Participants in the Symposium "Plants in the Development of Modern Medicine," reading left to right:

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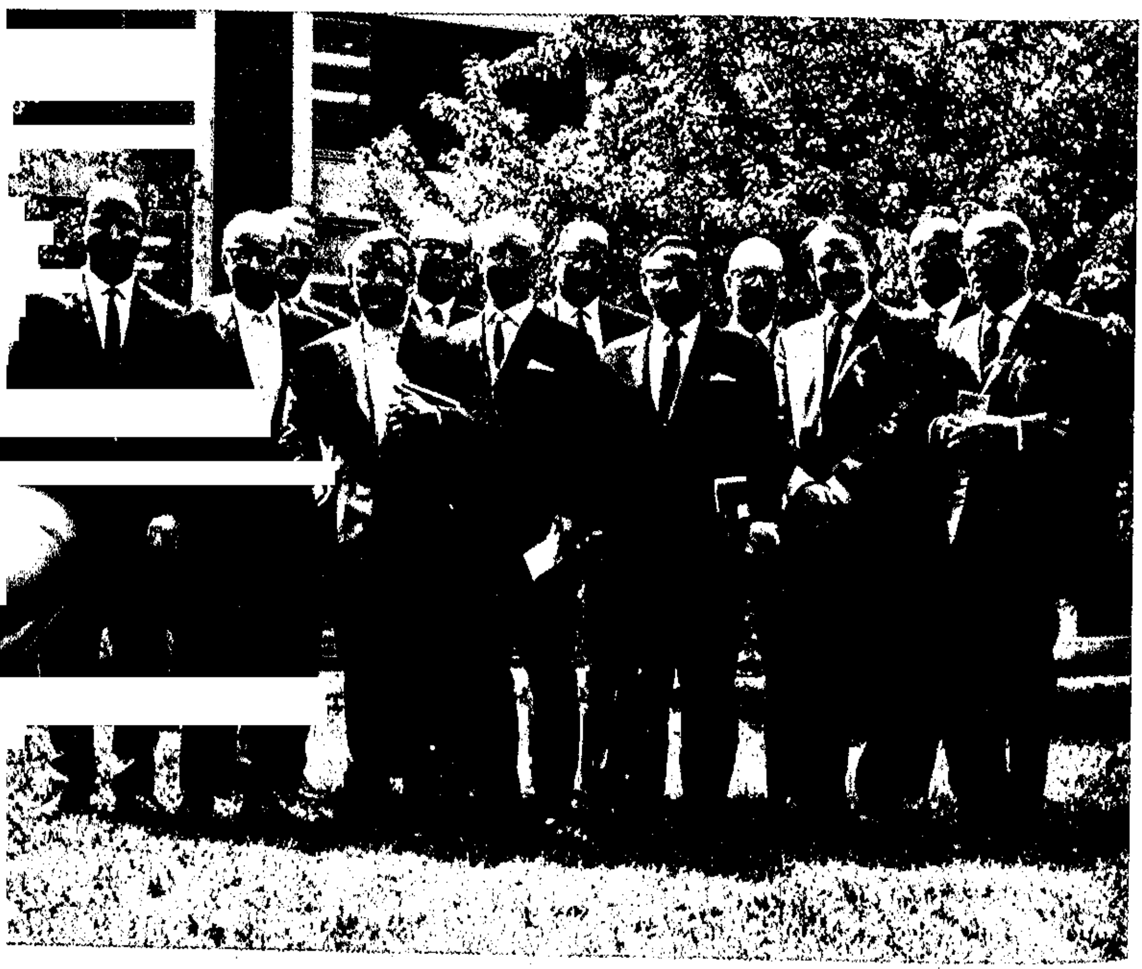

Plants in the Development of Modern Medicine

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The Future of Plants as Sources of New Biodynamic Compounds

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Nunc vos potentes omnes herbas deprecor, exoro maiestatem vestram, quas parens tellus generavit et cunctis dono dedit: medicinam sanitatis in vos contulit maiestatemque, ut omni generi identidem humano sitis auxilium utilissimum.

Precatio Omnium Herbarum

INTRODUCTION

The relationship between man and plants has been very close throughout the development of human cultures. Through most of man's history, *botany* and *medicine* were, for all practical purposes, synonymous fields of knowledge, and the shaman, or witch-doctor—usually an accomplished botanist—represents probably the oldest professional man in the evolution of human culture.

At no time in the development of mankind, however, has there been more rapid and more deeply meaningful progress in our understanding of plants and their chemical constituents than during the past quarter century. And this is curious, especially in view of the somewhat earlier deprecation in pharmaceutical chemistry of any emphasis on plants. The gradual sophistication of phytochemistry in the last half of the nineteenth century and the exaggeration of hope for specific remedies from vegetal sources for any and all ills set up a counter-current, a tendency to disparage any data concerning the potential value of physiologically active plants. The importance and exclusiveness of synthetic chemistry was exalted, and its potentialities were held to be so great that the Plant Kingdom could be sloughed off without ceremony. The "Coal Tar Age" was assured in therapeutics, wherefore there would be no need of harking back to remnants or even hints from earlier ages that counted on natural sources for their medicinal and other products. DeRopp has expressed it well, in discussing the delay until 1947 for the discovery by western science of such an ancient remedy as *Rauwolfia:*

> This situation results, in part at least, from the rather contemptuous attitude which certain chemists and pharmacologists in the west have developed toward both folk remedies and drugs of plant origin . . . They further fell into the error of supposing that because they had learned the trick of synthesizing certain substances, they were better chemists than Mother Nature who, besides creating compounds too numerous to mention, also synthesized the aforesaid chemists and pharmacologists. Needless to say, the more enlightened members of these professions have avoided so crude an error, realizing that the humblest bacterium can synthesize, in the course of its brief existence, more organic compounds than can all the world's chemists combined.

