

nite information is available about the octoploid forms. All the forms discussed are normally found growing wild with the exception of the triploids and these are often found wild as escapes from gardens.

Cytological evidence indicates that many of the triploids are plants in which diploids may have been the parents. It is to be assumed that many of these plants arose through chromosome duplication in cases of incompleting mitosis. Hexaploid sectors in the root tips of Sparks Aconite are clearly cases in which chromosome duplication might lead to the establishment of a new race.

With chemicals that induce polyploidy the plant breeder is provided with a tool that may enable him to produce double diploids or to treat sterile triploids so they may set seed. This is one of the fertile fields of research for the breeder of drug plants. The plants produce chemical substances with greater ease than the chemical laboratory.

Chemical analysis of cinchona hybrids indicates that a shift from one alkaloid to another may take place in the hybrids that have been produced. Such changes are known to occur in other plant products. In this, as yet unexplored, field some fundamental answer must be sought to explain the change that takes place in the chromosome mechanism which underlies these shifts in radical position or that exerts so profound an effect as shown in toxicity. It is suggested that the chromosome number be considered in the chemical analysis of these plants with a polyploid series of chromosome numbers. The status of the plant should be carefully considered. This is imperative with the problem of induced polyploidy through chemical treatment of plants. In the future all monographs published by the AMERICAN PHARMACEUTICAL ASSOCIATION should consider the cytological problems that are encountered in the preparation of monographs of drug plants.

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## A Brief History of Commercial Medicinal Plant Culture in the United States\*

By A. F. Sievers†

The desire to grow medicinal plants for the market comes to people of many classes, occupations and circumstances. Farmers, urban workers and business men at times become interested in such an undertaking, as evidenced by the hundreds of letters received annually by the U. S. Department of Agriculture requesting information on the subject. In most cases these inquiries are prompted by the belief that medicinal plant culture is a new and profitable enterprise. The high cost of medicines naturally suggests to many people that the plants furnishing the products that go into such medicines must be of high market value. Quite the contrary is the case. Botanical drugs, on the whole, are quite cheap and therein lies the principal reason why medicinal plant culture is not a well-established agricultural industry in this country. With few exceptions, our requirements of the crude drugs come from one of two sources—they are imported from abroad or they are collected from domestic wild plants. Many come from the tropics where they are grown or collected with very cheap labor.

Interest in the subject is usually greatest in periods when persons are more or less dissatisfied with their lot or forced to seek new means of a livelihood. During depres-

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sion years and when returns from staple crops are especially unsatisfactory there is a tendency to turn to such endeavor, usually with a serious misconception regarding the difficulties involved and the profits that may be expected. The period of greatest interest in the past was during the World War when the prices of crude drugs of foreign origin rose to levels previously unknown. A somewhat similar situation is again at hand and war conditions in central Europe may once more create a period of scarcity and high prices of many important botanicals coming from that region. Already the quotations on some items are substantially higher than normal and interest in the domestic cultivation of these is increasing daily. Not only are people considering their culture but manufacturers of preparations in which drugs and related plant products from foreign sources are used are becoming concerned about their supplies of these raw materials when present stocks are exhausted.

Many species now imported are adapted to some sections of this country and fortunately past experiments and studies by the Department and other agencies have provided much useful information on the soil and climatic requirements of such plants, methods of their culture, labor requirements, yields, markets, etc. One of the chief difficulties is the procurement of seed and other planting stock sufficient for even a relatively small acreage. It is believed that attempts to grow such plants should be limited to the few species that are most indispensable and have the best established market. *Digitalis*, *belladonna* and *henbane*, all leaf drugs, are well adapted to culture, have long been firmly established in medical practice and were most successfully grown in the past. To these might be added some of those from which are obtained the aromatic seeds such as *anise*, *fennel*, *coriander*, *celery* and others, and the condiments *sage*, *marjoram*, *tarragon*, etc. Among the species yielding volatile oils, *geranium* and *lavender* have possibilities but the latter requires several years to come into production.

