asked to translate classical literature, which may have played a role in the recovery of universities in Europe.

The medical school in Salerno slowly became quite successful. Members of the school were allowed to think freely and question authority, providing an intellectual atmosphere for growth. During this time a rebirth in codifying medical plants occurred. New approaches to treating disease were developed such as the use of seaweed (high in iodine) to treat goiter, cleaning a wound using alcohol distillates, and the rediscovery of mercurial ointments to treat skin sores and lice. So successful was this school of medicine that the churches began to build medical schools modeled after that in Salerno. Toward the end of the middle ages drug use and drug trade were firmly reestablished, thus paving the way for growth during the Renaissance.

1.6 PHARMACOLOGY AND THE RENAISSANCE

Several important events occurred during the Renaissance that drove the growth of pharmacology. First was the development of the movable type printing press. With this machine came the availability of books that could be dispersed and read. Knowledge could be obtained and spread with relative ease, enabling those interested to learn about medicinal plants and animals. Further, new knowledge could be dispersed far more easily and rapidly than ever before. At the same time glorious new geographical explorations were leaving from Europe to the far reaches of the Earth. The adventurers returned with exotic plants and stories on how these plants were used medically. Finally, the mind of the European was now open after centuries of religious constraints and new ideas and concepts began to evolve.

Herbalists in every country were gathering plants and knowledge in attempts to develop new medicines to treat disease. With the gain of medical knowledge came the birth of a formalized botany. German herbalists are considered to be the fathers of botany. One German physician condemned his fellow German herbalists for using names on their drug receptacles with Greek names that were no longer applicable. He authored a short poetic piece that expressed the feelings of society of that day toward the healers (come to think of it, many today still hold this belief):

> Three faces has the doctor:
> A god's when first he's sought
> And then an angel's, cures half wrought:
> But when comes due the doctor's fee,
> Then Satan looks less terrible than he!

What was the crowning achievement of this enlightened period? Probably a continuation of what had preceded this era—care in cataloguing plant medicines, how to prepare them, and how to use them. The printing press enabled these cataloguers to widely disperse their work. Two important names are associated with this period, Cordus and Vesalius. Valerius Cordus, during his relatively short life, edited and expanded the pivotal work of Dioscorides. His work marked the transition from magic, spells, and alchemy to a rational approach to chemical experimentation. In addition, Cordus developed the first true pharmacopeia, the *Dispesatorium pharmacopolarum*, which received wide use and served as the format for plethora of pharmacopeias that arose following the publication of his work. Vesalius's major contribution was the standardization of drug preparation in order to assure to some degree a uniformity in expected results following the use of any given drug.

One of the most important experimentalists of the time was a Swiss named Auerrolus Theophrastus Bombastus von Hohenheim, or Paracelsus as he called himself. His father was a physician and he, too, became a trained physician. After earning his degree he traveled extensively, learning the art of medicine from a number of different sources. An interesting character, he was appointed professor of medicine at Basel and shortly thereafter was erroneously thought to have been killed in a tavern brawl in Salzburg. A gruff, bombastic, but brilliant individual, he first described the concept of dose response relationship when he said (paraphrased), "Everything is a poison and nothing is a poison, it is only the dose that counts." As an experimentalist he noted a correlation between exposure to dust in mines and lung damage, he studied the effect of mineral baths on skin disorders, and the role of heavy metals in the treatment of disease. He may well have been the first to use pure chemicals as drugs.

Along with the growing appreciation for careful observations and record keeping came the increased interest in and the use of poisons. The most fascinating family of the era was the Borgias, an Italian family who manipulated the papacy and the empire in large part through their expertise in poisoning. An interesting aspect of this was the fact that they used arsenic trioxide, a water-soluble white powder without taste or aroma. The compound often was mixed with wine and was virtually nondetectable. It is often said that the Borgias gave rise to experimental toxicology. Although arsenic trioxide was used during the Renaissance, just recently the drug has been approved by the FDA for the treatment of cancer!

1.7 PHARMACOLOGY AND THE BAROQUE PERIOD

The next two centuries brought about changes in medicine and the developing field of pharmacology too numerous to discuss in detail. An attempt will be made to select some of the more important highlights of this interesting era. This period can be considered a groundbreaking time with respect to experimentalism. A motivating factor in drug discovery during this period was the introduction of new plants (and drugs) from places far away for this was the time of extended geographical exploration. The Spaniards brought back a variety of plant samples from South America, and the Portuguese discovered a trade route to the Far East and brought back many medicinal plants and spices.