Then, as we can all recall, the discovery, almost within a decade, of a series of so-called "Wonder Drugs," nearly all from vegetal sources, sparked a revolution. It crystallized the realization that the Plant Kingdom represents a virtually untapped reservoir of new chemical compounds, many extraordinarily biodynamic, some providing novel bases on which the synthetic chemist may build even more interesting structures. The startlingly effective drugs that have come from this decade or two of discovery are scattered throughout the Plant Kingdom. They range from muscle relaxants from South American arrow poisons, antibiotics from moulds, actinomycetes, bacteria, lichens and other plants; rutin from a number of species; cortisone precursors from sapogenins of several plants, especially from *Strophanthus* and *Dioscorea;* hypertensive agents from *Veratrum;* cytotoxic principles from *Podophyllum, Vinca* and other sources; khellin from *Ammi Visnaga;* reserpine from *Rauwolfia;* hesperidin from the citrus group; bishydroxycoumarin from *Melilotus;* and sundry others—not to mention the numerous psychoactive structures of potential value in experimental psychiatry, some new, some old, from many cryptogamic and phanerogamic sources.

Not only have new drugs from vegetal sources been discovered, but new methods of testing and refined techniques have led to the finding of novel uses for older drugs.

As a result of these advances, nearly one half of the 300,000,000 new prescriptions written currently in the United States contain at least one ingredient of natural plant origin. Even if we exclude the antibiotics and steroids, well over 17 percent of all American prescriptions filled in 1960 used one or more kinds of plant products—either produced directly from plants or discovered from plant sources and later synthesized. A more up-to-date analysis of American prescriptions covering over one billion written in 1967 gives the following breakdown: 25 percent contained principles from the higher plants; 12 percent were microbial-derived products; 6 percent were animal-derived substances; 7 percent had minerals as the active ingredient; 50 percent of the active principles were synthetic.

If so many revolutionary discoveries have been made in little more than a quarter century, what logical reason is there to presume that the end to such good fortune has come? Since even the flurry of phytochemical research engendered by the "Wonder Drugs" has barely scratched the surface of the Plant Kingdom, let us consider briefly the potentialities offered by this vast assemblage of species.

THE EXTENT OF THE PLANT KINGDOM

Linnaeus wrote that the "number of plants in the whole world is much less than is commonly believed," calculating that their number "hardly reaches 10,000." Another early estimate was made by Lindley who, in 1847, credited the Plant Kingdom with a total of nearly 100,000 species in 8,935 genera. He assigned 1,194 species to the algae; 4,000 to the fungi; 8,394 to the lichens; 1,822 to the bryophytes; 2,040 to the ferns and fern allies; 210 to the gymnosperms; and 80,230 to the angiosperms.

Intensification of exploration during the last century obliged taxonomists gradually to increase their horizons. But the estimates have not kept pace with botanical collecting and taxonomic research. Most of the currently accepted calculations have not been substantially altered since the early years of this century. They allow the Plant Kingdom between 250,000 and 350,000 species. This aggregation is usually thought to have the following distribution: Algae—18,000; Fungi (including Bacteria)—90,000; Lichens—15,000; Bryophytes—from 14,000 to 20,000; Pteridophytes—6,000 to 9,000; Gymnosperms—about 675 species in 63 genera; Angiosperms—about 200,000 species in some 300 families, of which 30,000 to 40,000 are Monocotyledons.

As a taxonomist and plant explorer, I have long felt this estimate to be totally unrealistic, especially in view of the continued description of 5,000 new species and varieties each year. Perhaps it is significant that botanists with long field experience in the tropics are unhappy with contemporary calculations. May not even the highest currently accepted census for the angiosperms—200,000 species in 10,000 genera and some 300 families—be deficient?

Richard Spruce, the British explorer of the Andes and Amazon for over 15 years during the last century, estimated that the vascular plants of the Amazon Valley numbered some 60,000 species, and, considering the sparsity and superficiality of plant-collecting up to his day, he wrote that there might "still remain some 50,000 or even 80,000 species undiscovered."

In the early years of the present century, Jacques Huber, the Swiss specialist on the Brazilian Amazon, set the arborescent flora of the eastern part of this area at some 2,500 species—even though he felt that Spruce's estimates were overly optimistic. It is interesting to note that Huber's student, the great modern authority on the Amazon flora, Adolpho Ducke, described more than 762 species and 45 new genera of higher plants from the Brazilian sector of the hylea.

Several contemporary plant explorers who have worked in northwestern South America express agreement that "there remains today little better or more exact judgment than that expressed by Spruce" more than a century ago.

José Cuatrecasas has, for example, described upwards of 800 new species. Bassett Maguire calculates that the "vascular flora of the New World tropics would be considerably in excess of 150,000 and may indeed reach the 200,000 figure" and that "certainly, there are yet 25% to be uncovered." Thus, Maguire expects from 37,000 to 50,000 species to be discovered and described from tropical America. Julian Steyermark estimates the flora of Venezuela to comprise between 20,000 and 30,000 species of phanerogams. I have calculated that Colombia, undoubtedly the richest country in number of plants in the New World, may have in the neighborhood of 50,000 species of flowering plants and ferns.

