# GENERAL PRINCIPLES OF PHARMACOLOGY

# 1 | Progress in Therapeutics

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Early in human history a natural bond formed between religion and the use of drugs. Those who became most proficient in the use of drugs to treat disease were the "mediators" between this world and the spirit world, namely, the priests, shamans, holy persons, witches, and soothsayers. Much of their power within the community was derived from the cures that they could effect with drugs. It was believed that the sick were possessed by demons and that health could be restored by identifying the demon and finding a way to cast it out.

Originally, religion dominated its partnership with *therapeutics,* and divine intervention was called upon for every treatment. However, the use of drugs to effect cures led to a profound change in both religious thought and structure. As more became known about the effects of drugs, the importance of divine intervention began to recede, and the treatment of patients effectively became a province of the priest rather than the gods whom the priest served. This process lead to a growing understanding of the curative powers of natural products and a decreasing reliance on supernatural intervention and forever altered the relationship between humanity and its gods. Furthermore, when the priests began to apply the information learned from treating one patient to the treatment of other patients, there was a recognition that a regularity prevailed in the natural world independent of supernatural whim or will. Therapeutics thus evolved from its roots in magic to a foundation in experience. This was the cornerstone for the formation of a science-based practice of medicine.

## CONTRIBUTIONS OF MANY CULTURES

The ancient Chinese wrote extensively on medical subjects. The *Pen Tsao,* for instance, was written about 2700 B.C. and contained classifications of individual medicinal plants as well as compilations of plant mixtures to be used for medical purposes. The Chinese *doctrine of signatures* (like used to treat like) enables us to understand why medicines of animal origin were of such great importance in the Chinese pharmacopoeia.

Ancient Egyptian medical papyri contain numerous prescriptions. The largest and perhaps the most important of these, the *Ebers papyrus* (1550 B.C.), contains about 800 prescriptions quite similar to those written today in that they have one or more active substances as well as vehicles (animal fat for ointments; and water, milk, wine, beer, or honey for liquids) for suspending or dissolving the active drug. These prescriptions also commonly offer a brief statement of how the preparation is to be prepared (mixed, pounded, boiled, strained, left overnight in the dew) and how it is to be used (swallowed, inhaled, gargled, applied externally, given as an enema). Cathartics and purgatives were particularly in vogue, since both patient and physician could tell almost immediately whether a result had been achieved. It was reasoned that in causing the contents of the gastrointestinal tract to be forcibly ejected, one simultaneously drove out the disease-producing evil spirits that had taken hold of the unfortunate patient.

The level of drug usage achieved by the Egyptians undoubtedly had a great influence on Greek medicine and literature. Observations on the medical effects of

various natural substances are found in both the *Iliad* and the *Odyssey*. Battle wounds frequently were covered with powdered plant leaves or bark; their astringent and pain-reducing actions were derived from the tannins they contained. It may have been mandrake root (containing atropinelike substances that induce a twilight sleep) that protected Ulysses from Circe. The oriental hellebore, which contains the cardiotoxic *Veratrum* alkaloids, was smeared on arrow tips to increase their killing power. The fascination of the Greeks with the toxic effects of various plant extracts led to an increasing body of knowledge concerned primarily with the poisonous aspects of drugs (the science of *toxicology*). Plato's description of the death of Socrates is an accurate description of the toxicological properties of the juice of the hemlock fruit. His description of the paralysis of sensory and motor nerves, followed eventually by central nervous system depression and respiratory paralysis, precisely matches the known actions of the potent hemlock alkaloid, coniine.

The Indian cultures of Central and South America, although totally isolated from the Old World, developed drug lore and usage in a fashion almost parallel with that of the older civilization. The use of drugs played an intimate part in the rites, religions, history, and knowledge of the South American Indians. New World medicine also was closely tied to religious thought, and Indian cultures treated their patients with a blend of religious rituals and herbal remedies. Incantations, charms, and appeals to various deities were as important as the appropriate application of poultices, decoctions, and infusions.

Early drug practitioners, both in Europe and South America, gathered herbs, plants, animals, and minerals and often blended them into a variety of foul-smelling and ill-flavored concoctions. The fact that many of these preparations were so distasteful led to an attempt to improve on the "cosmetic" properties of these mixtures to ensure that patients would actually use them. Individuals who searched for improved product formulations were largely responsible for the founding of the disciplines of *pharmacy* (the science of preparing, compounding, and dispensing medicines) and *pharmacognosy* (the identification and preparation of crude drugs from natural sources).