The introduction of these highly acclaimed and important new sources of drugs to European medicine was slow because each country carefully guarded their findings. However, two of the most important drugs had to be ipecacuanha and cinchona bark. The former was shown to have significant but relatively safe emetic properties. The drug became an important treatment for diarrhea and dysentery. In the decoction was a drug emetine that became the treatment of choice for amebic dysentery and amebic abscess. It wasn't until the twentieth century that newer drugs to treat amebiasis were introduced. The cinchona bark was important in treating fevers as an extract of the bark; often referred to simply as *The Bark*, it seemed to treat all fevers regardless of origin. The use of The Bark became so widespread throughout Europe that the cinchona tree became scarce. It is of interest that a similar situation occurred quite recently when the bark of old-growth Yew trees was shown to contain taxanes, which proved effective in treating cancer. So effective in fact that there was a very real fear that there were insufficient trees to support the production of the drug. We encourage you to read the story of taxol and how this problem was overcome.

Cinchona remained a very valuable medicine even up to WWII, when Allied soldiers in the South Pacific were exposed to malaria. Cinchona bark (quinine) was used extensively to treat the disease. After the Japanese invaded and controlled Java, an important source of the bark was lost, which necessitated the development of alternative medicines to treat this horrid disease.

In addition to the introduction of many new medicines, many important discoveries were made by scientists of the time. For example, William Withering, a British physician, first described the effects of an extract of the leaves of the purple foxglove on cardiac dropsy (congestive heart failure). From his careful experimentation, the dose-related difference in the effects of digitalis on the human body were first described and still remain pertinent today. Edward Jenner noted that milkmaids seldom got small pox but instead suffered a far less severe form of the disease known as cow pox. From this observation, soon he was inoculating an individual with the pus from a cow pox pustule and then later challenged that individual with small pox. Cow pox protected the person from small pox! William Harvey first reported that the circulatory system was a closed system using the heart to pump blood through the vasculature system. He also suggested that drugs taken orally entered the body through the gastrointestinal tract and were distributed throughout the body via the blood.

Work done during this period was severely hampered by the lack of chemical isolation and characterization techniques. However, it was during this time that the foundations for such approaches were developed. Individuals such as Robert Boyle, Joseph Priestly, and Antoine-Laurent Lavoisier were actively investigating the principles of physics, gasses, and chemical isolation. This time period provided the basis for the explosion of scientific investigation and the birth of modern pharmacology that occurred during the next century.

1.8 THE BIRTH OF MODERN PHARMACOLOGY

The basics of analytical chemistry had been introduced in the late eighteenth century and were rapidly applied to pharmacology. The seminal work in the field of active ingredient isolation was that of Friedrich Wilhelm Serturner, a German pharmacist with a deep interest in opium. Extracting opium with an acid, he isolated a water soluble compound that induced sleep in dogs and himself. He called the chemical *morphine*, in honor of the god of sleep. Within a relatively short period of time a variety of chemicals were isolated from crude plant sources and the beginnings of testing isolated chemicals, rather than a crude extract of a plant, for pharmacological activities began in earnest.

Francois Magendie studied a variety of chemical extracts of plants, focusing primarily on the newly defined class of chemicals called the alkaloids. He became so impressed with the chemicals that he developed a compendium of alkaloids that described the actions and indications of a variety alkaloids recently

isolated and described. More importantly, Magendie laid down the basic principles that remain unique to pharmacology today:

- Dose response effect, explored from the beginning but not quantitated until 1927
- Factors involved in ADME
- Identification of the drug site of action
- The mechanism of action of the drug
- Structure activity relationship

Much of the work done regarding the use of these principles in the scientific laboratory was done first by Magendie's pupil Claude Bernard, a gifted physiologist/early pharmacologist. He developed a number of theories—some proved wrong, such as the coagulation theory of anesthesia, and some proved quite valid, such as the use of morphine before chloroform to enhance the anesthetic properties of chloroform. This latter observation was one of the first to describe drug–drug interactions.

Magendie's other student, equally gifted as Bernard but less well known, was James Blake. Enamored with technology of the time, Blake used newly developed instrumentation to determine blood pressure, blood circulation time, and was probably the first to report on structure activity relationships as they pertain to drug discovery. He was truly a renaissance man as he was involved in a variety of pharmacological, medical, and veneologic enterprises. He even served as president of the California Academy of Science, where he reported on his studies in meteorology, geology, and biochemistry to name a few. The contributions of Magendie and his students Bernard and Blake laid the groundwork for modern pharmacology.

A significant advance made during the first half of the nineteenth century was research into anesthesiology. Surgical techniques developed far faster than did methods to decrease or eliminate the pain associated with surgery. As a result the mark of a good surgeon was the speed with which he could complete a given procedure. The first anesthetic to gain popularity was nitrous oxide, although it must be said that the interest in this gas was more at medical side shows than medical practice. A dentist, Horace Wells, demonstrated that tooth extraction could be completed painlessly if the patient were under the influence of nitrous oxide. Unfortunately, when the procedure was performed at the Massachusetts General Hospital, in front of the medical leaders of the time, the demonstration was a failure as the patient squawked and fought the extraction. As is the case all too often in science, the establishment attacked Wells for the failure and Wells retired in disgrace.