Even outside of the truly tropical areas, certain floras are extremely rich. The Brazilian state of Rio Grande do Sul, for example, has 4,300 species, calculated to comprise about one-tenth of the flora of the whole country. This means that a census of the Brazilian flora would be placed somewhere near 43,000 species. Martius' monumental *Flora Brasiliensis*, written by many specialists over a period of 66 years and finished in 1906, enumerated 22,766 species in 2,253 genera. Our concept of Brazil's flora has, consequently, doubled in only half a century.

In view of the probability that the Plant Kingdom is more extensive than generally thought, a review of the possible size of its several groups might be significant.

Contemporary specialists now believe that some 1,500 species of Bacteria are known. Approximately 12 percent of them are ubiquitous marine types. Despite their great importance as causative agents of human ills, the classification of the Bacteria has been less thoroughly studied than that of other groups, and they are often more readily discerned from their biological effects than from their morphology.

The Fungi are now variously estimated at from 30,000 to 100,000 species. Ubiquitous, a highly successful group of plants, albeit one of the most ancient, they are dominant organisms in today's flora, notwithstanding their usual microscopic size. A contemporary specialist states that even 100,000 might be a conservative estimate, and that the grand total could be well over 200,000. A conservative estimate recently considered the Fungi to be constituted as follows: Phycomycetes, 1,000 species; Ascomycetes, 12,000 (with some calculations as high as 40,000); Basidiomycetes, 13,500; Fungi Imperfecti, 10,500 (with some calculations up to 30,000).

Although the Fungi may be one of the most significant groups of plants in human affairs, they have been relatively insignificant as sources of medicinally valuable compounds. Many are highly toxic to man; some are narcotic. It has long been thought that alkaloids are nearly absent from the Fungi, but modern work refutes this concept. Recent research has shown that 2 percent of a random sampling of fungi are alkaloidal, that quaternary compounds (choline, muscarine, etc.) occur widely in mushrooms, and that betaines, simple amines, and peptides are not uncommon.

Three recent developments have brought the Fungi into sharp relief: 1) the large number of antibiotic substances found in this group; 2) the importance and ubiquitous occurrence of aflotoxins and other food toxins; 3) the study of hallucinogenic mushrooms with their unusual and potently biodynamic constituents—the curious narcotic hydroxindole alkylamine, psilocybine, from a number of "sacred" Mexican mushrooms and derivatives of ibotenic acid from the hallucinogenic *Amanita muscaria.* The study of Fungi as allergens and as indirect poisons is still embryonic. Since the discovery in 1960 of the toxic and carcinogenic aflotoxin compounds due to fungal infection of foodstuffs, more than 700 papers on the difurano-coumarin constituents in the Fungi have engendered interest in aflotoxins and mycotoxins in general, opening new avenues of research.

The Algae, all aquatic but about 56 percent marine, comprise a most varied group of organisms estimated at from 19,000 to approximately 32,500 species. One group alone—the Diatoms—accounts for some 6,000 to 10,000 species. Recent research has indicated that these plants are promising indeed for a variety of biodynamic effects: antibiotic activity; central nervous and neuroactive effects; antiviral, wound healing, anticoagulant, antiyeast, antifungal and antihelminthic properties. Many of the Algae are toxic, especially among the Blue-green Algae, of which 150 species are known to be poisonous. The importance of the algal groups as sources of biologically active compounds is destined to increase as studies of marine organisms is intensified, since this represents the most significant group of plants living in the sea.

Attention has recently been focused on the Lichens as a neglected source of biodynamic constituents. They number from 16,000 to 20,000 species in about 450 genera. Bacteria-inhibiting properties have been found in many of them. About one-half of the temperate zone Lichens possess lichen acids capable of inhibiting gram-positive Bacteria and even tuberculosis Bacilli and some Fungi.

The Bryophytes—mosses and liverworts—have, it seems, been somewhat neglected from the phytochemical point of view. They may number from 14,000 to 25,000 species concentrated in the wet tropics, where taxonomically they are very poorly known. I am convinced that many surprises await future chemical studies of the Bryophytes.

The Pteridophytes, occasionally valued in folk medicine because of their mucilage content, have not contributed many biodynamic constituents. It is true, however, that phytochemical research has been far from intense, partly because of the lack of toxic and other biological effects. Modern techniques of analysis may reveal compounds of significance in many of the nearly 10,000 species in 250 genera of ferns and fern allies. A hint of the unexpected results that could lie in store is provided by the recent isolation from the comparatively small family *Lycopodiaceae* of nearly 100 extraordinarily interesting alkaloids.

The Spermatophytes, dominant on land today, comprise two divisions that are highly unequal from the point of view of biodynamic constituents. The Gymnosperms, with 700 species in 65 genera, have been of medicinal interest primarily as sources of essential oils and resins, the most notable exception being *Ephedra* with its unusual alkaloidal constitution. The Angiosperms, on the other hand, have been man's prime source of medicinal and, indeed, of all other economic plants, partly because, since they are the obvious part of land vegetation, man is most familiar with them. Even though most of man's medicines have historically an angiospermous origin, the potentialities of this group of plants have really been but superficially examined.

It may be of interest here to indicate, in order of decreasing importance, the principal drug-yielding families of Angiosperms according to a survey of more than one billion American prescriptions written in 1967: Dioscoriaceae, Papaveraceae, Solanaceae, Scrophulariaceae, Rutaceae, Rubiaceae, Liliaceae, Bromeliaceae, Rhamnaceae, Caricaceae, Plantaginaceae, Sterculiaceae, Gramineae, Leguminosae, Umbelliferae, Ericaceae.