There has long been a tendency of some physicians to prescribe large numbers of drugs where one or two would be sufficient. We can trace the history of this polypharmaceutical approach to Galen (A.D. 131–201), who was considered the greatest European physician after Hippocrates. Galen believed that drugs had certain essential properties, such as warmth, coldness, dryness, or humidity, and that by using several drugs he could combine these properties to adjust for deficiencies in the patient. Unfortunately, he often formulated general rules and laws before sufficient factual information was available to justify their formulations.

By the first century A.D. it was clear to both physician and protopharmacologist alike that there was much variation to be found from one biological extract to another, even when these were prepared by the same individual. It was reasoned that to fashion a rational and reproducible system of therapeutics and to study pharmacological activity one had to obtain standardized and uniform medicinal agents.

At the turn of the nineteenth century, methods became available for the isolation of active principles from crude drugs. The development of chemistry made it possible to isolate and synthesize chemically pure compounds that would give reproducible biological results. In 1806, Serturner (1783–1841) isolated the first pure active principle when he purified morphine from the opium poppy. Many other chemically pure active compounds were soon obtained from crude drug preparations, including emetine by Pelletier (1788–1844) from ipecacuanha root; quinine by Carentou (1795–1877) from cinchona bark; strychnine by Magendie (1783–1855) from nux vomica; and, in 1856, cocaine by Wohler (1800–1882) from coca.

The isolation and use of pure substances allowed for an analysis of what was to become one of the basic concerns of pharmacology, that is, the quantitative study of drug action. It was soon realized that drug action is produced along a continuum of effects, with low doses producing a less but essentially similar effect on organs and tissues as high doses. It also was noted that the appearance of toxic effects of drugs was frequently a function of the dose–response relationship.

Until the nineteenth century, the rapid development of pharmacology as a distinct discipline was hindered by the lack of sophisticated chemical methodology and by limited knowledge of physiological mechanisms. The significant advances made through laboratory studies of animal physiology accomplished by early investigators such as Françoise Magendie and Claude Bernard provided an environment conducive to the creation of similar laboratories for the study of pharmacological phenomena.

One of the first laboratories devoted almost exclusively to drug research was established in Dorpat, Estonia, in the late 1840s by Rudolph Bucheim (1820–1879) (Fig. 1.1). The laboratory, built in Bucheim's home, was devoted to studying the actions of agents such as cathartics, alcohol, chloroform, anthelmintics, and heavy metals. Bucheim believed that "the investigation of drugs . . . is a task for a pharmacologist and not for a chemist or pharmacist, who until now have been expected to do this."

Although the availability of a laboratory devoted to pharmacological investigations was important, much more was required to raise this discipline to the same prominent position occupied by other basic sciences; this included the creation of chairs in pharmacology at other
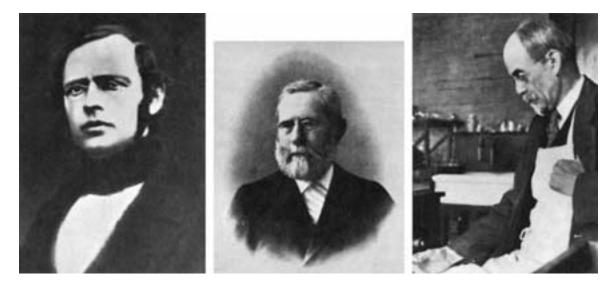
**FIGURE 1.1**

The three important figures in the early history of pharmacology are (left to right) Rudolf Bucheim, Oswald Schmiedeberg, and John Jacob Abel. They not only created new laboratories devoted to the laboratory investigation of drugs but also firmly established the new discipline through the training of future faculty, the writing of textbooks, and the founding of scientific journals and societies.

academic institutions and the training of a sufficient number of talented investigators to occupy these positions. The latter task was accomplished largely by Bucheim's pupil and successor at Dorpat, Oswald Schmiedeberg (1838–1921), undoubtedly the most prominent pharmacologist of the nineteenth century (Fig. 1.1). In addition to conducting his own outstanding research on the pharmacology of diuretics, emetics, cardiac glycosides, and so forth, Schmiedeberg wrote an important medical textbook and trained approximately 120 pupils from more than 20 countries. Many of these new investigators either started or developed laboratories devoted to experimental pharmacology in their own countries.

