1

General Introduction

WHAT IS PHARMACOGNOSY?

Pharmacognosy, which literally means a knowledge of drugs or pharmaceuticals, has been a part of the healing arts and sciences since mankind first began to treat illnesses. It has developed from ancient civilizations that used parts of plants and animals to concoct various potions to eliminate pain, control suffering, and counteract disease. Pharmacognosy has risen from the mysterious incantations of voodoo tribes and has survived the unwritten secret recipes of medicine men. It has progressed from an era of empiricism to the present age of specific therapeutic agents. Today, pharmacognosy is a highly specialized science that represents one of the major disciplines of pharmaceutic education. A number of the drugs used by the ancients are still employed in much the same manner by today's medical practitioners. Although it is true that extraction, separation, isolation, and identification of the component constituents of plant and animal drugs have occurred in relatively recent years, nevertheless the purpose for which many of these medicinal substances are employed today parallels closely the use for which they were intended by our predecessors in the study of pharmacy and medicine.

Because of the interest it engenders in many of the scientists of today, pharmacognosy is a respected discipline that has no counterpart in the other professions. Perhaps because the lay public has heard little about the term pharmacognosy, there is a lack of recognition and, further, a lack of association of the term with the specific subject matter it represents. However, an intuitive curiosity is inherent in the average person who reads or hears of opium, morphine, foxglove, insulin, reserpine, thyroid, penicillin, blood plasma, polio vaccine, and even the much maligned castor oil!

During the past few years, as a result of the intense concern with all aspects of ecology, there has been a renewed interest in so-called "natural" foods and drugs. The availability of an extremely wide variety of these products, ranging from fenugreek tea to ginseng chewing gum, has stimulated the public to learn more about them. Consequently, a vast literature on natural drugs written by laymen and intended to inform other laymen has come into existence. Much of this literature is relatively inaccurate, consisting of beliefs and opinions substituted for facts. The pharmacist must, of course, be aware of the existence of such pseudopharmacognostic writings, primarily to be able to caution his patients concerning them and to correct any factual misinformation gained from reading them. Chapter 16 in this text provides accurate, up-to-date information on these so-called "health foods" and herbs.

In order to gain proper perspective about a science that deals with plant and animal

drugs and their constituents, it is exceedingly helpful to survey past records and to recognize those who have contributed to the subject matter that constituted the field of pharmacognosy in its beginning. By trial and error, primitive man must have acquired biologic knowledge that was useful in determining which plants and animals possessed food value and which were to be avoided because they were unpalatable, poisonous, or dangerous. His observations were handed down from one generation to another and were added to by his progeny. The healing powers of certain herbs, roots, and juices were undoubtedly discovered by accident; but once these attributes were learned, they were too important to be forgotten. The Babylonians made clay models of the human body, and early writings indicate that they were aware of the medicinal effects of a number of plants. It is a well-known fact that the ancient Egyptians were adept at embalming the dead and that they possessed an understanding of the human anatomy as well as a knowledge of the medicinal uses of many plants and animals, according to the *Papyrus Ebers*. This famous document, written in 1550 B.C., was found in the tomb of a mummy and is now preserved at the University of Leipzig.

Dioscorides, a Greek physician who lived in the first century A.D., wrote his "De Materia Medica" in 78 A.D. in which he described about 600 plants that were known to have medicinal properties. Of these, a surprisingly large number are still important in modern medicine. Aloe, belladonna, colchicum, ergot, hyoscyamus, and opium are a few that were used then in much the same manner as they are used today. Galen (131–200 A.D.) was a Greek pharmacist-physician who lived in Rome and who described the method of preparing formulas containing plant and animal drugs. He devoted considerable time to compiling this knowledge, which was distributed throughout 20 books. As a tribute to his accuracy in recording his observations, the term "galenical" pharmacy was originated.

From this humble beginning, medicine and pharmacy gradually emerged along separate paths: the physician diagnosed the ailment and prescribed the remedy, and the apothecary or pharmacist specialized in the collection, preparation, and compounding of the substance. Thus, the term **materia medica**, meaning medicinal materials, was synonymous with the substances and products derived from natural sources and was employed by the physicians of that era.

The term **pharmacognosy** was introduced by C. A. Seydler, a medical student in Halle/Saale, Germany, in 1815. This name is formed from two Greek words, *pharmakon*, drug, and *gnosis*, knowledge. The most comprehensive idea of the scope of pharmacognosy was presented by Flückiger who stated that pharmacognosy "is the simultaneous application of various scientific disciplines with the object of acquiring knowledge of drugs from every point of view."

Pharmacognosy may be defined as "an applied science that deals with the biologic, biochemical, and economic features of natural drugs and their constituents." It is a study of drugs that originate in the plant and animal kingdoms. Modern aspects of the science include not only the crude drugs but also their natural derivatives. Digitalis leaf and its isolated glycoside, digitoxin; rauwolfia root and its purified alkaloid, reserpine; and thyroid gland with its extracted hormone, thyroxine, are all part of the subject matter of pharmacognosy.

In some instances drug constituents have been partially replaced in commerce by synthetic compounds of identical chemical structure and therapeutic properties; such **natural** and **synthetic substances** often can be distinguished by physical and chemical tests. For example, natural camphor is obtained from the camphor tree by steam distillation; it is dextrorotatory in its

reaction to polarized light. In contrast, synthetic camphor may be manufactured by either of two methods: by **total synthesis** from vinyl chloride and cyclopentadiene (a completely synthetic process) or by **semisynthesis** from pinene derived from pine stumps (not entirely a synthetic process but a chemical modification of a natural product). Synthetic camphor is racemic and can be differentiated easily from the natural form.

Epinephrine, caffeine, codeine, ephedrine, menthol, penicillin, and other chemicals may also be obtained from either the natural source or by partial or total synthesis. They are considered a definite part of pharmacognosy.

In a broad sense, pharmacognosy embraces a knowledge of the history, distribution, cultivation, collection, selection, preparation, commerce, identification, evaluation, preservation, and use of drugs and economic substances that affect the health of humans and other animals. Such economic substances extend beyond the category of crude drugs and their derivatives to include a variety of commercial and medicinal products often requiring complicated methods of preparation: allergens, allergenic extracts, antibiotics, immunizing biologics, flavoring agents, and condiments. In a restricted sense, the definition of pharmacognosy implies a particular knowledge of methods of identification and evaluation of drugs.

As a part of the pharmaceutic curriculum, pharmacognosy forms an important link between **pharmacology** and **medicinal chemistry** on one hand and between **pharmaceutics** and **clinical pharmacy** on the other.

Pharmacology, like pharmacognosy, is an outgrowth of materia medica, the ancient science that dealt with all aspects of medicinal agents. Now, in this more specialized era, pharmacognosy deals primarily with information on the sources and constituents of natural drugs, and pharmacology is concerned with their actions and effects.

Methods of procurement and preparation affect the price of drugs; thus, insofar as economics are concerned, pharmacognosy is intimately associated with the phases of pharmacy administration that deal with prescription pricing. The relationship of pharmacognosy to dispensing pharmacy and clinical pharmacy is obvious when one considers the number of naturally derived drugs that are handled by the pharmacist in this age of drug specialties. Because of his knowledge of drug constituents, the pharmacist is able to predict not only the chemical and physical incompatibilities encountered in compounding but also the therapeutic incompatibilities that the patient may encounter when utilizing a drug concomitantly with other prescribed or self-selected medications.

When supplying both prescription and over-the-counter (OTC) medication to patients, the pharmacist also provides information required for the safe and effective use of such drugs. The pharmacist further serves as an information source of all aspects of drugs to his colleagues in the medical, dental, and nursing professions. These advisory roles are made possible by the vast background of the pharmacist, the drug expert, in fields such as pharmacognosy, pharmacology, medicinal chemistry, and pharmaceutics.

Any treatise on plant and animal products encompasses a wide variety of uses inasmuch as natural substances are employed in almost every known industry. Although the pharmacist is mainly concerned with those substances having application to public health, he realizes that many of these therapeutic aids are also utilized as beverages, as spices and condiments, in confectioneries, and as technical products.

Coffee beans and tea leaves both yield caffeine, which has medicinal application; yet the original sources are mainstays in the diet of the American public. Winter-

green oil and ginger are used pharmaceutically, but a much greater quantity of each is utilized by the soft drink industry. Mustard seed and clove have definite therapeutic application, but they are in more demand in the spice and condiment trade. Cinnamon oil and peppermint oil are valuable carminatives; however, they enjoy an enviable reputation as popular flavoring agents in candies and chewing gums. Certain industries depend on large supplies of rosin, turpentine, linseed oil, acacia, pectin, and numerous other natural products that have a relatively limited application in the field of pharmacy.

CRUDE DRUGS

Crude drugs are vegetable or animal drugs that consist of natural substances that have undergone only the processes of collection and drying. The term **natural substances** refers to those substances found in nature that comprise whole plants and herbs and anatomic parts thereof; vegetable saps, extracts, secretions, and other constituents thereof; whole animals and anatomic parts thereof; glands or other animal organs, extracts, secretions, and other constituents thereof; and substances that have not had changes made in their molecular structure as found in nature. The term **crude**, as used in relation to natural products, means any product that has not been advanced in value or improved in condition by shredding, grinding, chipping, crushing, distilling, evaporating, extracting, artificial mixing with other substances or by any other process or treatment beyond what is essential to its proper packing and to the prevention of decay or deterioration pending manufacture.