Estimates of the extent of the Angiosperms vary greatly. Most botanists have accepted 200,000 to 250,000 species in 300 families and 10,500 genera. The Monocotyledons are credited usually as making up a quarter as many species as the Dicotyledons. I believe that we must allow somewhere near half a million species for the Angiosperms; but, even if we accept the smaller estimates, the opportunities for phytochemical research are almost virgin and unlimited. The field for expanded investigations for the near future nowhere holds greater potentialities than amongst the Angiosperms, unless perhaps the Fungi, botanically so much less thoroughly understood, may prove to be equally promising. Wherefore, I want to consider a few random aspects of the Angiosperms as isolated indications of the future that the Plant Kingdom as a whole offers in any search for new biodynamic compounds.

ALKALOIDS AND GLYCOSIDES IN PLANTS

Perhaps the most conspicuous phytochemical research during the past decade has been directed toward alkaloids in the Angiosperms. The activity of alkaloid research cannot better be shown than by the growth in the number of structures isolated. In 1800, alkaloids were not known; in 1949, about 1,000 were recognized; ten years later, this figure was increased to 2,175; by 1969, the total stands at 4,350. Of this total, 256 occur in non-angiospermous plant groups: Agaricaceae, 34; Hypocreaceae, 51; other Fungi, 40; Algae, 5; Cycadaceae, 6; Equisetaceae, 5; Lycopodiaceae, 95; Pinaceae, 2; Gnetaceae, 9; Taxaceae, 9. This concrete figure of 3,094 alkaloids in the Angiosperms means that approximately 94 percent of the alkaloids are known from this segment of the Plant Kingdom, against only 6 percent from all other plant groups.

Within the Angiosperms, there is an apparent disparity in occurrence of alkaloids between the Monocotyledons and the Dicotyledons. The latest figures indicate that only 488 of the total of 3,094 alkaloids in the Angiosperms, or slightly under 16 percent, are found in the Monocotyledons, distributed amongst 12 of the 45 families.

Since the Monocotyledons are generally considered to represent about one quarter of the total number of species in the Angiosperms, this apparent disparity may be appreciated as of doubtful significance, especially in view of the fact that, in general, many of the large monocotyledonary families, such as the Orchidaceae, have not been so thoroughly investigated by phytochemists as the major and certain alkaloid-rich dicotyledonary families.

In the Monocotyledons, the richest alkaloid families have seemed to be the related Amaryllidaceae and the Liliaceae. In the neighborhood of 200 alkaloids are known from each family. In the former, with 1,050 species in 90 genera, alkaloids have been isolated from 33 genera; in the latter, with 3,700 species in 250 genera, alkaloids occur in 31 genera. These two families have long been thought to represent the only outstandingly alkaloid-rich Monocotyledons. This assumption may well have been fallacious. That there is still much to do in alkaloid studies in the Monocotyledons cannot better be illustrated than by the largest monocotyledonary family—in fact, the largest angiospermous family—the Orchidaceae, with 25,000 to 35,000 species in about 600 genera. A recent survey of plant alkaloids cited only 24 alkaloidal species in 11 genera, but actually only two alkaloids—dendrobine and nobiline from *Dendrobium nobile*—had ever been isolated. If the Orchidaceae have, as botanists believe, stemmed from a common remote ancestor with the Amaryllidaceae and Liliaceae, there might be justification in expecting the orchids to have a higher percentage of alkaloid-bearing species. A spot test survey for alkaloids which I carried out on 1,454 species on herbarium specimens in the Orchid Herbarium of Oakes Ames indicated 66 definitely positive, 48 doubtful or with a trace—for a total of 114, or 8 percent. Actual phytochemical work carried out recently on fresh orchid material has shown the presence of alkaloids in 324 species of 1,073 examined—a much larger proportion, 32 percent. An extrapolation of this figure would indicate that the Orchidaceae are far richer in alkaloids than even the Amaryllidaceae or Liliaceae.

Amongst the Dicotyledons, alkaloid distribution has been shown to be seemingly much more complex and capricious. At least one family is

100 percent alkaloidal—Papaveraceae. The Himantandraceae—a family of one genus with one or perhaps two species—has yielded 21 alkaloids. Alkaloids are almost lacking in some families, such as the Rosaceae and Labiatae. One family, the Apocynaceae (admittedly the most intensively studied of all plant families since the discovery of reserpine) accounts for 18 percent of all known alkaloids, with 765 having been isolated from 26 percent (46 of 180) of its genera.

Alkaloid distribution in the Dicotyledons probably may look less erratic when more is known about some of the minor or rare families. At the present time, however, even in the larger families, good information is available, in general, for those which, because they have yielded valuable medicinal compounds, have been intensely studied: for example, Apocynaceae, Solanaceae. But even in most of the larger families (Compositae, 13,000 species; Leguminosae, 13,000; Rubiaceae, 5,500; Euphorbiaceae, 4,000), only a small proportion of the species has as yet been analyzed.

Recent and current research is fast increasing our knowledge of the number of families in which alkaloids are present. Field spot tests indicate that the rare monocotyledonary family Velloziaceae should be studied. The Salvadoraceae, Elaeocarpaceae, Lythraceae, Convolvulaceae, and Myristicaceae are known to be decidedly interesting to the alkaloid chemist, with the potentiality, in several of these groups, of the discovery of new types of alkaloids. Other families, long known to have possessed alkaloids, are now shown to be definitely richer than once thought or to yield interesting new structures—e.g., Euphorbiaceae, Rhamnaceae.