One of Schmiedeberg's most outstanding students was John Jacob Abel, who has been called the founder of American pharmacology (Fig 1.1). Abel occupied the chair of pharmacology first at the University of Michigan and then at Johns Hopkins University. Among his most important research accomplishments is an examination of the chemistry and isolation of the active principles from the adrenal medulla (a monobenzyl derivative of epinephrine) and the pancreas (crystallization of insulin). He also examined mushroom poisons, investigated the chemotherapeutic actions of the arsenicals and antimonials, conducted studies on tetanus toxin, and designed a model for an artificial kidney. In addition, Abel founded the *Journal of Experimental Medicine,* the *Journal of Biological Chemistry,* and the *Journal of Pharmacology and Experimental Therapeutics.* His devotion to pharmacological research, his enthusiasm for the training of students in this new discipline, and his establishment of journals and scientific societies proved critical to the rise of experimental pharmacology in the United States.

Pharmacology, as a separate and vital discipline, has interests that distinguish it from the other basic sciences and pharmacy. Its primary concern is not the cataloguing of the biological effects that result from the administration of chemical substances but rather the dual aims of (1) providing an understanding of normal and abnormal human physiology and biochemistry through the application of drugs as experimental tools and (2) applying to clinical medicine the information gained from fundamental investigation and observation.

A report in the *Status of Research in Pharmacology* has described some of the founding principles on which the discipline is based and that distinguish pharmacology from other fields of study. These principles include the study of the following:

- The relationship between drug concentration and biological response
- Drug action over time
- Factors affecting absorption, distribution, binding, metabolism, and elimination of chemicals
- Structure-activity relationships
- Biological changes that result from repeated drug use: tolerance, addiction, adverse reactions, altered rates of drug metabolism, and so forth
- Antagonism of the effects of one drug by another
- The process of drug interaction with cellular macromolecules (receptors) to alter physiological function (i.e., receptor theory)

In the past 100 years there has been extraordinary growth in medical knowledge. This expansion of information has come about largely through the contributions of the biological sciences to medicine by a systematic approach to the understanding and treatment of disease. The experimental method and technological advances are the foundations upon which modern medicine is built.

## DRUG CONTROL AND DEVELOPMENT

Before the twentieth century, most government controls were concerned not with drugs but with impure and adulterated foods. Medicines were thought to pose problems similar to those presented by foods. Efficacy was questioned in two respects: adulteration of active medicines by addition of inert fillers and false claims made for the so-called patent (secret) medicines or nostrums. Indeed, much of the development of the science of pharmacy in the nineteenth century was standardizing and improving prescription drugs.

A landmark in the control of drugs was the 1906 Pure Food and Drug Act. Food abuses, however, were the primary target. Less than one quarter of the first thousand decisions dealt with drugs, and of these, the majority were concerned with patent medicines.

The 1906 law defined *drug* broadly and governed the labeling but not the advertising of any substance used to affect disease. This law gave the *Pharmacopoeia* and the *National Formulary* equal recognition as authorities for drug specifications. In the first contested criminal prosecution under the law, action was taken against the maker of a headache mixture bearing the beguiling name of *Cuforhedake-Brane-Fude.* In 1912, Congress passed an amendment to the Pure Food and Drug Act that banned false and fraudulent therapeutic claims for patent medicines.

Prescription drugs also were subject to control under the 1906 law. In fact, until 1953 there was no fixed legal boundary between prescription and nonprescription medications. Prescription medications received a lower priority, since food and patent medicine abuses were judged to be the more urgent problems.

For the next 30 years, drug control was viewed primarily as a problem of prohibiting the sale of dangerous drugs and tightening regulations against misbranding. Until the 1930s, new drugs posed little problem because there were few of them.

## MODERN DRUG LEGISLATION

The modern history of United States drug regulation began with the Food, Drug and Cosmetic Act of 1938, which superseded the 1906 Pure Food and Drug Act. The 1938 act was viewed as a means of preventing the marketing of untested, potentially harmful drugs. An obscure provision of the 1938 act was destined to be the starting point for some of the most potent controls the Food and Drug Administration (FDA) now exercises in the drug field. This provision allowed the prescription drug to come under special control by requiring that it carry the legend "Caution—to be used only by or on the prescription of a physician."