Crude drugs are used infrequently as therapeutic agents; more often, their chief principles are separated by various means and are employed in a more specific manner. These principles are known as **derivatives** or **extractives**. Regardless of whether the derivative or extractive is a single substance or a mixture of substances, it is considered the **chief constituent** of the drug.

The process of drug extraction is a generally accepted method of obtaining these active principles. Extraction removes only those substances that can be dissolved in the liquid or liquid mixture referred to as the **solvent**, or, more specifically, as the **menstruum**. The undissolved portion of the drug that remains after the extraction process is completed is called the **marc**. The product of the extraction process is known as the **extractive** and is usually a mixture of substances. A large-scale drug extractor of the type currently used in the pharmaceutic industry is illustrated in Figure 1–1.

The **geographic source** and **habitat** are the region in which the plant or animal yielding the drug grows. Sometimes this term is applied erroneously to the drugs themselves. Drugs are collected in all parts of the world, though the tropics and subtropics, where plant species abound, yield more drugs than do the arctic and subarctic regions. The Mediterranean basin, including Asia Minor, yields more drugs than any other region of the world. However, India, the East Indies, central Europe, northern South America, Mexico, Central America, North America, and other regions yield numerous and valuable drugs.

Neither the **scientific name** of the plant nor the **commercial name** of the drug is necessarily an indication of the true habitat of drug plants. For example, the specific name of *Acacia senegal* seems to indicate that this plant, which yields gum arabic, is most abundant in Senegal. Actually, the bulk of the commercial gum now comes from trees cultivated in Sudan. In other cases, plants are common to a much larger territory than the specific name indicates, such as *Prunus virginiana*. Peru balsam, for example, does not come from Peru but is produced in El Salvador, and most of the Spanish licorice now comes from Asia Minor.

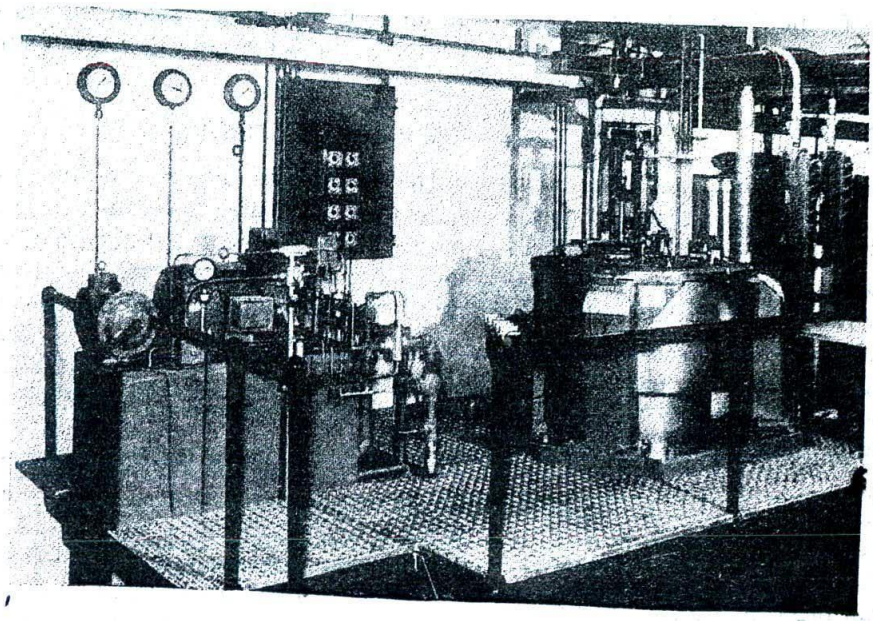

Fig. 1–1. A fully automatic industrial drug extractor. Its operating cycle, which involves pressures up to 2000 lb per sq in and a centrifugal force of 1000 × g, can be programmed to meet process requirements. (Courtesy of Dr. Madis Laboratories, Inc.)

Plants growing in their native countries are said to be **indigenous** to those regions, such as *Pinus palustris* in the southern United States, *Aconitum napellus* in the mountainous regions of Europe, and others. Plants are said to be **naturalized** when they grow in a foreign land or in a locality other than their native homes, such as *Datura stramonium*, which was introduced into the United States from Europe. Some of these plants may have been introduced with the seeds of cultivated plants, some by birds or ocean currents, others by ballast of ships, and so on.

Drugs can be collected from wild plants, or plants can be cultivated for the production of drugs.

Cultivated medicinal plants have been propagated for centuries in China, India, Europe, and many other lands. Plant cultivation was known to the people of ancient civilizations inasmuch as sculptures and drawings depict hand pollination of the date palm by the Assyrians in 9000 B.C. and cultivation of rice and barley by the Chinese and Egyptians in 5000 B.C.

In Europe, medicinal plant gardens of the monasteries date back to the early Christian era. Since shortly after the discovery of America and continuing to the present, many countries have made definite attempts to cultivate drug and economic plants. Thus, vanilla, which is native to Mexico and Central America, is now produced at such distances from its original habitat as the islands of Réunion, Tahiti, and Mauritius. Cocoa, another native of Mexico, is now produced in large quantities in Nigeria and Ghana, in Sri Lanka, and in Indonesia.

Cinchona, native to the South American Andes, was developed as a crop in Indo-

nesia. By 1900, the South American production was practically nil, owing to the wanton destruction of wild trees; thus, the Dutch in the Netherlands East Indies held a world monopoly on cinchona. A similar situation existed with coca, another South American plant transported to that area.

In many instances plants have been cultivated in their native habitats, either because of dwindling natural supply or to improve the quality of the drug. Before World War II, the Japanese had established large plantations of camphor trees in Formosa and held a virtual monopoly in natural camphor. Other drugs, such as Ceylon cinnamon and opium, are produced entirely from cultivated plants.

Extensive cultivation of certain drug plants is conducted in specific geographic areas of the United States. Louisiana produces castor oil from cultivated plants. Occasionally, however, some circumstances will completely eliminate a certain section as a drug-producing region. Formerly, mints were extensively cultivated in southwestern Michigan and northern Indiana. Peppermint, spearmint, and other mints were grown in mile-long rows, particularly near Mentha, Michigan. In the early 1950s, a fungus blight invaded the fields of that area, and within a few years it was considered uneconomical to attempt further cultivation. At present, Washington and Oregon have assumed leadership in the production of mints and mint oils, although both Michigan and Indiana have relocated their areas of cultivation.

It is important to ascertain that plants cultivated in a certain geographic area will develop the desired type and amount of constituents. The differences in the relative amounts of volatile constituents often determine the character of the oil and, consequently, the demand for that particular oil. California orange oil is marketed at more than twice the price of Florida oils. The preference for Michigan peppermint oils over Washington and Oregon oils is because of the types of constituents developed—the Michigan oils taste better.

COMMERCE IN DRUGS

The **commercial origin** of a drug refers to its production and its channels of trade. Drugs frequently bear a geographic name indicating the country or region in which they are collected, the country or city from which they are shipped, or their variety. These names do not necessarily reflect the area where the plant grows. English hyoscyamus leaves are gathered from plants growing in England and are principally consumed in that country; Indian rhubarb is the product of plants growing in various parts of India; Spanish licorice is a botanic variety of *Glycyrrhiza glabra*, originally produced in Spain but now produced elsewhere; and Oregon grape root is a species of *Mahonia* and may or may not come from Oregon. The commercial origin may change in the course of time, as with cinchona, vanilla, and coca previously mentioned.

Since World War II, most of the drug items have been shipped directly from the producing areas to New York City. Although many drug collectors and dealers conducted their business through a governmental agency in the past, little drug commerce now passes through such an agency. The exceptions are the communist countries and their European satellites, where governmental agencies control all commerce.

PREPARATION OF DRUGS FOR THE COMMERCIAL MARKET

Collection

Collection of drugs from cultivated plants always ensures a true natural source and a reliable product. This may or may not be the case when drugs are collected from wild plants. Carelessness or ignorance on the part of the collector can result

in complete or partial substitution. This is especially true when drugs are difficult to collect or the natural source is scarce. Many drugs are collected from wild plants, sometimes on a fairly extensive scale (tragacanth, senna) when collection is the vocation of the gatherer, and sometimes on a limited scale when collection is an avocation (podophyllum, hydrastis). Because drugs come from all over the world, collection areas are almost universal, and collectors may vary from uneducated natives to highly skilled botanists.

Certain areas of the United States are particularly noteworthy as collection areas. White pine, podophyllum, ginseng, and many other native American drugs are collected in the Blue Ridge Mountain region, of which Asheville, North Carolina, is one of the important collection areas. Native American drugs are usually collected by individuals, such as farm children and part-time agricultural laborers.

The proper time of harvesting or collecting is particularly important because the nature and quantity of constituents vary greatly in some species according to the season. The most advantageous collecton time is when the part of the plant that onstitutes the drug is highest in its content of active principles and when the material vill dry to give the maximum quality and ippearance.