It is advisable that those who contemplate the growing of such plants inform themselves regarding the experiences of others

who engaged in this enterprise in the past. Some of the difficulties encountered will doubtless be met with again but some mistakes made can perhaps thus be avoided. With this in mind the following brief history of the most important attempts at commercial medicinal plant culture in the United States is presented.

The possibilities of medicinal plant culture in the United States have been profoundly affected by changes and trends in the practice of medicine and in our economic and social life. The basis of the so-called herb-growing industry of colonial days and of much of the nineteenth century was the use of savory or flavoring herbs in cooking and of other herbs as components of medicinal teas and related preparations for which the pressed herbs of the times were largely used. The first-mentioned use still exists and the growing of savory herbs in the garden and in a limited way for sale in city markets continues and is in fact increasing. Commercial *sage* culture was probably the best example of this branch of the industry. The use of medicinal teas has undoubtedly declined to a mere fraction of what it was at one time. The business in pressed herbs was still considerable at the turn of the present century but soon thereafter many that formerly found a ready market could not be sold. The market became restricted largely to manufacturers of galenicals and proprietaries of the day and the sale of pressed herbs over the drug store counters became yearly less important.

The most successful of the early endeavors to grow and market medicinal plants were community enterprises, for which our present social order is generally not so well adapted. Reference is to the various Shaker Societies that flourished for a while in the nineteenth century in which the growing and collecting of a variety of flavoring and medicinal herbs were successfully accomplished. Such societies existed in numerous communities in New England, New York and elsewhere in the East and Middle West. Those interested are referred to the literature on the subject such as "Gleanings from Old Shaker Journals," published in 1916 by C. E. Sears, which contains many items of interest. Some

of these Shaker Societies marketed herbs valued as high as \$8000 in a season and collectively the annual volume of business was quite large for those days. They not only cultivated and collected the crude drugs but converted them into various products. A catalog issued by the United Society of Shakers at New Lebanon, New York, states that this society was first established in 1800 and lists "Medicinal plants, barks, herbs, seeds, flowers and select powders: therapeutic extracts, ointments, inspissated juices, essential oils, double distilled and fragrant waters."

With the passing of these early activities there followed a period during which the cultivation of botanical herbs appears to have declined almost to the vanishing point, especially so far as concerns the great majority of the species previously cultivated. Regarding these there appears to be little information on what occurred up to the beginning of the World War although it is known that some experimental work with these was going on. Commercial growing of a few plants such as ginseng, goldenseal, wormwood, peppermint and American wormseed has continued without interruption for many years.

No reliable statistics are available on the amount of ginseng and goldenseal root produced from cultivated plants. Since numerous persons grow both and their cultural requirements are somewhat alike, they are usually considered companion crops although ginseng root is grown only for export whereas goldenseal root and herb are used in this country to the extent of probably several hundred thousand pounds annually. There are probably not more than several hundred acres of these plants. Small plots, many of them less than an acre, are scattered throughout the northeastern, northcentral and Pacific Coast states. The growers of these plants have experienced many difficulties and few of those who undertake their culture bring their plantings successfully through the four- to seven-year period required to mature their roots. Severe declines in market value have discouraged many others. Goldenseal root declined from four dollars to fifty cents a pound within a few years and the normal exporting of ginseng to China, where its principal market lies, is interfered with during periods of disturbed conditions there.