A major defect of the generally strong 1938 law was its inadequate control of advertising. Regulations now require that the "labeling on or within the package from which the drug is to be dispensed" contain adequate information for the drug's use; this requirement explains the existence of the package insert. If the pharmaceutical manufacturer makes claims for its product beyond those contained in an approved package insert, the FDA may institute legal action against the deviations in advertising.

The 1938 act required manufacturers to submit a New Drug Application (NDA) to the FDA for its approval before the company was permitted to market a new drug. *Efficacy* (proof of effectiveness) became a requirement in 1962 with the Kefauver-Harris drug amendments. These amendments established a requirement that drugs show "substantial evidence" of efficacy before receiving NDA approval. Substantial evidence was defined in the amendments as evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug, on the basis of which such experts could fairly and responsibly conclude that the drug would have the claimed effect under the conditions of use named on the label.

Drug regulation in the United States is continuing to evolve rapidly, both in promulgation of specific regulations and in the way regulations are implemented (Table 1.1). The abolition of patent medicines is an outstanding example, as is control over the accuracy of claims made for drugs. Since the 1962 amendments, the advertising of prescription drugs in the United States has been increasingly controlled—to a greater extent than in most other countries. All new drugs introduced since 1962 have some proof of efficacy. This is not to say that misleading drug advertisements no longer exist; manufacturers still occasionally make unsubstantiated claims.

| TABLE 1.1 | Phases of Clinical Investigation |
|---|---|
| **Phase** | **Purpose** |
| I | Establish safety |
| II | Establish efficacy and dose |
| III | Verify efficacy and detect adverse affects |
| IV | Obtain additional data following approval |

## CLINICAL TESTING OF DRUGS

Experiments conducted on animals are essential to the development of new chemicals for the management of disease. The safety and efficacy of new drugs, however, can be established only by adequate and well-controlled studies on human subjects. Since findings in animals do not always accurately predict the human response to drugs, subjects who participate in clinical trials are put at some degree of risk. The risk comes not only from the potential toxicity of the new drug but also from possible lack of efficacy, with the result that the condition under treatment becomes worse. Since risk is involved, the primary consideration in any clinical trial should be the welfare of the subject. As a consequence of unethical or questionably ethical practices committed in the past, most countries have established safeguards to protect the rights and welfare of persons who participate in clinical trials. Two of the safeguards that have been established are the *institutional review board* (IRB) and the requirement for *informed consent.*

The IRB, also known as the ethics committee or human subjects committee, originally was established to protect people confined to hospitals, mental institutions, nursing homes, and prisons who may be used as subjects in clinical research. In the United States any institution conducting clinical studies supported by federal funds is required to have proposed studies reviewed and approved by an IRB.

People who volunteer to be subjects in a drug study have a right to know what can and will happen to them if they participate (informed consent). The investigator is responsible for ensuring that each subject receives a full explanation, in easily understood terms, of the purpose of the study, the procedures to be employed, the nature of the substances being tested, and the potential risks, benefits, and discomforts.

## PHASES OF CLINICAL INVESTIGATION

The clinical development of new drugs usually takes place in steps or phases conventionally described as clinical pharmacology (*phase I*), clinical investigation (*phase II*), clinical trials (*phase III*), and postmarketing studies (*phase IV*). Table 1.1 summarizes the four phases of clinical evaluation.

### Phase I

When a drug is administered to humans for the first time, the studies generally have been conducted in healthy *men* between 18 and 45 years of age; this practice is coming under increasing scrutiny and criticism. For certain types of drugs, such as antineoplastic agents, it is not appropriate to use healthy subjects because the risk of injury is too high. *The purpose of phase I studies is to establish the dose level at which signs of toxicity first appear.* The initial studies consist of administering a single dose of the test drug and closely observing the subject in a hospital or clinical pharmacology unit with emergency facilities. If no adverse reactions occur, the dose is increased progressively until a predetermined dose or serum level is reached or toxicity supervenes. Phase I studies are usually confined to a group of 20 to 80 subjects. If no untoward effects result from single doses, short-term multiple-dose studies are initiated.

### Phase II

If the results of phase I studies show that it is reasonably safe to continue, *the new drug is administered to patients for the first time.* Ideally, these individuals should have no medical problems other than the condition for which the new drug is intended. Efforts are concentrated on evaluating efficacy and on establishing an optimal dose range. Therefore, dose–response studies are a critical part of phase II studies. Monitoring subjects for adverse effects is also an integral part of phase II trials. The number of subjects in phase II studies is usually between 80 and 100.