Harvesting

The mode of harvesting varies with each drug produced and with the pharmaceutic requirements of each drug. Some drugs may be collected by hand labor; however, when the cost of labor is an important factor, the use of mechanical devices is often more successful in economic production of the drug. With some drugs, where the skillful selection of plant parts is an important factor (digitalis), mechanical means cannot replace hand labor.

Drying

By drying the plant material, one removes sufficient moisture to ensure good keeping qualities and to prevent molding, the action of enzymes, the action of bacteria, and chemical or other possible changes. Drying fixes the constituents, facilitates grinding and milling, and converts the drug into a more convenient form for commercial handling. Proper and successful drying involves two main principles: control of temperature and regulation of air flow. Control of the drying operation is determined by the nature of the material to be dried and by the desired appearance of the finished product. The plant material can be dried either by the sun or by the use of artificial heat.

With some natural products, such as vanilla, processes of fermentation or sweating are necessary to bring about changes in the constituents. Such drugs require special drying processes, usually called "curing."

Garbling

Garbling is the final step in the preparation of a crude drug. Garbling consists of the removal of extraneous matter, such as other parts of the plant, dirt, and added adulterants. This step is done to some extent during collection, but should be carried out after the drug is dried and before it is baled or packaged. Although garbling may be done by mechanical means in some cases, it is usually a semiskilled operation.

Packaging, Storage, and Preservation

The packaging of drugs depends on their final disposition. In commerce, if transportation, storage, and ultimate use for manufacturing purposes are involved, it is customary to choose the type of packaging that provides ample protection to the drug and gives economy of space. Leaf and herb material is usually baled with power balers into a solid compact mass that is then sewn into a burlap cover. Bales that are shipped overseas weigh from 100 to 250 lb. Senna leaves from India come in bales of 400 lb; stramonium from Argentina in bales of 700 lb. Drugs that are likely to deteriorate from

absorbed moisture (digitalis, ergot) are packed in moisture-proof cans. Gums, resins, and extracts are shipped in barrels, boxes, or casks.

Packaging is often characteristic for certain drugs. The standard package for all grades of aloe is a 55-gallon steel drum, and this type of container is also employed for balsam of Peru. Matting-covered packages of cinnamon from the Far East, seroons (bales covered with cowhide) containing sarsaparilla from South America, lead flasks with oil of rose from Bulgaria, and many other odd forms of packaging are noted in the drug trade.

Proper storage and preservation are important factors in maintaining a high degree of quality of the drug. Hard-packed bales, barks, and resinous drugs usually reabsorb little moisture. But leaf, herb, and root drugs that are not well packed tend to absorb amounts of moisture that reach 10, 15, or even 30% of the weight of the drug. Excessive moisture not only increases the weight of the drug, thus reducing the percentage of active constituents, but also favors enzymatic activity and facilitates fungal growth.

Light adversely affects drugs that are highly colored, rendering them unattractive and possibly causing undesirable changes in constituents. The oxygen of the air increases oxidation of the constituents of drugs, especially when oxidases are present. Therefore, the warehouse should be cool, dark, and well ventilated with dry air.

The protection of drugs against attacks by insects must not be overlooked. The insects that infest vegetable drugs belong chiefly to the orders Lepidoptera, Coleoptera, and Diptera.

For destruction of insects and prevention of their attacks, a number of methods have been employed. The simplest method is to expose the drug to a temperature of 65°C. This method is probably the most efficient not only in preventing insect attacks but also in preventing many other forms of deterioration. For the fumigation of large lots of crude drugs, such as those stored in warehouses and manufacturing plants, the use of methyl bromide has met with considerable success.

Small lots of drugs may readily be stored in tight, light-resistant containers. Tin cans, covered metal bins, or amber glass containers are the most satisfactory. Drugs should not be stored in wooden boxes or in drawers and never in paper bags. Not only is deterioration hastened, but odors are communicated from one drug to another, attacks by insects are facilitated, and destruction by mice and rats may occur. If drugs in small quantities are stored in tight containers, insect attack can be controlled by adding to the container a few drops of chloroform or carbon tetrachloride from time to time. In the case of digitalis and ergot, whose low moisture content must be maintained at all times, a suitable cartridge or device containing a nonliquefying, inert, dehydrating substance may be introduced into the tight container.

Because high temperatures accelerate all chemical reactions, including those involved in deterioration, drugs must always be stored at as low a temperature as possible. The ideal temperature is just above freezing, but since this is impractical in most cases, the warehouse or other storage place should be as cool as possible. Certain drugs, such as the biologics, must be stored at a temperature between 2° and 8°C.

Animal Drugs

Animal drugs are produced from wild or domesticated animals. Wild animals must be hunted (whale, musk deer) or fished for (cod and halibut), and thus, in a sense, their collection parallels the collection of vegetable drugs. Many animal drugs, however, are produced from domesticated animals and, therefore, correspond to the cultivated vegetable drugs. When drugs consist of insects, the drugs are either collected from wild insects (cantharides) or definite attempts are made to cultivate

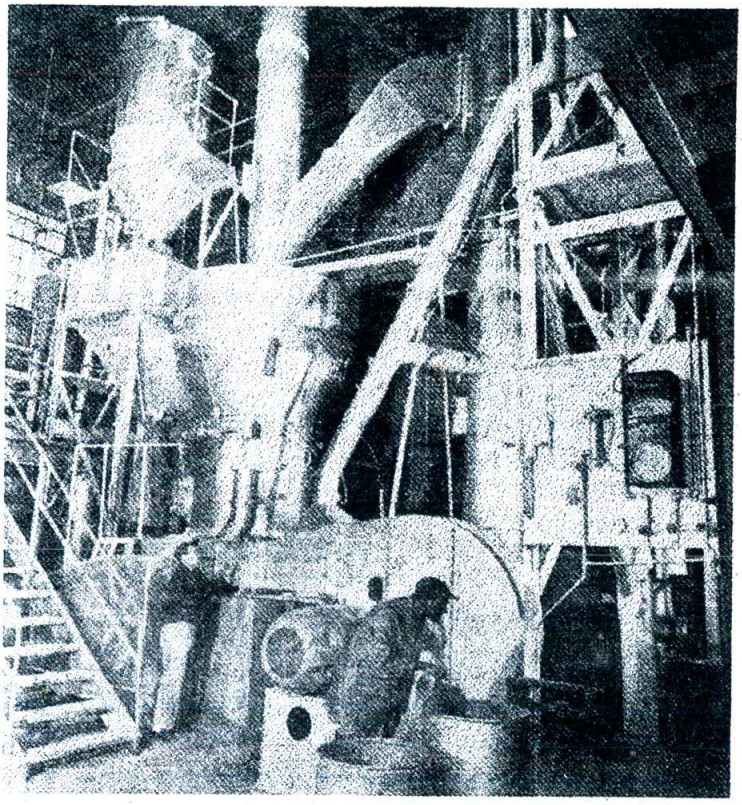

Fig. 1–2. A grinding mill used in large-scale commercial production of crude drugs. (Courtesy of S.B. Penick and Company.)

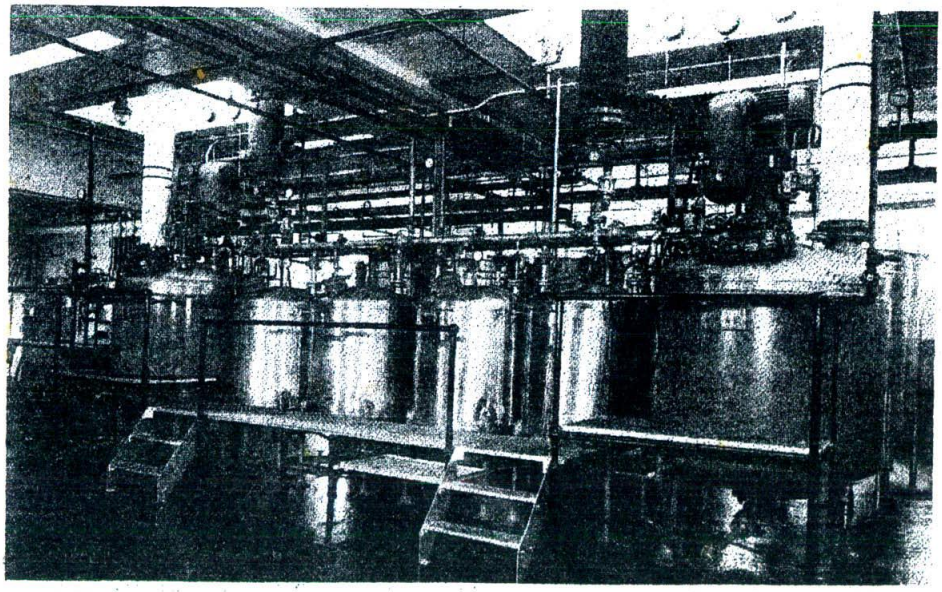

Fig. 1–3. Semiautomatic vacuum and atmospheric reflux reactors used to produce various kinds of resins, enzymes, and extracts. (Courtesy of Dr. Madis Laboratories, Inc.)

them, i.e., to furnish the insects with food and shelter and to maintain optimum conditions for their propagation (honeybee).