The culture of peppermint as a source of the herb has never been extensive, but as a source of oil this plant has been grown in the United States for more than a century. The crop was introduced in central

New York but as early as 1835 the plant was found to be well adapted to the black muck soils of northern Indiana and southwestern Michigan and for many years about 90 per cent of the American peppermint oil has been produced in that area. About 25 or 30 years ago mint culture was started on similar soil types in western Oregon and Washington, which region now furnishes the balance of the domestic production. No peppermint oil has been produced in New York State for some time. Spearmint is grown as a companion crop but in much smaller amounts. In 1938 there were 29,070 acres of mint under cultivation which yielded over 890,000 pounds of oil. Nine-tenths of this was produced in the Midwest. The average yield per acre was about 31 pounds and the average price received about \$2.00 per pound. Growers claim this is below the cost of production. About 12 years ago several short crops resulted in very high prices, oil being sold in some instances for as high as \$25 a pound. The inevitable overproduction followed immediately with the usual consequences.

Japanese peppermint, the oil of which is the only commercial source of natural menthol, and which is cultivated extensively in Japan, was grown to the extent of several hundred acres in central California for several seasons within the past fifteen years. When grown under irrigation this crop was cut two or three times in a season and the season's yield of oil was about 60 pounds although as much as 200 pounds to the acre were obtained in some cases. This oil contained from 75 to 80 per cent of uncombined menthol. The crop was grown largely under contract, which permitted a reasonable profit. However, these contracts could not be renewed on the same price basis after menthol prices declined and the crop was soon abandoned.

Perhaps the most interesting essential oil crop in the country is the American wormseed which has been cultivated for the production of chenopodium oil, a well-known anthelmintic, for more than 100 years in a small area in central Maryland. It is a curious fact that the crop never became established elsewhere but this may be due to the erroneous belief that once prevailed that oil produced in any other region is lacking in quality. In later years experiments in South Dakota and Illinois have indicated that in these places good oil can also be produced. According to the 1930 census there were at that time 139 growers with 368 acres which produced 15,000 pounds of oil. Prior to that its production was frequently much greater, especially in 1924 when 600 acres were grown. The industry, once fairly prosperous, has in recent years suffered continuously from overproduction, largely because acreage has not been adjusted with regard to the declining consumption of the oil due to increasing use of other anthelmintics.

Another essential oil crop that requires mention here is wormwood. Many years ago wormwood was cultivated in Wisconsin where the oil was distilled with crude equipment. Since then its culture has

become more confined to the midwest where mint growers cultivate small acreages from year to year, in accordance with market conditions. The only important outlet for the oil is as a component of liniments, for which the amount required is relatively small. Wormwood has also been cultivated for the herb which at one time was in good demand. It is one of the crops given numerous trials during the World War period.

Other special plants in this general group have been grown for limited periods but various conditions and circumstances caused their cultivation to be discontinued. Space does not permit more than brief mention of these sporadic and widely separated attempts to grow such plants.

Sage was grown quite successfully at times, especially in Michigan and Wisconsin, from about the turn of the century to the War period. It was grown for the spice and meat-packing trade, however, rather than for medicinal purposes. About 30 years ago, there was considerable interest for a few years in drug plant culture in northern Texas where one individual, according to available records, cultivated a variety of plants with some success. Larger yields were claimed to be possible on account of the longer growing season but the long distance from the principal markets was a disadvantage. With the death of the most interested person the enterprise was abandoned.

In Wisconsin a unique project was undertaken in 1912 when the state legislature established the Wisconsin Pharmaceutical Experiment Station at Madison, Wisconsin. Researches on various phases of medicinal plant culture were undertaken but these plants were grown in sufficient quantity to constitute at least a semi-commercial undertaking. During the period of shortage of important drugs, quantities of digitalis of excellent quality were furnished to hospitals and institutions. Surplus materials were sold on the open market. The project did not survive.