There is no need here to elaborate further on the alkaloids nor to delve deeply into the many other secondary organic plant constituents. In almost all, if not all, cases, the same potentialities are inherent and are made manifest by modern investigations. Next in importance as biodynamic constituents, especially as toxic compounds in plants, are the several classes of glycosides. They may be more widespread in the Plant Kingdom than the alkaloids. Among the most valuable are the cardiac glycosides and genins, of which some 300 are known from the Angiosperms, concentrated especially in the Apocynaceae, Asclepiadaceae, Liliaceae, Moraceae, Ranunculaceae, Scrophulariaceae, and other families. Many of the plants containing these cardenolides have been used in primitive societies as arrow- and ordeal-poisons. Steroidal sapogenines have, in recent years, attracted much attention in medicine, although pharmacological knowledge of this group of glycosides long antedates their chemical elucidation. Some of the species containing these compounds (e.g., *Strophanthus*) have, likewise, been valued for ages in the preparation of arrow-poisons. An extensive search through the Plant Kingdom for biodynamic sapogenins has, over a period of twelve years, screened 6,000 species representing 208 families in 1,397 genera—almost all Angiosperms—from nearly all parts of the world. This screening program, which represented two-thirds of the families recognized in Engler and Prantl, indicated that the most conspicuous genera for steroidal sapogenine were *Agave, Yucca, Dioscorea*. These 6,000 samples, incidentally, were screened for other organic constituents as well, and 10 percent were found to contain alkaloids, 64 of which were new structures. Approximately 150 natural flavonoids are known, occurring as heterosides, and more than 33 biological activities for 30 of these plant pigments have been reported. While rutin has been the outstandingly important flavonoid, other activities, including antiviral and cytotoxic effects, have also been noted for this group of compounds.

Many other categories of biodynamic plant constituents commonly occur in the Angiosperms, but the examples cited suffice to indicate what a future lies ahead when the Plant Kingdom is fully and systematically investigated. It should be borne in mind that there are well over 2,000 organic plant principles of known structure that lie outside of the alkaloid-glycoside classification and that many of them have or have had some application in or bearing on medical problems. The census of terpenoids, coumarins, anthraquinones, phenolic compounds such as tannins, essential oils, and many other organic constituents of Angiosperms are most certain to be increased greatly in number and novelty when, with sophisticated modern techniques of chemistry, the Plant Kingdom is screened as intensively for them as it has been recently for alkaloids.

ETHNOBOTANICAL SEARCH FOR NEW DRUGS

Were one not forewarned, one might assume that this grand advance in our understanding of the distribution of organic vegetal compounds had resulted from an organized search on the part of the botanist and chemist alone. Such an assumption would fall far short of giving a true picture of this modern awakening, which has been possible primarily because of the implementation of the interdisciplinary outlook in science. Great strides toward a breakdown of narrow "compartmentalization" and an upbuilding of the interplay of sundry, often seemingly unrelated, disciplines have led directly to the success that has been evident in the field.

Perhaps in no other effort has the interdisciplinary approach been so essential and so effective. The basic disciplines involved, naturally, have been botany, chemistry, and pharmacology; but anthropology, archaeology, linguistics, history, sociology, comparative religion, and numerous other specialities have likewise contributed appreciably to the search for new biodynamic plants. This intertwining of data and points of view from sundry fields has often been called *ethnobotany* or, in respect to drug plants, *ethnopharmacology*.

A number of avenues are open in a search for new biodynamic plant constituents. The most obvious, perhaps, is a random or semi-random screening of plants. This method is expensive in time and money, but it has been employed in several recent surveys, some of which have concentrated on a search for specific constituents—alkaloids, sapogenins, flavonoids, and so on. Others have been geographically limited but have sometimes been chemically more inclusive—covering alkaloids, saponines, flavonoids, including leucoanthocyanins, tannins, cyanogenic and cardiac glycosides, unsaturated sterols, triterpenoids, organic acids and phenols, essential oils and their components, etc. More or less extensive surveys have been carried out on plants from Australia and New Zealand, Borneo and Papua, Malaya, Hawaii, Taiwan, parts of Brazil, Colombia, Russia, and other countries, not to mention specific sections of the United States and Europe.

Other random surveys have been centered upon a search for plant constituents active for specific diseases or for very definite biological properties. Thus, there have been surveys for antiviral and antibacterial activity, for cytotoxic effects, and for a broad spectrum of other properties. Perhaps one of the most ambitious random searches has been the screening of plants for possible antineoplastic activity by the Cancer Chemotherapy National Service Center, which has tested more than 26,000 plant extracts, representing some 6,500 species. Farnsworth has truly said that "in the light of present knowledge and experience . . . a random selection and testing of plants selected from a broad cross section of families and genera will prove of greatest value in attempts to discover new entities for the treatment of clinical malignancies." Faced with the amazing size of the Plant Kingdom—even of only the higher plants—this random sampling requires the investment of great sums of money and the availability of many kinds of specialists, and demands as well relatively long periods of time: even if such a program could be carried out at the present time, it could be realized only by a large company or by a government agency.

Another approach concentrates intensive investigation on plants with folk uses reported in both ancient and modern literature. This literature, diffuse and often—in fact, usually—uncritical and of hearsay nature, is found in many fields: anthropology, ethnology, history, a variety of chronicles, exploration and travel, missionary reports, and many other human activities where direct contact has been sustained with primitive societies.

Ethnobotanical literature goes back 3700 years to the Code of Hammurabi. Many specialists might think it folly to examine such old literature. Yet, had we critically evaluated the writings of the Egyptian papyri, we might not have had to wait until the 1940's for an acquaintance with the antibiotic properties of certain fungi.