Drugs such as lanolin and milk products, as well as hormones, endocrine products, and some enzymes, are obtained from domesticated hogs, sheep, or cattle. The slaughterhouse is the usual source of glandular products and enzymes, and the larger packing establishments have departments for the recovery and refinement of these therapeutic agents and pharmaceuticals. Processing and purification of the animal drugs vary with the individual drug.

EVALUATION OF DRUGS

To evaluate a drug means to identify it and to determine its quality and purity.

The identity of a drug can be established by its actual collection from a plant or animal that has been positively identified. Research investigators must be absolutely certain of the origin of their samples; hence, "drug gardens" are frequently established by institutions engaged in pharmacognostic research. Another method of identification is the comparison of a representative unknown sample to a published description of the drug and to authentic drug samples.

Quality refers to the intrinsic value of the drug, i.e., the amount of medicinal principles or active constituents present. These constituents are classified into groups of nonprotoplasmic cell contents and can be found in the section of this chapter on "Classification of Drugs." These groups include carbohydrates, glycosides, tannins, lipids, volatile oils, resins and resin-combinations, steroids, alkaloids, peptide hormones, enzymes and other proteins, vitamins, antibiotics, biologics, allergens, and others.

A high grade of quality in a drug is of primary importance, and effort should be made to obtain and maintain this high quality. The evaluation of a drug involves a number of methods that may be classified as follows: (1) organoleptic, (2) microscopic, (3) biologic, (4) chemical, (5) physical (Fig. 1–4).

Organoleptic (lit. "impression on the organs") refers to evaluation by means of the organs of sense and includes the macroscopic appearance of the drug, its odor and taste, occasionally the sound or "snap" of its fracture, and the "feel" of the drug to the touch.

The microscope is not only essential to the study of adulterants in powdered plant and animal drugs but also is indispensable in the identification of the pure powdered drug. Powdered drugs possess few macroscopic features of identification other than color, odor, and taste; hence, the microscopic characteristics are important.

The pharmacologic activity of certain drugs has been applied to their evaluation and standardization. Assays on living animals as well as on intact or excised organs often indicate the strength of the drug or its preparations. Because living organisms are used, the assays are called biologic assays or bioassays.

Because the active constituents of many natural drugs have been determined, chemical methods of evaluating crude drugs and their products are useful and, consequently, are widely employed. For many drugs, the chemical assay represents the best method of determining the official potency.

The application of typical physical constants to crude drugs is rare. However, physical constants are extensively applied to the active principles of drugs, such as alkaloids, volatile oils, fixed oils, and others.

CLASSIFICATION OF DRUGS

In pharmacognosy, drugs may be classified according to (1) their morphology, (2) the taxonomy of the plants and animals from which they are obtained, (3) their therapeutic applications, and (4) their

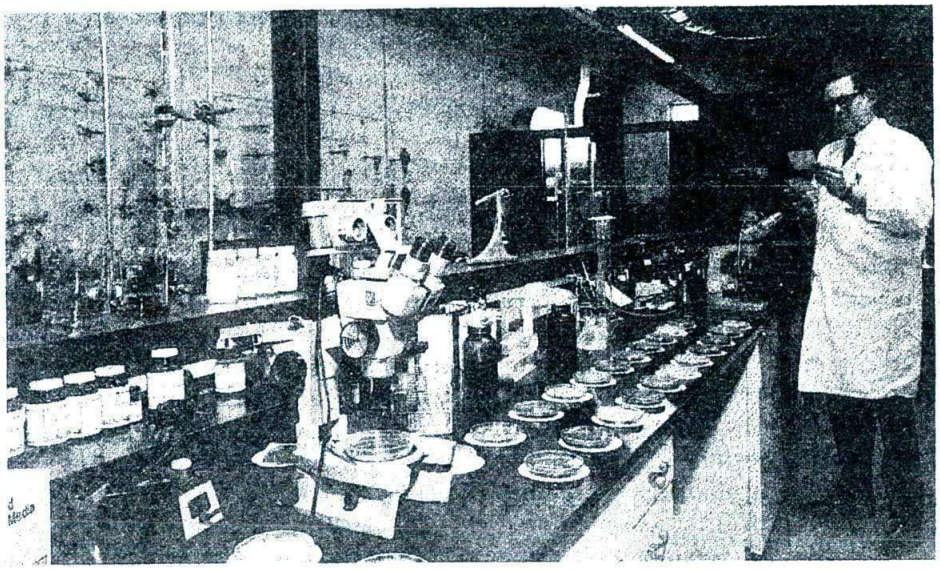

Fig. 1–4. A drug quality-control laboratory where chemical, physical, microbiologic, and pharmacognostic tests are carried out on natural drug products. (Courtesy of Dr. Madis Laboratories, Inc.)

chemical constituents. Each of these methods of classification has advantages and disadvantages, and the emphasis depends on the ultimate goal of the individual. If a person is expected to identify specific drugs and to ascertain their adulterants, a **morphologic** classification is applicable. In this system, the drugs are grouped according to the part of the plant or animal represented, such as roots, leaves, organs, or glands. However, the form of the commercial article is not always distinguishable and cannot be readily placed in its proper category.

Consideration of the natural relationship or phylogeny among plants and among animals gives rise to a **taxonomic** classification. With the present-day knowledge of the evolutionary development of living organisms, this arrangement has served adequately for many years. A large number of plant families have certain distinguishing characteristics that permit drugs from these families to be studied at one time; thus, drugs consisting of cremocarp fruits (anise, fennel, caraway) are considered with other members of the Umbelliferae, drugs obtained from plants having alternate leaves, cymose flowers, and fruits that are capsules or berries (belladonna, hyoscyamus, stramonium) are considered with the Solanaceae, and drugs possessing square stems, opposite leaves, and bilabiate flowers (peppermint, spearmint, thyme) are considered with the Labiatae. This type of arrangement is sometimes called the botanic arrangement for plant drugs or the zoologic arrangement for animal drugs. In the latter case, all arthropods are grouped, as are all mammals, fish, and other natural phylogenetic types.

Inasmuch as drugs are employed medicinally because of their therapeutic effects, a third method of study is the **pharmacologic or therapeutic** classification. All of the cathartic drugs are associated with this classification regardless of morphology, taxonomy, or chemical relation. Thus, cascara sagrada, senna, podophyllum, and castor oil are considered at one time because of their action on the intestinal tract. Similarly, digitalis, strophanthus, and squill are grouped together because they affect cardiac muscle. This type of consid-

eration forms the basis for the science of pharmacology.

Because the activity and therapeutic use of drugs are based on chemical constituents, it would appear that a chemical classification is the preferred method of study. Most drugs contain a variety of constituents, some therapeutically active, others only chemically active, and still others antagonistic to each other. Certain plant families exhibit definite types of chemical principles; for example, mydriatic alkaloids (atropine, scopolamine) characterize the Solanaceae, volatile oils represent the Umbelliferae, and oleoresins abound in the Pinaceae. By studying all drugs containing alkaloids at one time, it is possible to establish relationship between them. In a like manner, drugs containing volatile oils, or resins, or tannins, or glycosides can be classified in their respective phytochemical groups.

The pharmacist no longer gathers his own plant and animal drugs, he rarely finds it necessary to identify and determine the purity of crude drugs, and he is never called on to examine powdered drugs microscopically. However, he is expected to know the chemical nature of his drugs, regardless of their nature or synthetic origin, so that he may predict incompatibilities, solubility, palatability, and therapeutic and toxic effects. The modern pharmacist is a "drug specialist," and in that capacity he is consulted by other members of the health professions.

Modern pharmacognosy is built on the significant aspects of cell physiology and biochemistry as they affect the biosynthetic development of the constituents of plants and animals. Our expanding knowledge of the chemical constituents of plants has revealed the existence of a close relationship between these chemicals and the taxonomic position of the plants themselves. In other words, certain chemical compounds have been found to characterize certain botanic groupings (taxa).

Depending on its relative biosynthetic complexity, the compound may be characteristic of a limited number of species, an entire family, or even a whole class or order of plants. The biosynthetically complex alkaloid, morphine, occurs only in 2 species of the genus *Papaver (P. somniferum* and *P. setigerum)*, but the somewhat simpler protopine is found in all plants of the poppy family. Compounds that are biosynthetically simple are so widely distributed that they lack systematic significance. Nicotine, for example, with its close relationship to the ubiquitous nicotinic acid, has been found in many remotely related plants, such as the club mosses and the composites.

Nearly 3 centuries ago, the London apothecary James Petiver published the results of his experiments that demonstrated that closely related plants frequently possess similar physiologic activities, or, as he put it, "herbs of the same make . . . have like virtue." Today his findings are not surprising, for it is recognized that plants containing similar or identical chemical constituents also have similar medicinal properties. Thus, because all species of *Cinchona* contain quinine, all are useful in the treatment of malaria. Similarly, in lists of plants used by native people, the same genera and families occur repeatedly. This is true for botanics used for everything from contraception to arrow poisons, indeed, for any purpose that is an expression of the plants' physiologic activity.