In 1913 an interesting attempt at commercial drug plant culture was made at Omro, Wisconsin. Close coöperation between the grower and the Bureau of Plant Industry made it possible to secure detailed records. The experiences of the company are typical of that of others during that period. The plants grown were burdock, wormwood, spearmint, sage and belladonna. Five-eighths of an acre of burdock produced 480 pounds of roots and 100 pounds of leaves, the returns from which just covered the costs. From 8 acres of wormwood about \$300 net was received. The crop was cut with a binder, the tops stripped by hand and sold as herb and the stems distilled. The herb furnished two-thirds of the gross returns. In another year 7 acres produced 3400 pounds of herb but only part of this could be sold. Spearmint was largely destroyed by rust and weeds. Sage appeared to be a promising crop, judged from the small plot grown, but the price at the time was 60 cents a pound. By far the most profitable crop was belladonna, half an acre of which brought a net income of over \$400. Most of the

crop was sold for \$1.30 a pound. A change in the personal affairs of the owner caused this venture to be discontinued after 1915.

The rapid decline in the imports of such important botanicals as digitalis, henbane and belladonna with the beginning of the World War in 1914 led to the most active period in medicinal plant culture in our history. Not only were individuals attracted to this enterprise by the high prices of these drugs but manufacturers of medicines resorted to their cultivation to assure themselves of the necessary supplies. Some of the manufacturers had already experimented for years with such plants and, consequently, had a valuable background of experience. The literature of the period and unpublished reports show that such companies grew digitalis, cannabis,<sup>1</sup> belladonna and henbane in Minnesota, Michigan, Indiana, New Jersey and Pennsylvania. In most cases several acres of these plants were under cultivation. With the return of normal prices after the War these activities were largely discontinued but the growing of digitalis is being continued by some of these firms. Apparently this drug can be grown to better advantage than the others, perhaps because a drug of more uniform potency is thus assured. Cannabis appears to have been a rather satisfactory crop and several of these firms report having grown this until recent years.

Near Richmond, Virginia, a drug farm was started in 1916 after several years of experimenting. There were six acres of digitalis and smaller acreages of cannabis, belladonna and stramonium, also small plantings of catnip, wormwood, calamus and orris root. Only digitalis, which was yielding about 1000 pounds per acre, was continued after 1916 and is still being grown there.

Among the incorporated groups who were attracted to medicinal plant culture in that same period there were two that were not manufacturers of pharmaceuticals and who, therefore, did not provide their own market, yet they were the largest producers. In Virginia, near Washington, D. C., a company was organized for that specific purpose and continued in business from 1915 to 1920. During the period of its greatest activities this company had under cultivation 15 acres of belladonna, 10 acres of digitalis, 10 acres of cannabis and 5 acres of sage. There were also 1½ acres of woodland planted to ginseng and goldenseal but nothing was realized from these. During the period that imports were restricted the company realized good prices for belladonna, digitalis and sage but those interested in the project declared that overhead expenses and general operating costs in that region were too high to permit sustained profitable cultivation of these crops even at wartime prices except on a large scale.

The other of the two companies is a large grower of peppermint in Michigan. On its large farm in the southwestern part of the state this company had under cultivation in 1918, 44 acres of henbane, 9 acres of belladonna and 10 acres of burdock. Hen-

<sup>1</sup> See footnote 2 on page 412.

bane was their most successful crop. The yield was about 700 pounds of dry herb per acre and a total of about 40 tons of this drug was sold from the farm in three years. Officials of the company state that none of these crops could be grown at a profit when their importation was renewed after the war, hence all were discontinued after 1920. Separation of the leaves from the stalks in the case of henbane and belladonna, and the drying of these in structures suitable for the purpose are mentioned as the most important items of expense.

The cultivation of two species of *Datura* was undertaken in Minnesota at about this time by a company for use in a special product. Three or four acres were grown and the quality of the crop was very good. While production costs were moderate they, nevertheless, greatly exceeded the market value of the drug before the war and the venture was naturally discontinued with the return of normal prices. This company also experimented with these species in California and finally planted about 30 acres there but lost the entire crop through the ravages of beetles.