William Morton, a colleague and partner of Wells, the man who set up the nitrous oxide demonstration at Massachusetts General, feared that nitrous oxide was not reproducibly strong enough to provide the needed anesthesia and sought a more powerful anesthetic. Ether was selected as the next anesthetic for testing. Morton developed the technique for ether delivery and provided a demonstration again at Mass. General, and this time the demonstration was a total success. He also reported on ether-induced vomiting in children, an experience this author is all too familiar with following tonsil extraction in the early 1950s.

James Young Simpson was dissatisfied with the time required for ether-induced anesthesia and received from a chemist friend of his, three chloroform-based liquids. He then tested these products on his friends and family for anesthetic potential! Of the samples tested, chloroform provided the most rapid and effective anesthesia. Simpson went on to use chloroform with great success in controlling pain of childbirth but this did not come without controversy. The church fought the use of anesthetics in something so divine as childbirth. Even at this time fundamentalism was still supreme but Simpson ultimately won the day by arguing that the Bible states clearly how Adam was put to sleep before Eve was born from him.

The success of both ether and chloroform resulted in much debate about the merits of each. Chloroform was preferred in England and Europe, whereas ether was preferred in the United States. A great deal of work was done on which anesthetic was better, and although no true conclusion was attained, this scientific undertaking was one of the first in comparative pharmacology addressing the risks and benefits of different drugs.

During this time the fathers of modern pharmacology were establishing their laboratories in Germany. Rudolf Buchheim, recognized as the first German pharmacologist, was able to eliminate a number of old and ineffective therapies, and produced a new compendium of drugs based on the proven effects of the drugs. He taught pharmacology out of his home and studied the pharmacokinetics of minerals and heavy metals and ascribed to the belief that drugs must be studied in a systematic way to provide a rational background for drug therapy. His pupils then established the field of pharmacology throughout the Germanic countries. One of his students, Oswald Schmiedeberg, has been credited with training all the Americans who established pharmacology in the United States.

During the nineteenth century, the concept of isolating pure chemicals with bioactivities was established. The pure chemical then could be characterized structurally and could be evaluated carefully and accurately for varying biological activities. The success of this approach meant that health practitioners could provide their patients the benefits of these isolated characterized bioactive natural products. As pharmacology matured further, the concept of making synthetic drugs through chemical synthesis began to take hold.

The rise of chemistry at this time made this approach possible. John Dalton described the atomic theory, making it possible to understand how inorganic molecules fit together. Kekule described the aromatic ring of organic compounds. In addition, synthetic chemistry was coming of age. A driving force for the production of synthetic drugs was the economic problem with quinine and the bark of the cinchona tree and the hope for safer more effective drugs coming from the chemist's bench.

In 1872, Schmiedeberg established his laboratories in a newly renovated building in Strassburg, which became the first well-equipped modern laboratory for pharmacology. As stated before, these new and up-to-date facilities attracted many of the brightest young U.S. students of pharmacology. His research included investigations on the similarities between the chemical muscarine and electrical stimulation and that the effects of both could be blocked by atropine. As can be seen, the ability to study single drug entities greatly enhanced the quantity and quality of the pharmacological research being done in the latter portion of the nineteenth century.

Another important contribution of the Schmiedeberg lab was the careful studies on how drugs were "detoxified" and removed from living tissue. He showed the importance of glucuorinic acid and the liver in removal of drugs from the body via the kidney. His laboratory and the students within it were so prolific that a journal, often referred to as *Schmiedeberg's Archives* (formally known as *Archives for Experimentelle Pathlogie and Pharmakologie*), was established. The importance of this event rests in the fact that it established pharmacology as an independent field of investigation and the important role pharmacology would play in medical education.

Schmiedeberg's successor, Rudolf Bohm, isolated and characterized anti-helmentic therapy. Of interest, Bohm also demonstrated that there are times when a crude preparation on a botanical is safer and more effective than the chemically pure isolate.

The number of exciting findings made during the latter portion of the nineteenth century are too numerous to describe, as are the scientists involved in this research. Suffice it to say that the latter part of the nineteenth century was an amazing time in pharmacology, bringing together all the advances made in the recent past and utilizing them to propel pharmacology into the twentieth century, and the importance of this exciting field in the next 108 years. The advances made during the twentieth century provide the basis of this textbook, and the ever-growing importance of pharmacology as a discipline. Hopefully, this chapter provided an interesting read and new insight into how the field of pharmacology developed into the discipline it is today.

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