Understanding of these facts has led to the development of a relatively new branch of science known as chemotaxonomy or biochemical systematics. Composed of nearly equal parts of chemistry and biology, this discipline attempts to utilize chemical facts to obtain a more exact understanding of biologic evolution and natural relationships. Its principles and findings are of particular interest to the student of pharmacognosy, who may apply them to determine potential sources of known drugs or to explore those areas of the biologic kingdom in which new ones are most

likely to be discovered. Tyler's compilations of chemical characteristics of plant families of medicinal importance provide a useful starting point.

CHEMISTRY OF DRUGS

The living organism may be considered a biosynthetic laboratory not only for chemical compounds (carbohydrates, proteins, fats) that are utilized as food by humans and animals but also for a multitude of compounds (glycosides, alkaloids, terpenes) that exert a physiologic effect. These chemical compounds give plant and animal drugs their therapeutic properties. Drugs are used as such in their crude form or they may be extracted, the resulting principles being employed as medicinal agents. It is obvious, therefore, that any study of pharmacognosy must embrace a thorough consideration of these chemical entities. The usual term for these entities is **constituents;** however, because the plant or animal is composed of many chemical compounds, it is common practice to single out those compounds that are responsible for the therapeutic effect and to call them **active constituents.**

These active constitutents are differentiated from **inert constituents,** which also occur in plant and animal drugs. Cellulose, lignin, suberin, and cutin are usually regarded as inert matter in plant drugs; in addition, starch, albumin, coloring matters, and other substances may have no definite pharmacologic activity and also are considered inert constituents. In animal drugs, keratin, chitin, muscle fiber, and connective tissue are regarded as inert. Often the presence of inert substances may modify or prevent the absorbability or potency of the active constituents. To eliminate the undesirable effects of inert matter in the crude drug or its preparations, active principles are extracted, crystallized, and purified for therapeutic use. These constituents have been referred to as "secondary" plant substances. No completely satisfactory explanation has been advanced for their presence in a great number of plant families; nevertheless, their occurrence in related genera and their chemical relationships indicate that they may play roles of some significance in plant metabolism.

Active constituents may be divided into two classes: **pharmaceutically active** and **pharmacologically active.** Pharmaceutically active constituents may cause precipitation or other chemical changes in a medicinal preparation. For instance, neither cinchona bark nor its extracts could be used in formulating preparations containing iron salts because the cinchotannic acid would combine with these salts and cause precipitation. Cinchotannic acid, then, is a pharmaceutically active constituent. The use of quinine hydrochloride obviates this incompatibility because it is a purified crystalline compound that does not contain the slightest trace of cinchotannic acid. In contrast, the rheotannic acid present in rhubarb serves as an astringent to prevent the griping action usually associated with anthraquinone drugs of that type. In this case, rheotannic acid is one of the pharmacologically active constituents. Depending on the particular activity of the constituent and on the other constituents or ingredients with which it is associated, certain principles may be placed in one or the other category.

Pharmacologically active constituents are responsible for the therapeutic activity of the drug. They may be either single chemical substances or mixtures of principles, the separation of which is neither practical nor advantageous. The single chemicals are exemplified by sugars, starches, plant acids, enzymes, glycosides, steroids, alkaloids, proteins, hormones, and vitamins. The mixtures include fixed oils, fats, waxes, volatile oils, resins, oleoresins, oleo-gum-resins, and balsams.

The secondary constituents of drug plants are influenced by 3 principal factors: heredity (genetic composition), ontogeny

(stage of development), and environment. Genetic effects induce both quantitative and qualitative changes, but those caused by environmental influences are primarily quantitative. Plants of the same species that resemble one another closely in form and structure (phenotypically) may, nevertheless, be quite different in genetic composition (genotypically). This often results in distinct differences in chemical composition, particularly with reference to secondary constituents. Such plants are said to belong to different chemical races.

Perhaps the best-known pharmacognostic examples of chemical races are found in the ergot fungus *Claviceps purpurea*. Individual strains have been isolated representing chemical races that produce superior yields of single desired alkaloids, e.g., ergotamine, instead of the usual small concentrations of complex mixtures of alkaloids. Other examples include chemical races of certain species of *Eucalyptus* that exhibit large variations in the content of cineole and related constituents in their volatile oils. Chemical races of *Strophanthus sarmentosus* differing markedly in their content of glycosides and sapogenins have also been reported.

Ontogeny also plays a significant role in the nature of the active constituents found in medicinal plants. Although it might be expected that the concentration of secondary metabolites would increase with the age of the plant, it is not generally appreciated that the identity of these constituents may also vary according to the stage of development. The cannabidiol content of *Cannabis sativa* reaches a peak early in the growing season and then begins to decline. When this decline occurs, the concentration of tetrahydrocannabinol begins to increase reciprocally and continues until the plant approaches maturity. Old plants, as well as stored plant material, are characterized by high concentrations of cannabinol. In the opium poppy, *Papaver somniferum*, the morphine content of the capsules is highest 2 to 3 weeks after flowering. If the latex is harvested earlier, related alkaloids such as thebaine and codeine predominate. On the other hand, if harvesting is delayed too long, the morphine decomposes.

Environmental factors that can produce variations in secondary plant constituents include soil, climate, associated flora, and methods of cultivation. Because all these factors are more or less related, they are difficult to evaluate individually. For example, many alkaloid-containing plants accumulate higher concentrations of such constituents in moist regions than in arid lands. However, this may actually be related to the soil, which is usually poor in nitrogen in arid regions, and rich nitrogen sources are usually required for good yields of alkaloids. This is not necessarily the case with volatile oil-bearing plants because excess nitrogen does not necessarily cause an increase in their yields. Indeed, such plants abound in dry areas as opposed to moister habitats.

One phase of pharmacognosy that has assumed a role of importance in recent years is the study of the biochemical pathways leading to the formation of secondary constituents used as drugs. This study is commonly referred to as **drug biosynthesis** or **biogenesis.** Just as an understanding of the chemical synthesis of phenobarbital or other synthetic drugs is of fundamental importance to the student of medicinal chemistry, a knowledge of the biochemical synthesis of drugs of natural origin is of equal importance to the student of pharmacognosy (Fig. 1–5).

Any discussion of crude drugs and their derivatives must necessarily begin with the plant or animal that formed them by an inherent **biosynthetic process.** The biosynthesis of many plant constituents is often complex and sometimes still not completely known. More information about this interesting phase of plant physiology will be presented in subsequent chapters as the individual types of constituents are discussed. The biosynthetic processes

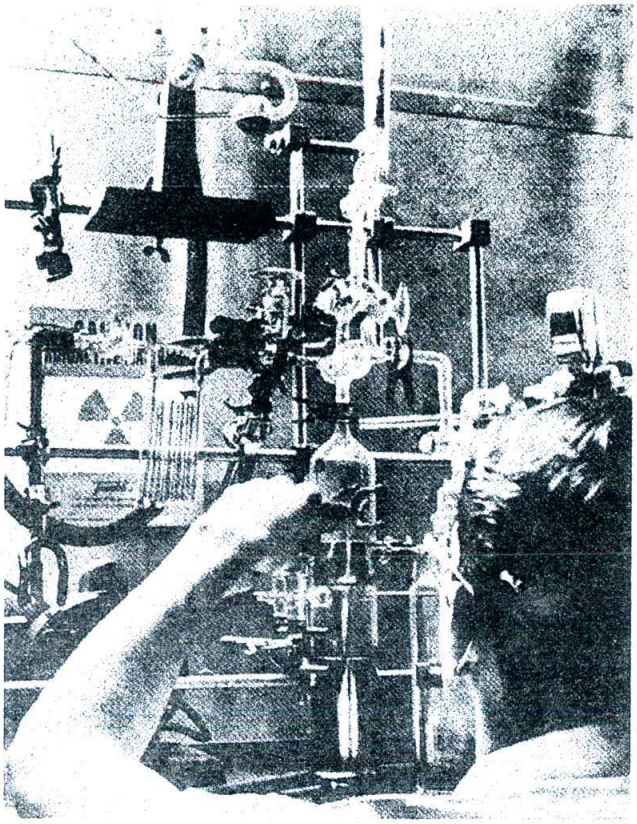

Fig. 1–5. Radioactive carbon used in drug metabolism study at the radiochemistry laboratory, Pfizer Medical Research Laboratories, Groton, Connecticut. Drugs labeled with radioactive materials reveal information concerning biosynthesis, molecular structure, and other phases of plant and animal metabolism. (Courtesy of Charles Pfizer and Company, Inc.)

whereby animal cells form hormones, proteins, and enzymes are also under investigation by research workers.

Early experiments devoted to the elucidation of such chemical pathways were fraught with difficulty and often yielded equivocal results. Because suitable experimental methods were unavailable, researchers turned to speculation and the formulation of hypothetic reaction sequences. Some of these "paper chemistry" hypotheses have proved to be remarkably accurate predictions of actual metabolic pathways in the living organism. For example, as early as 1912, the Swiss chemist, G. Trier, proposed that amino acids and their simple derivatives, which were widely distributed in nature, served as precursors of structurally complex alkaloids. Nearly 40 years passed before this brilliant insight could be verified experimentally.