During this period of high prices belladonna seems to have aroused the interest of more people than any of the other plants mentioned. In addition to those cases already referred to, there were many individuals in various parts of the country who grew belladonna exclusively and with some success. The largest acreage of belladonna in any one region was that in California. In that state interest in the crop was largely due to Dr. Albert Schneider who had a lifetime interest in medicinal plant culture. The first planting of the crop in northern California was made by him. Space permits only a brief statement concerning the acreage, production, etc. In 1918, almost 100 acres were reported, which was more than twice the acreage reported from any other state. No complete records are available but some idea of the acreage and number of growers in the several states in 1918 may be obtained from the following tabulation based on information secured through questionnaires sent by the Bureau of Plant Industry in the late fall of 1918 to all growers whose names were on file.

Estimated Belladonna Acreage and Number of Growers in the United States in 1918

State	Number of Growers	Number of Acres
Michigan	13	45.5
Indiana	7	32.7
New Jersey	4	34.7
Pennsylvania	6	41.7
California	24	95.6
Maryland, Virginia, Illinois } Wisconsin, Oregon, Iowa }	6	23.3
Total	60	273.5

These growers reported a total harvest of 83 tons of herb, somewhat less than half of which was separated into leaves and stems at harvest time. Eleven tons of roots were also harvested. Since some growers undoubtedly failed to receive questionnaires or failed to make replies, the actual produc-

tion for the year must have exceeded this amount.

During the period 1913 to 1919, *Cannabis*<sup>2</sup> was grown for the drug trade in the vicinity of Florence, South Carolina. According to available records, there was an increase of from 8 acres in 1913 to 30 acres in 1916, 1917 and 1918, and a decline to 6 acres in 1919. Thereafter the crop was completely abandoned. These acreages were distributed among several growers, most of whom grew only an acre or two. The crop was prepared for market during the winter by stripping the leaves and tops from the stems by hand, a tedious and expensive procedure. Many difficulties were experienced in marketing the crop. Dealers objected to the product for various reasons at times and the limited and declining market clearly indicated the doubtful future of the crop. There has been no attempt to revive the industry since that time. Federal legislation enacted in 1937 prevents the growing of this drug crop in the United States.

Occasionally attempts were made in the past 20 years to grow Levant wormseed as a source of *santonin* in various sections of the country. The company operating in Virginia near Washington, D. C., already referred to, got the plant started well on rather poor soil after growing the seedlings in the greenhouse. However, the summer rains caused the plants to die from crown rot. The unripe tops contained a high percentage of *santonin*. An eastern manufacturer of pharmaceuticals had considerable success with a small-scale planting in the San Joaquin Valley in California, but the limited market for *santonin* discouraged any commercial planting. The Bureau of Plant Industry tried the plant in a number of localities and found it best adapted to irrigated regions in the West with little rain and high temperatures in summer. As a result of these trials a small company undertook the production of *santonin* in 1927 in northeastern Oregon, and this has been continued without interruption. Many difficulties were encountered in processing the crop, but a satisfactory extraction plant was finally developed. The growing of the crop under irrigation has given little trouble and the yield of *santonin* has been satisfactory. The very limited domestic consumption of *santonin* and its well-organized production in several European countries are factors that limit such an industry to a very small scale.

Although the amount of castor oil used for various technical purposes is far greater than the quantity used medicinally, the castor-bean plant, source

<sup>2</sup> The Marihuana Tax Act of 1937 imposes an occupational tax upon all persons who import, manufacture, sell, deal in or dispense marihuana (*Cannabis sativa*). Under this enactment marihuana may be transferred only pursuant to an order on a form issued in blank for that purpose by the Commissioner of Internal Revenue and upon payment of transfer tax at the rate of \$1.00 or \$100 per ounce, depending upon whether the transferee is registered or unregistered.