There is still probably much to be learned from a careful sifting of the medieval European herbals, which are usually passed over as having been thoroughly exhausted. Two other literature sources can be of great help. One—and its wealth is still underestimated—the accumulated writings of the early explorer-naturalist-physician-herbalist researchers of the sixteenth and seventeenth centuries: those intrepid, enquiring, insatiable chroniclers of things and events in new lands. They set down everything. In many cases it is still possible to winnow the grain from the chaff—yet this task still begs for a thorough effort. The Dutch botanist of the seventeenth century, Rumphius, for example, whose work is basic to the natural history of the East Indies, accumulated notes on folk uses of more than 700 species of plants. Insisting on verifying personally whenever possible what natives reported, he nonetheless wrote down what he considered fact as well as hearsay, or, as he said, "fables, superstitions and old women's babblings . . . certainly not, as it were, that I put a firm trust in them," but because "in those faery tales always some grain of Truth, some unseen natural virtue lies hidden, and to excite amateurs to diligent search, I assure them that in these lands many secrets of nature are revealed daily erstwhile unknown to Europeans and seemingly unworthy of belief."

The writings of naturalists and others of the New World—some still in manuscript form—are replete with yet unverified reports of therapeutic and biodynamic values of plants. In some cases, the specific identification of the plant is relatively easy. A concerted attack on such repositories of first-hand information, old though they be, might profitably be intensified. One shining example is that incredible treasury of folk knowledge of ancient Mexico: *Nova plantarum, animalium et mineralium mexicanorum historia,* written from data gathered personally in the field between 1570 and 1575 by Dr. Francisco Hernandez, physician to the King of Spain.

This approach, though often frustrating because of the casualness of diagnosis of specific ills or, more commonly, the lack of proper botanical identification of source plants, has been outstandingly, even spectacularly, successful in a number of instances. While one or two examples suffice to prove the point, many are the instances where folk uses of plants, had they been seriously followed up, might have led much earlier to valuable discoveries. The rediscovery of the use in Mexico and the exact botanical identification of several potent hallucinogens—especially the "sacred" mushrooms and morning glories—all fully outlined in detail in early historical chronicles and missionary reports, is perhaps the most recent example of ancient folk reports' having led to significant phytochemical advances.

An example from the Old World that has sparked a revolutionizing discovery in medical chemistry is provided by the uses in ancient and modern India of the snake root, *Rauwolfia,* clearly set forth in the Vedas dating from 1500 B.C., which should have led experimenters at a much earlier date to study the isolation of reserpine and the hypotensive properties of the constituents of this plant.

Another, and perhaps even more important, source of literature is that made up by modern ethnobotanical writings. This source is far more extensive and reliable than is usually suspected. It ranges from complete studies of the uses of and beliefs about plants in primitive societies to incidental but oftentimes highly significant remarks on one or two species of plants by travellers, missionaries, or explorers. A first step in evaluating and utilizing this scattered information on living cultures would be to gather the sources together in one large bibliography—a seemingly colossal task but actually not incommensurate with the data on folk medicine which could conservatively be expected to accrue therefrom. Botanists, anthropologists, and other investigators have been increasingly aware of ethnobotany. The past century has been unusually prolific in this type of literature. A realistic consolidation of this wealth of modern literature might indicate that, geographically and culturally, there exists a better coverage, spotty though it undoubtedly is, than has hitherto been expected.

Even from the use of modern literature, however, ethnobotany has its limitations. It is sometimes botanically uncritical or anthropologically unsophisticated—deficient even from both points of view. Seldom are voucher specimens cited to permit verification of identifications, and the diagnosis of ills and diseases is usually open to serious question. Frequently, when ethnobotanical data are found in floras, no specific tribe or group of people or no accurate geographic location is cited for the uses.

All in all, it would appear to be unwise and optimistic to base—as pharmaceutical houses have done on occasion—an entire natural products program on literature reports alone. In this day of computerization, however, a thorough utilization of the far-flung literature annotations of an ethnopharmacological nature ought not to be beyond the realm of easy possibility and could, in conjunction with other interdisciplinary approaches, help immeasurably in an extension of research into part of the Plant Kingdom's still hidden chemical wealth.

Perhaps the outstanding example, at least in modern times, of the use of the literature, complemented by data from other sources, is the Cancer Chemotherapy National Service Center screening of plant extracts for antineoplastic activity or cytotoxic properties. The world literature, systematically searched "for references since the beginning of writing," indicated "how completely the history of the herbal treatment of cancer has been identified with the history of medicine, indeed of civilization." The earliest of the literature studied was dated 2838 B.C. Many unpublished sources were likewise tapped in this survey, including archival material, solicited and unsolicited letters from around the world, and field notes of cancer therapeutic interest from herbarium records. Against the background provided by this exhaustive search, the random screening, already mentioned, of more than 6,500 species of plants for antineoplastic activity provided a truly interdisciplinary attack on the problem—and one giving the greatest hope for success, since it was not based wholly on one approach.

Another approach lies in tapping the wealth of ethnopharmacological data on labels in the world's herbaria. Information hidden away on these labels represents first-hand observations made in the field by the plant collectors; thus it is usually of much greater reliability than literature sources. And, since the information is physically attached to a specimen, no uncertainty about the plant's identity can arise. The most ambitious search, shortly to be published, has been carried out by Altschul and consists of a sheet by sheet search of the 2,500,000 specimens in the several herbaria at Harvard University—resulting in more than 7,500 reports of medicinal or toxic uses of plants in primitive societies the world over.