Within the last 4 decades, isotopically labeled organic compounds have become generally available. These so-called "tracer" substances can be administered to a plant or animal and their subsequent metabolism can be followed to determine whether the compound functions as a precursor or moiety of the metabolite in question. The classic example of such experimentation is the use of $^{14}CO_2$ by Melvin Calvin and his associates at the University of California to determine the path of carbon during photosynthesis. In recent years numerous studies of the biosynthetic pathways of medicinally important plant and

animal constituents have been carried out, and scientific papers devoted to this topic are appearing at such a rapid rate that any detailed review of the subject would be outdated before it could be published. Fortunately, the basic steps in the pathways leading to most types of primary and secondary biologic constituents have been elucidated.

Some of these fundamental reaction sequences leading to the different types of secondary constituents used as drugs will be presented in the chapters dealing with the individual drugs and their constituents, but to facilitate a general understanding of the pathways involved and their interrelationships, they are summarized in Fig. 1–6. Emphasis is placed on the pharmaceutically important secondary constituents because the student has already acquired a knowledge of the biosynthesis of most primary constituents (sugars, fats, amino acids, etc.) in prerequisite courses in biochemistry. However, basic pathways of primary metabolism are reviewed briefly in the appropriate sections to give some indication of the relationships of the secondary pathways to the more fundamental biochemical processes.

THE FUTURE OF PHARMACOGNOSY

The plant kingdom has long supplied us with a large number of excellent drugs.

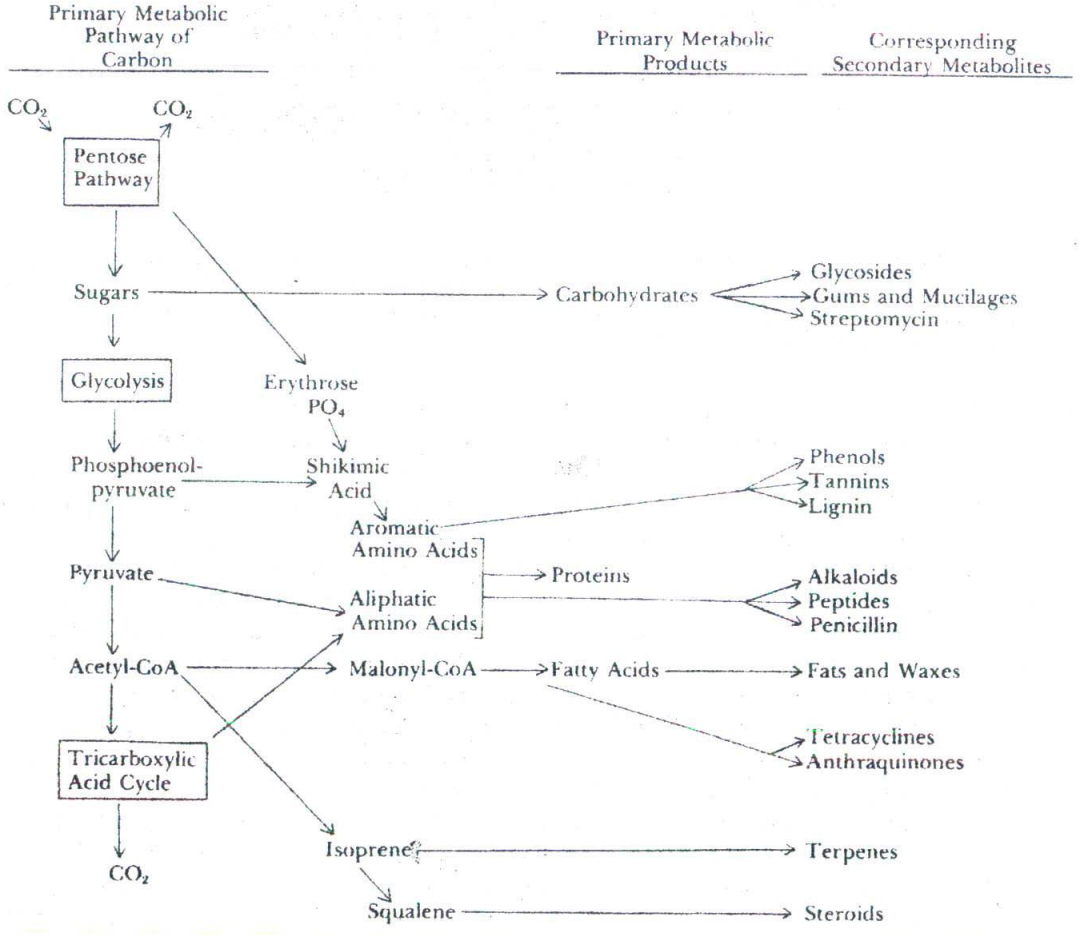

Fig. 1–6. Interrelationships of biosynthetic pathways leading to secondary constituents in plants.

Morphine, digitoxin, ergotamine, and vincristine are just a few examples. In addition, the natural plant drugs have served as useful prototypes for even better medicines. With help from the synthetic chemist, morphine became hydromorphone, lysergic acid was converted into methysergide, cocaine yielded procaine, physostigmine metamorphosed into neostigmine, and even salicin changed into acetylsalicylic acid. The list could go on and on.

Yet in spite of this outstanding record of past achievement, solid scientific research in the field is languishing in this country today, and some have expressed concern for its future. Surprisingly, this lack of scientific interest coincides with a "green wave" of lay interest in herbs and natural medicines that is unparalleled in modern history. American "health-food" stores sold more than $190 million worth of herbs in 1985, and books and pamphlets describing the putative use of these products amounted to another $33 million in sales.

Plant Drug Research in the United States

With so much lay interest in plant drugs, why, then, has quality scientific research in the field fallen on such hard times? The reasons usually advanced include problems in obtaining adequate patent protection, in the supply of raw materials, in acquiring appropriate personnel, in testing and evaluating plant extracts, in the attitudes of researchers, and the like. All of these reasons are valid, but they are not the basic reason. The basic reason for the lack of emphasis on plant drug research in the United States today is that, with a single exception, the programs have not been successful in yielding new, marketable medicines. The Smith Kline & French Company supported a screening program of alkaloid-containing plants for more than a decade without obtaining a single new product. Twenty-five years of effort by researchers for the National Cancer Institute, who tested some 40,000 plants, did not identify a single new agent of general use in the treatment of human cancer.

The only notable exception to these and other unsuccessful efforts was the discovery of vincristine and vinblastine in the Madagascar periwinkle by researchers at Eli Lilly and Company. A screening of plants with interesting folkloric usages uncovered these useful anticancer substances in the 40th of 200 plants examined. It is interesting to note that the Lilly researchers included the plant in their tests not because of its reputed antitumor properties but because of its reputation as a hypoglycemic agent.

Aside from serendipity, what did the Lilly program have that the many unsuccessful programs lacked? Successful discovery and development of new plant drugs in the strict regulatory climate that prevails in the United States must be a broad interdisciplinary effort involving experts in a number of fields, including plant taxonomy, ethnobotany, pharmacognosy, biochemistry, analytical chemistry, pharmacology, pharmaceutics, and medicine. Few organizations provide the opportunity to bring the expertise of such a large number of individuals to bear on a single problem. Educational institutions cannot do it easily because of the barriers erected along school and even departmental lines. Major pharmaceutical companies do have all the expertise required and, if used appropriately, as was obviously the case in the Lilly project, the results can be successful. Still, this lack of effective cooperation of researchers in a variety of fields accounts, in large measure, for the recent lack of success in the development of new plant drugs in this country.

Plant Drugs in Germany

At the same time that critics are decrying the lack of plant drug development in the United States and expressing pessimism about its future for all of the reasons just reviewed, research and development in the field continues to flourish in another

nation that is quite similar to ours from the point of view of technologic advancement. That nation is the German Federal Republic (West Germany). There, new plant drug preparations (so-called phytopharmaceuticals) and even new plant constituents are continually being introduced into the market by a relatively large number of manufacturers. See Table 1–1 for some typical examples of these products. How does one account for this difference?

In the first place, a strong tradition of natural drug use in Germany still prevails. A recent survey there showed that nearly 76% of the women interviewed drank herbal teas for their beneficial effects, and about 52% of them turned to herbal remedies for the initial treatment of minor illnesses.

In addition, the regulatory climate regarding new drug introduction is much more favorable in Germany. In the United States, costs of drug development have risen so high—$50 to $100 million per new product—that innovation is stifled and the activity is restricted to a few of the largest pharmaceutic manufacturers. This is not the case in Germany, where even some of the smaller companies have the resources to innovate in the plant drug field. This serves to stimulate competition and thereby encourages new product development.

The situation in Germany, which is not unlike that prevailing in other European countries, does require that plant drugs be standardized and of proven safety and efficacy. Standardization is no particular problem with modern instruments and techniques. Safety of long-used natural products is generally assumed, if no side effects have been reported. However, if evidence of toxicity is found, the drug is promptly withdrawn from the market. An example of a drug subjected to such an action is comfrey, or symphytum. Although no longer available in Germany because of its content of carcinogenic pyrrolizidine alkaloids, it is still sold in every "health-food" store in the United States. Yet it is generally agreed that our nation has much stricter drug laws than any other!