Each state has enacted legislation controlling the sale and distribution of cannabis and, in many cases, the production or cultivation of the cannabis plant.

of castor oil, which is used for both medicinal and technical purposes, was a cultivated crop of some importance in the Middle West during the period following the Civil War until about 20 years ago. Kansas and Oklahoma were the principal producing states and during the early period the beans were crushed in mills located in the Mississippi Valley. In Oklahoma the maximum acreage and production were 2549 acres and 22,481 bushels, respectively, during the early years of this century. According to annual reports of the Kansas State Board of Agriculture that state produced 766,000 bushels from 68,170 acres in 1879. In 1916, the last year included in these reports, only 360 bushels were produced. In 1918 an organized campaign for castor-bean culture was undertaken by the War Department, but the purpose was to supply castor oil for lubricating purposes and, hence, it need not be discussed here. There is at present no domestic commercial production of castor beans.

Two other crops should be mentioned briefly although here again the medicinal use of their products is altogether secondary. Mustard seed is produced in California and Montana in greatly varying amounts. In 1938 the production in these states was 2,600,000 and 15,000,000 pounds, respectively. The other crop is the pungent red pepper of which several varieties are grown in the South and Southwest. Here, as in the case of mustard, its use as a condiment provides the market outlet. From 5000 to 7000 acres, yielding about a million pounds, are grown in southern California, Arizona, New Mexico, Louisiana, Mississippi and South Carolina. These two crops are of some importance in the spice industry but are given only mere mention here because they are not usually considered in connection with medicinal plant crops.

## Correlation of the Evaluation of Disinfectants by the Agar Cup-Plate Method and Clinical Experience\*

By Rhett G. Harris† and William A. Prout‡

Recently the authors were asked to evaluate a series of germicides and determine their efficiency, by *in vitro* methods, for use in the obstetric wards of the Roper Hospital, Charleston, S. C. Usually the criteria for such recommendations are reached by performing tests based upon

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dilution of the substances under investigation and then determining the time required for the serially diluted material to destroy bacterial growth. Examples of such methods are the Rideal-Walker test, the well-known F. D. A. phenol coefficient and the tissue culture and manometric procedures. If a germicide must diffuse through mucous material to reach the site where its action is desired, as in the birth canal before and after parturition, it is felt by the present authors that methods based upon diffusion would be better than those based upon dilution and simulate more, *in vitro*, the actual conditions under which germicides are used in obstetrics. One such test, the agar cup-plate method which was devised by Himebaugh and published by Ruehle and Brewer in 1931, has been studied by Rose and Miller (1939) in detail, and has been found to yield consistently good results, providing standard procedures are followed. This test was therefore chosen to be used in these investigations.

### EXPERIMENTAL

*Method of Procedure.*—Sterile Petri dishes were poured with 20.0 ml. of melted, cooled nutrient agar ( $pH$  7.2–7.4) containing in suspension 0.10 ml. of a 24-hour nutrient broth culture of *Staphylococcus aureus*. The plates were allowed to harden after which time test “cups” were cut from the agar with a sterile cork borer having a diameter of 15.0 mm. To this “cup” was added 0.20 ml. of the solution under investigation; the plate was covered with a porous, unglazed porcelain cover, incubated at 37.5° C. for 24 hours at which time measurements of the zones of inhibition were made. The zones produced by the various germicides requested in this investigation are shown in Table I.

Table I.—Widths of Inhibition Zones Produced by Germicides

	Germicide	Zone of Inhibition, Mm.
1.	Merthiolate (Tr. 1:1000)	18.0
2.	Iodine (3.5% solution)	16.0
3.	Iodine (3.5% tincture)	12.0
4.	Mer cresin	12.0
5.	Metaphen (Tr. 1:200)	9.0
6.	Mercurochrome (surgical)	9.0
7.	Mercurochrome (4.0% tincture)	8.0
8.	Mercurochrome (4.0% solution)	6.0
9.	Hexylresorcinol (ST 37)	5.0
10.	Amphyl (undiluted)	4.0
11.	Amphyl (2.0% solution)	3.5
12.	Amphyl (5.0% solution)	3.5

The question arising after the completion of such a series of tests is, obviously, of what significance are