By far the best avenue of approach, however, is ethnobotanical field work among as yet intact aboriginal societies. Here a great challenge arises: there are not enough trained ethnobotanists to carry out the necessary research against the rapidity of disintegration of primitive cultures. Botanists usually are too occupied with the vast effort of collecting essential to their own phytogeographic or monographic studies to spend time in the slow detective work necessary for assembling the pieces of an ethnobotanical puzzle. While they often do make observations of far-reaching value in pointing out avenues of approach for later intensive work, too many botanists have manifested definite hostility to the thought of paying heed to native lore. The anthropologist, likewise, normally so deeply committed to unraveling obscure or complicated sociological enigmas, is occasionally able to signalize an important point of departure for the ethnobotanist. The anthropologist is, unfortunately, often discouraged from the pursuit of proper ethnobotanical research because of the collecting of voucher specimens, a chore which has sometimes been erroneously portrayed by professional botanists as so complex and burdensome as to be distasteful to or even impractical for an anthropologist. Since there does not appear to be much hope for the immediate and prompt training of a sufficient number of men specifically in ethnobotany, the botanist and, to a lesser extent perhaps, the anthropologist must take the initiative, in view of the fast ebbing away of time, to study many aspects of man and his knowledge and use of plants with biodynamic properties.

What really explains the recent advances in ethnopharmacological studies and the discovery, during the present century, of so many more interesting and promising plant constituents than ever before in the history of pharmacy and medicine? The primary cause is undoubtedly the development and application of the interdisciplinary approach. No longer are those often very divergent fields of science that impinge upon man and his relationship to his ambient vegetation so highly compartmentalized that the specialist in one field never has an opportunity of speaking with a colleague from another. Many examples illustrate the efficacy of this approach. I want to use but one from my own work: the intricately interdisciplinary story of the hallucinogenic morning glories of Mexico.

The early chroniclers in Mexico, shortly after the Conquest, wrote about one of the strangest of the sacred Aztec psychotomimetics: the vision-inducing seed of a vine called *ololiuqui.* Several early sources crudely illustrated it as a convolvulaceous plant, and Hernandez offered a sophisticated drawing which left no doubt that *ololiuqui* was a morning glory.

Religious persecution drove the use of ololiuqui into hiding. For four centuries ethnologists failed to find a morning glory employed in Mexico in magico-religious rites. Furthermore, botanists and phytochemists were confounded, since no intoxicating substances were known to exist in the Convolvulaceae. Then, in 1916, the American ethnobotanist Safford suggested that ololiuqui must have been a species of *Datura;* that the Indians, in an attempt to protect their sacred ololiuqui from prying and irreverent Spanish eyes, had deliberately misled and duped the early chroniclers. He reasoned that 1) no morning glory was known to be narcotic; 2) the flowers of the morning glories were tubular and might be substituted by the natives for those of a *Datura;* 3) the narcosis described for ololiuqui agreed well with that caused by *Datura;* and 4) *Datura* was and, indeed, still is widely employed in aboriginal Mexico as a divinatory hallucinogen. Safford's identification was readily accepted, and, even to this day, is relatively well established in the scientific literature.

Despite occasional botanical and anthropological articles in Mexico insisting that ololiuqui was, in effect, a morning glory, Safford's "identification" gained a foothold because no voucher specimens of a convolvulaceous plant so used were ever cited, even though preliminary pharmacological study of seeds of a wild Mexican morning glory called *piule* indicated that, in frogs, they produced a kind of "half-narcosis" and that an active principle—possibly an alkaloid linked with a glycoside—might be present.

In 1939, ethnobotanical field work which I carried out in Oaxaca finally provided an identifiable convolvulaceous specimen from a plant cultivated in a curandero's dooryard as his source of narcotic seeds for use in divination. It was *Rivea corymbosa.* This discovery and a review of ololiuqui's history was published. Several pharmaceutical houses soon investigated the seed but found no indication of intoxicating principles.

Against the background of this impasse, a psychiatrist—Osmund—decided to experiment and found that seeds of *Rivea corymbosa* are, in reality, highly hallucinogenic. In 1955 he reported that the seeds induce apathy and anergia, together with heightened visual perception and increased hypnagogic phenomena; he found no mental confusion but instead an acute awareness combined with alteration of time perception, followed a few hours later by a period of calm, alert euphoria. Here, it is appropriate, perhaps, to harken back to Hernandez' statement that, through ololiuqui, Aztec "priests communed with their gods . . . to receive a message from them, eating the seeds to induce a delirium when a thousand visions and satanic hallucinations appeared to them." He wrote, further, that the narcotic was so powerful that "it will not be wrong to refrain from telling where it grows, for it matters little that this plant be here described or that Spaniards be made acquainted with it."

Then, the phytochemical investigation of *Rivea corymbosa* seeds fortunately fell into the hands of the chemist Hofmann, discoverer of LSD, who had studied deeply the related ergot alkaloids of *Claviceps purpurea.* Amazingly, he discovered, in the seed of this morning glory, member of one of the most advanced groups of the Angiosperms, several ergoline alkaloids allied to the synthetic LSD, some of them identical with the hallucinogenic alkaloids isolated from ergot, a comparatively primitive fungus. Thus, modern, highly sophisticated psychiatry and chemistry came into play to vindicate ancient folklore reports and contemporary ethnobotanical studies.

Further field work, also in Oaxaca, has established the use as a sacred hallucinogen in divination rites of yet another morning glory, *Ipomoea violacea,* probably the *tlitliltzen* of the ancient Aztecs; and the same ergoline alkaloids have been isolated from *Ipomoea violacea* as from *Rivea corymbosa.*

This whole research, incidentally, has led to a phytochemical examination of the Convolvulaceae. It is now known that these chemical structures are not at all uncommon in the family, occurring in both Old and New World convolvulaceous genera. Thus, the early ethnobotanical writings of Spanish missionaries and chroniclers have had a hand, four centuries later, in sophisticated phytochemical investigations of a whole family of plants!