Proof of effectiveness of the German development programs is the area in which appreciable cost savings are afforded to the pharmaceutic industry in Germany. A doctrine of reasonable certainty is substituted for strict clinical trials. Heavy emphasis is placed on the reports of clinical experience supplied by general practitioners, and this is supplemented by evidence found in the literature and by data supplied by manufacturers. The result is, as previously stated, approval of a number of plant remedies not available in the United States. Such drugs are not only the most common products used for self-medication but also are widely prescribed by physicians, especially for minor ailments.

Of course, it may be argued that the stringent American regulations are necessary. We did successfully avoid the thalidomide problem that plagued Germany and other European countries, but even

Table 1–1. Some German Plant Drugs Unavailable in the United States

Product Trade Name	Active Constituent(s)	Use
Baldrisedon	*Valeriana mexicana* extract	Sedative
Crataegutt novo	*Crataegus oxycantha* extract	Cardiotonic
Harzol	(Phytosterins) *Hypoxis rooperi*	Prostate adenoma
Helixor	*Viscum album* extract	Cytostatic
Legalon	(Silymarin) *Silybum marianum*	Antihepatotoxic
Lomaherpan Creme	*Melissa officinalis* extract	Antiviral
Salvystat	*Salvia officinalis* extract	Antiperspirant
Tebonin forte	*Ginkgo biloba* extract	Circulatory stimulant

our strict rules did not prevent the non-steroidal anti-inflammatory agent benoxaprofen (Oraflex) from being introduced and misused extensively here until it was ultimately withdrawn. It would seem that the answer lies in regulations strict enough to protect the public health but not so formidable as to discourage and prevent innovative research. It is possible that some appropriate relaxation of the present regulations may eventually come about. One factor that may facilitate this is the growing influence of those concerned with the proper preservation and use of our natural resources. They are sometimes referred to collectively as the "green wave."

Influence of the "Green Wave"

The "green wave" will not only continue to gain momentum, it will, in all probability, reach the shore, where it will have a powerful impact. Those consumers who now honestly believe that "natural is better" are not going to be satisfied with a we-don't-know answer when they ask if catnip really has a useful sedative effect, or if garlic actually reduces high blood pressure, or if ginseng definitely increases resistance to disease. Their ever-increasing political influence may force the government to act, probably in two ways.

A government that underwrites a program for engineers to send people to the moon will probably find it necessary to provide some support to biologic scientists to investigate plant drugs to cure human disease. But the government, afflicted as it always is with a perpetual shortage of funds, will probably look for another way to achieve the same objective. It may, therefore, ease somewhat the unnecessarily rigid standards for marketing new drugs, particularly drugs from plants long in use as folk remedies, and thus stimulate more producers to begin research and development of them. The healthy competition thus engendered will provide the answers so long sought for some of the older drugs; it will also stimulate the search for new ones. We would hope that the easing of regulations might be accompanied by increased patent protection, thus providing additional incentives to innovators.

There is certainly no end in sight of raw material awaiting investigation. Only about 5 to 10% of the quarter million plant species have ever been studied either chemically or with respect to their physiologic activity. Although it may well be that those with the most obvious activities have already been identified, certainly other, very good ones remain undiscovered in this vast backlog. Improvement in screening procedures yet to come, but already foreshadowed, will be helpful in identifying new and useful drugs.

New Bioassays

One of the great stumbling blocks for those seeking drugs with new physiologic activities, or in fractionating extracts to determine the identity of the active constituent, has been the lack of simple bioassay procedures. Fairly elaborate screening techniques have existed, but they require the collaboration of skilled pharmacologists and are, in addition, costly. Recently, researchers have reported considerable success with a simple bioassay utilizing brine shrimp *(Artemia salina)*. The viable eggs of this tiny creature are readily available in the dry state from pet shops, where they are stocked as food for tropical fish. After hatching in a brine solution, the shrimp are exposed to varying concentrations of the test material and an LC_{50} (median lethal concentration) value in μg/ml is calculated. It has been determined that the activities of a broad range of compounds are manifested as toxic to the shrimp. The method is rapid, reliable, inexpensive, and may be conveniently applied in-house by chemists, botanists, or others who lack the resources and the technical ability required to carry out standard bioassays. For just these reasons, it has been successfully utilized in several studies involving the screening of large numbers of plant species

for compounds with useful biologic activities.

Another procedure of this sort that is still in a rudimentary stage of development but that shows considerable promise for the future is the so-called potato-disc assay. This involves observation of the inhibition of crown gall tumors induced on potato discs by *Agrobacterium tumefaciens* by various plant extracts or constituents being screened in a preliminary fashion for their anticancer potential. Results so far have been encouraging and have correlated well statistically with other much more elaborate and costly cell-culture procedures, at least for certain kinds of antitumor activity.

This is not to imply that either one of these methods will be used in its present form in the future. Rather, they must be seen as forerunners of even more simple and reliable procedures for determining bioactivity. In the year 2000, they will probably be remembered with the same degree of amazement and even disbelief we now express for the old-fashioned pregnancy test that involved injecting the patient's urine into a rabbit and then sacrificing the animal to examine the condition of its ovaries. The modern woman, suspecting pregnancy, simply dips a plastic strip bearing certain monoclonal antibodies into a urine specimen and looks for a color change. This kind of specific enzyme immunoassay carried out at home by the patient herself could scarcely have been envisioned 15 years ago. Fifteen years from now our assay procedures for bioactive plant constituents will be similarly improved.

New Analytic Methods

Our analytical capabilities also will be improved. Because of their complex nature, plants were once considered extremely difficult to fractionate for the purpose of isolation and identification of active constituents. The second half of this century saw steady improvement in analytic techniques. Selective solvent extraction, as outlined by G. Dragendorff in the 1880s, gave way in this century to adsorption chromatography, which in turn spawned ion exchange, paper partition, and thin-layer techniques before developing into high pressure liquid chromatography (HPLC) and gas chromatography. Coupled with mass spectrometry, this last methodology has been extremely useful. So-called multiple stage or tandem mass spectrometry (ms/ms) has now come upon the scene, permitting identification and quantitation of nanogram quantities of constituents in tissue samples approximating 1 mg without prior extraction or purification. Other powerful techniques useful for structural determination of complex plant constituents include x-ray crystallography and nuclear magnetic resonance spectroscopy in its several variations.

It is evident that further refinements in all of these techniques, coupled perhaps with some unexpected new developments, will lead eventually to the ultimate "black box" analyzer. A few milligrams of plant tissue placed in one side will be converted into a printout on the other, listing all of the constituents of interest and their concentrations in the sample. This device, which even today is only a few steps away from reality, will certainly expedite the screening of plant materials for useful constituents. Coupled with improved and simplified bioassay techniques, it is bound to reveal numerous new and significant medicinal agents.

New Culture Techniques

One of the present problems in producing plant drugs is securing adequate amounts of the proper raw material. Collection in quantity of properly identified, sometimes scarce, wild growing plants is becoming increasingly difficult as civilization encroaches on once-virgin territory, for example, the Amazon Basin. This difficulty will be overcome in the years ahead by plant-cell-culture methodology. Production of large quantities of undifferentiated plant cells is already possible, although we

now know that apparently homogeneous populations are, in fact, quite heterogeneous with respect to their ability to biosynthesize and accumulate desired secondary constituents. Selection procedures are thus necessary to obtain high-yielding subpopulations.

Present limitations of plant-cell-culture techniques include slow growth, expensive media, and the tendency to store desired metabolites in the tissues rather than to excrete them into the media, where they are more easily recovered. Such production is now economically feasible only when the compounds produced are both costly and unique as plant products. Some compounds that may currently be produced in high yields in such cultures and approach qualifying under these guidelines include diosgenin from *Dioscorea deltoidea*, serpentine from *Catharanthus roseus*, and ubiquinone-10 from *Nicotiana tabacum*.

In the future, existing production techniques will be greatly improved as a result of new information regarding factors influencing the formation of secondary plant constituents. Research has already shown that certain pharmaceutically desirable secondary natural products are phytoalexins, that is, compounds synthesized only when the plant is subjected to physical, chemical, microbiologic, or fungal damage. Examples include gossypol in *Gossypium arboreum* and homoharringtonine and related alkaloid esters in *Cephalotaxus harringtonia*. Increased yields of both of these compounds resulted from the addition of heat-denatured conidia of the wilt-producing fungus *Verticillium dahliae* to cell-suspension cultures. Yields of codeine and morphine in *Papaver somniferum* cell-supension culture were also greatly improved by similar methods.

Numerous studies have shown, therefore, that stress conditions in plant-cell-suspension cultures, such as interaction with an appropriate pathogen, can induce the formation of secondary constituents in cases in which such constituents are not produced in quantity under normal conditions. It is necessary in such cases to develop initially those conditions leading to maximum cell mass and then to induce secondary natural product formation. This approach is currently employed commercially in the production of the quinone shikonin by *Lithospermum erythrorhizon* cell-suspension cultures.

Alternative methods will be developed for plants unable to accumulate large cell masses in a relatively short time. In such cases, isolation and immobilization of either a key enzyme or the intact plant cells themselves seem feasible. Immobilized *Papaver bracteatum* cells have been shown capable of producing codeine from codeinone at a bioreactor conversion of 20 to 30% and of maintaining the reaction over a period of 27 days. A desirable feature of the process is the fact that 88% of the codeine is excreted into the medium, where it can be easily recovered.