### Phase III

When an effective dose range has been established and no serious adverse reactions have occurred, large numbers of subjects can be exposed to the drug. In phase III studies the number of subjects may range from several hundred to several thousand, depending on the drug. *The purpose of phase III studies is to verify the efficacy of the drug* and to detect effects that may not have surfaced in the phase I and II trials, during which exposure to the drug was limited. A new drug application is submitted at the end of phase III. However, for drugs intended to treat patients with life-threatening or severely debilitating illnesses, especially when no satisfactory therapy exists, the FDA has established procedures designed to expedite development, evaluation, and marketing of new therapies. In the majority of cases, the procedure applies to drugs being developed for the treatment of cancer and acquired immunodeficiency syndrome (AIDS). Under this procedure, drugs can be approved on the basis of phase II studies conducted in a limited number of patients.

### Phase IV

Controlled and uncontrolled studies often are conducted after a drug is approved and marketed. Such studies are intended to broaden the experience with the drug and compare it with other drugs.

## SPECIAL POPULATIONS

One of the goals of drug development is to provide sufficient data to permit the safe and effective use of the drug.

Therefore, the patient population that participates in clinical trials should be representative of the patient population that will receive the drug when it is marketed. To a varying extent, however, *women, children, and patients over 65 years of age have been underrepresented in clinical trials of new drugs.* The reasons for exclusion vary, but the consequence is that prescribing information for these patient populations is often deficient.

## ADVERSE REACTION SURVEILLANCE

Almost all drugs have adverse effects associated with their use; these range in severity from mild inconveniences to severe morbidity and death. Some adverse effects are extensions of the drug's pharmacological effect and are predictable, for example, orthostatic hypotension with some antihypertensive agents, arrhythmias with certain cardioactive drugs, and electrolyte imbalance with diuretics. Other adverse effects are not predictable and may occur rarely or be delayed for months or years before the association is recognized. Examples of such reactions are aplastic anemia associated with chloramphenicol and clear cell carcinoma of the uterus in offspring of women treated with diethylstilbestrol during pregnancy. Postmarketing surveillance programs and adverse reaction reporting systems may detect such events. The best defense against devastating adverse actions is still the vigilance and suspicion of the physician.

## Study QUESTIONS

**1.** The primary consideration in all clinical trials is to
   (A)  Determine the safety of the drug
   (B)  Determine the efficacy of the drug
   (C)  Ensure that there is no risk to the subject
   (D)  Provide for the welfare of the subject
**2.** To conduct reliable clinical trials with a potential new drug, it is necessary to establish a dose level that toxicity first appears. This is commonly determined in
   (A)  Phase I Studies
   (B)  Phase II Studies

   (C)  Phase III Studies
   (D)  Phase IV Studies
**3.** The history of pharmacology includes a long list of heroes. The person considered to be the founder of American pharmacology is
   (A)  Claude Bernard
   (B)  Rudolph Bucheim
   (C)  John Jacob Abel
   (D)  Oswald Schmeideberg

### ANSWERS

**1.  D.**  There is always some degree of risk in clinical trials; the object is to minimize the risk to the patient. The primary consideration in any clinical trial is the welfare of the subject. The safety of the drug is one objective for certain clinical trials as is the efficacy of the drug in other trials.
**2.  A.**  Phase I studies are carried out in normal volunteers. The object of phase I studies is to determine the dose level at which signs of toxicity first appear. Phase II studies are carried out in patients in which the drug is designed to be effective in. It is conducted to determine efficacy and optimal dosage. Phase III studies are a continuation of phase II, but many more patients are involved. The purpose of phase III studies is to verify efficacy established earlier in phase II studies and to detect adverse effects that may not have surfaced in earlier studies. Phase IV studies are conducted when the drug has been approved and is being marketed. The purpose of these studies is to broaden the experience with the drug and to compare the new drug with other agents that are being used clinically.
**3.  C.**  John Jacob Abel occupied the first chair of a department of pharmacology in the United States. This was at the University of Michigan. Abel subsequently left Michigan to chair the first department of pharmacology at Johns Hopkins University. Claude Bernard was an early French physiologist and pharmacologist. Rudolph Bucheim established one of the first pharmacology laboratories at the University of Dorpat (Estonia). Oswald Schmiedeberg is considered the founder of pharmacology. He trained approximately 120 pupils from around the world, including the father of American pharmacology, John Jacob Abel.

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