THE FUTURE

Now: what about the future of the Plant Kingdom as a source of biodynamic constituents?

When it is realized that there are more than 50 categories of secondary organic constituents known from the world of higher plants alone and that only a small fraction of the higher plants have been phytochemically investigated—and then usually only for one or two categories of constituents—the wide-open field for research must be obvious. Sophisticated modern microtechniques, furthermore, can greatly amplify the horizon attainable by today's phytochemists. Even though it represents nothing more than an "educated guess," I would venture to say that less than 10 percent of the organic constituency of the Angiosperms are known, that fully 90 percent remains for discovery and investigation.

Justification for doubt might exist. When one combines, however, the spectacular advances in the chemistry of secondary organic vegetal constituents with the many pointers provided by modern ethnobotany—then, and only then, does this "guess" appear perhaps not to be extravagant.

A few examples of phytochemical advances have been mentioned, and many more are, under any circumstances, well known to all of us who work directly or tangentially in this field of research.

What is certainly not so obvious are the very numerous and diverse indications of as yet uninvestigated biodynamic activity from ethnobotanical observations. Long lists of such indications might be cited, but, in conclusion, I shall enumerate only a few that have resulted from my own ethnobotanical field observations and from those of some of my colleagues and students made in the New World tropics, mainly in the Amazon Valley. When one realizes how closely these observations are circumscribed, in number of researchers, in time and in geographical area, an understanding of how many thousands might be available from a large number of investigators working over a long time and across the five continents may be appreciated.

New and chemically unexplained arrow poison plants, recently collected in the Amazon, belong to species of the myristicaceous *Virola*, the thymelaeaceous *Schoenobiblos*, and the lauraceous *Ocotea*. The Flacourtiaceae, especially *Ryania*, are numbered amongst the most toxic plants of the Amazon. Several species of Caryocaraceae, Humiriaceae, Marcgraviaceae, and Quiinaceae, from which alkaloids and other highly active constituents are not yet known, are elements of the toxic flora of the northwest Amazon. An as yet undescribed and chemically unstudied species of the bombacaceous *Patinoa* possesses ichthyotoxic principles and is employed by the Tikuna Indians to stupefy fish. Members of the Bignoneaceae and Monimiaceae are frequently indicated as poisonous elements in the neotropical flora. A recently collected species of *Piper* is chewed by the Motilone Indians of Colombia for its tongue-numbing properties. The Connaraceae, allied to the richly alkaloidal family Leguminosae, has species recognized or utilized as poisons, but phytochemical studies have largely neglected this promising small family. The Ericaceae, especially in the Andean highlands, deserves deeper investigation. *Aristolochia* has recently attracted attention because of interesting new compounds in some of its species and several Amazonian species are important folk medicines. The Acanthaceae call for more intense chemical study as a result of several unexpected reports of the use of several genera as fish poisons and as an ingredient of an hallucinogenic snuff. The recent discovery in a South American *Psychotria* of *N,N*-dimethyltryptamine argues for a new examination of great sections of the Rubiaceae. Furthermore, a number of rubiaceous plants have been reported as toxic, even though nothing is known of their active principles: *Duroia, Psychotria, Palicourea, Retiniphyllum,* among other genera. In spite of its well-known alkaloidal content, the Solanaceae bears much deeper study, especially some of the minor and rarer genera of the Andes, some of which have significant folk uses in medicine or magic: *Cestrum, Latua, Iochroma, Brunfelsia.* The Araceae, poorly known from the taxonomic point of view and even less understood phytochemically, is put to many interesting uses by Indians in tropical America, and many species are well worth careful study for their reputation as poisons and medicines, such as oral contraceptives. The Lythraceae should be placed high on the priority list for phytochemical examination, partly because of the interesting phytochemical studies on *Heimia,* an auditory hallucinogen. Even such improbable families as the Cucurbitaceae, Amaranthaceae, and Olacaceae might prove surprisingly rewarding in various biodynamic principles. A thorough phytochemical study of the Malpighiaceae is long overdue. Folk beliefs concerning the properties of many tropical American species of apocynaceous genera that have never been investigated, in spite of the preeminence of this family as an alkaloid-rich group, indicate promise in a search for still more active compounds. Nothing is known of the chemistry of the interesting Andean families Gomortegaceae and Desfontainaceae, members of which are employed as intoxicants in Chile.

I would fain extend this list. To do so, however, would only emphasize and re-emphasize the near virginity of the field that, even in this one part of the world, awaits the ethnopharmacologist and phytochemist willing to follow interdisciplinary lines of approach. When the opportunities around the world are considered, the almost limitless potentialities may easily be appreciated.

Even though the Father of Systematic Botany, Linnaeus, thought that there were no more than some 10,000 species of plants in the world, he did comprehend the great potentialities ahead when, in 1754, he wrote what has aptly been described as his creed:

> Man, ever desirous of Knowledge, has already explored many things; but more and greater still remain concealed; perhaps reserved for far distant generations, who shall prosecute the examination of their Creator's work in remote countries, and make many discoveries for the pleasure and convenience of life. Posterity shall see its increasing Museums, and the knowledge of the Divine Wisdom, flourish together; and at the same time all the practical sciences . . . shall be enriched; for we cannot avoid thinking, that what we know of the Divine works are much fewer than those of which we are ignorant.

Selected References

In view of the many fields touched upon in the foregoing pages, a complete bibliography to cover all aspects discussed and their ramifications would be excessively long and involved. Consequently, a very brief list of chosen references is offered with the purpose only of suggesting avenues for continued consideration of some of the points raised in the discussion.

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