Another approach to circumventing a slow growth rate in plant-cell-suspension cultures is to transfer the plant genes, which code for the enzymes catalyzing the desired biosynthetic reactions, into a bacterial or fungal cell. This could lower fermentation times to 24 to 48 hours instead of the 6 to 8 weeks necessary for fermentation with a typical plant-cell suspension. Many gene products are required to produce desired secondary metabolites. The technology to accomplish this is not yet available, but one- or two-step enzyme-catalyzed conversions should be possible now. More complicated reaction sequences will soon follow.

In the future, successful commercial production of plant drugs by cell-culture techniques will depend on the development of strategies that increase yields and shorten fermentation times. The manipulations of plant cells, plant genes, and plant enzymes, rather than of the plants themselves, should provide us with a host of useful medicinal agents.

Types of New Plant Drugs

Just what kind of new drugs will scientists be attempting to find in nature or to cultivate in this manner in the 21st century? Diseases for which satisfactory cures still remain to be developed include

1. Viral diseases, such as herpes (genitalis, simplex, and zoster), AIDS, and certain cancers;
2. Diseases of unknown etiology, including arthritis, some cancers, muscular dystrophy, and parkinsonism;
3. Self-inflicted diseases, such as alcoholism, drug dependency, obesity, smoking, and stress;
4. Genetic diseases, ranging from cystic fibrosis and hemophilia to sickle-cell disease.

In addition, improved drugs need to be developed for the control of symptoms such as pain. A nonaddicting narcotic is, for example, urgently needed. Also required are treatments for conditions not readily positioned in any one of the above categories, for instance, elevated cholesterol levels, hypertension, and even the general susceptibility to diseases of various kinds, both infectious and noninfectious.

It is in this last area that some promising progress has already begun to occur with plant drugs, progress that evokes the promise of eventual breakthroughs of considerable importance. In recent years, the concept of immunotherapy (the stimulation of the body to develop and improve its own defenses) has developed from a mere theoretical concept into a very promising field of drug therapy. Many compounds effecting this beneficial process by a variety of different mechanisms have been tentatively identified in higher plants. Low-molecular-weight compounds include terpenoids, alkaloids, phenols or quinones, and lipids. Active compounds of high molecular weight are the glycoproteins, polysaccharides, nucleoproteins, and proteins. Constituents of both types have been identified in such well-known drug plants as *Arnica montana, Baptisia tinctoria, Echinacea purpurea* or *E. angustifolia, Eupatorium cannabinum* or *E. perfoliatum,* and *Thuja occidentalis.* The continued investigation of all aspects of these immunostimulants should prove a fertile field of scientific endeavor in the future.

Another area in which plant principles are exhibiting considerable promise is that of hepatoprotective drugs. Such agents are urgently needed not only to protect the liver from infections such as viral hepatitis but also to help prevent damage from accidentally or purposely ingested toxins, ranging from amatoxins to ethyl alcohol. Silymarin, a mixture of flavonolignans obtained from the seeds of the milk thistle, *Silybum marianum,* is currently marketed in Europe and used for just these purposes with considerable success. There are a number of traditional plant remedies that have long been employed in Oriental medicine for their antihepatotoxic properties. One of these that has come to the attention of the public in this country because it is currently being marketed here as an adaptogen (an agent that strengthens the resistance of the body to all forms of stress) is the fruit of *Schisandra chinensis.* Although the species has yielded more than 30 lignans, some of which were reported to suppress chemically induced liver damage in mice and rats, there is, as yet, very little evidence to substantiate the claim that it has useful hepatoprotective properties in human beings or that it increases bodily resistance to disease or other forms of stress. What is needed with *Schisandra* and other similarly used plants, including the familiar turmeric, *Curcuma longa,* is additional scientific and clinical investigation.

The list of potentially useful plant drugs could be extended considerably, but one more general example is worthy of mention. The so-called adaptogenic drugs, e.g., ginseng (*Panax* spp.) and eleuthero (*Acanthopanax senticosus*), require detailed study to show if they do exert such a salubrious action; if so, we need to uncover the

mechanism (how does it differ from immunostimulation?), the exact identity of the active principles, and many similar questions that remain unanswered. If we are ultimately able to determine that the effects attributed to ginseng are not only real but significant, then this slow-growing root will become a prime candidate for the application of future cell-culture methodology.

The Future

Within the next quarter century, the achievements of science and technology will be so great that, when brought to bear upon the mysteries of nature that have long puzzled us, those mysteries will yield their secrets with amazing rapidity. It will be a fascinating and eventful period. We will know not only the causes of disease but the cures for most. The plant and animal kingdoms will continue to serve mankind in the 21st century just as they have done since the dawn of history. Significant new drugs of natural origin and new methods of producing them will continue to be important parts of that service.

ORGANIZATION OF THIS TEXT

In Chapters 2 through 14, drugs and drug constituents are discussed individually. Drugs that are official now, were official in the past, or have been used medicinally without official recognition are listed in each chapter. The nomenclature, history, preparation for the commercial market, descriptions, constituents, standards, uses, dose preparations, prescription specialties (if any), and other pertinent information for each are featured. Because pharmacognosy is a subject concerned with natural products, emphasis remains on the biologic aspects of these drugs. Although the chemical classification is employed, the drugs must still be considered the results of plant and animal metabolism.

The chapters devoted to these active constituents and the drugs containing them are:

2. CARBOHYDRATES AND RELATED COMPOUNDS. Compounds composed of carbon, hydrogen, and oxygen as polyhydroxy aldehyde or ketone alcohols: sucrose, lactose, starch, acacia, tragacanth, agar, pectin.

3. GLYCOSIDES. Substances that on hydrolysis yield one or more sugars among the products of the reaction: barbaloin, glycyrrhizin, vanillin, salicin, amygdalin.

Also included are **Tannins**, a group of complex phenolic compounds capable of combining with proteins: hamamelitannin, gallotannic acid.

4. LIPIDS. Compounds comprising fixed oils, fats, and waxes.

Fixed Oils and Fats. Glyceryl esters of fatty acids that are saponified by alkalies: olive oil, peanut oil, sesame oil, castor oil.

Waxes. Esters of fatty acids with high-molecular-weight monohydric alcohols: beeswax, spermaceti, carnauba wax.

5. VOLATILE OILS. Essential oils that represent the odoriferous principles of plants: peppermint oil, clove oil, cinnamon oil, anise oil, rose oil.

6. RESINS AND RESIN COMBINATIONS. Compounds comprising resins, oleoresins, oleo-gum-resins, and balsams.

Resins. Solid or semisolid amorphous products of complex chemical nature: rosin, podophyllum resin, jalap resin.

Oleoresins. Resins and volatile oils in homogeneous mixtures: turpentine, copaiba.

Oleo-gum-resins. Oleoresins and gums in homogeneous mixtures: asafetida, myrrh.

Balsams. Resins with mixtures of aromatic substances such as benzoic acid, cinnamic acid, or both: benzoin, tolu balsam, Peru balsam, styrax.

7. STEROIDS. Derivatives of cyclopentenophenanthrene: estrogens, androgens, adrenal cortex hormones, cardioactive aglycones, bile acids, cholesterol, ergosterol.

8. ALKALOIDS. Nitrogenous crystalline or oily compounds, usually basic in character:

atropine, morphine, quinine, cocaine, reserpine.

9. PEPTIDE HORMONES. Active principles secreted by certain endocrine glands: glucagon, insulin, oxytocin, vasopressin, ACTH.

10. ENZYMES AND OTHER PROTEINS. Organic catalysts produced by living organisms: pepsin, pancreatin, rennin, papain, trypsin.

Nitrogenous organic substances composed of amino acid units: gelatin, heparin, protamine.

11. VITAMINS. Chemical compounds necessary for normal growth and function of animals: thiamine, riboflavin, cyanocobalamin, ascorbic acid, tocopherol.

12. ANTIBIOTICS. Chemical entities produced biosynthetically that are destructive or inhibitory to microorganisms: penicillin, cephalosporin, polymyxin, tetracycline, erythromycin, kanamycin, griseofulvin, gentamicin.

13. BIOLOGICS. Products composed of antigenic matter or antibody preparations capable of developing a state of immunity in the patient: adsorbed diphtheria toxoid, hepatitis B vaccine, poliomyelitis vaccines, immune globulins, diphtheria antitoxin; also biologics related to human blood: albumin human, antihemophilic factor.

14. ALLERGENS. Substances, usually protoplasmic in origin that cause unusual responses in hypersensitive individuals: pollen grains, mold spores, feathers, animal dander, poison ivy.

Two additional chapters are included in this text. They are devoted to drug-related topics of considerable significance to many practicing pharmacists.

15. POISONOUS PLANTS. Higher plants and fungi that produce toxic effects when introduced into the human body: jimson weed, nightshade, water hemlock, amanita, inocybe.

16. HERBS AND "HEALTH FOODS." Products of natural origin used by the laity in the self-treatment of disease states or less-than-optimal health conditions. Many are without therapeutic effect, and some are toxic.

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