afford the most striking means of differentiation. The calyx of true horehound, which is only about half as large as those of *Ballota acetabulosa* and *Ballota hirsuta*, is tubular, whereas the calyx of both *Ballota* species is nearly funnel-shaped. The margin of the calyx of *Ballota acetabulosa* has 10 to 20 very obtuse lobes, in fact it is almost crenate (Fig. 1-c); this distinguishes it from the dentate margin of *Ballota hirsuta*, whch has 10 to 20 acute lobes (Fig. 1-a); in both species the lobes terminate in very short nearly awl-like teeth barely one-half cm. in length; both thus differ markedly from *Marrubium vulgare*, which, as is well known, has 10 awl-shaped recurved teeth about 2 mm. in length (Fig. 1-b).

Under the microscope the leaves of *Marrubium vulgare* show tufted hairs, which are usually curved or bent and almost sessile (Fig. 2-e). Those of the leaves of *Ballota hirsuta* are usually straight and are somewhat elevated by a multicellular basal stalk (Fig. 2-d). In both cases one hair generally attains a considerably greater length than the others and may contain 2 or 3 cells; this elongation is perhaps more frequent and pronounced in *Ballota hirsuta* than in true horehound. The tufted hairs of *Ballota acetabulosa* have a long, oftentimes much bent central stalk, from which many straight hairs branch (Fig. 2-f). Other types of hairs are present on the leaves of the three species, but they are not especially characteristic. The non-glandular hairs in the throat of the calyces furnish another microscopical characteristic which distinguishes both *Ballota species* from true horehound. In the former these hairs contain tiny prismatic crystals, presumably of calcium oxalate—they are insoluble in acetic acid and soluble in hydrochloric acid. The hairs in the throat of the calyx of *Marrubium vulgare* show no crystals.

No chemical data regarding *Ballota hirsuta* appears to be available in the literature, and it is therefore impossible to state whether it might be valuable as a substitute for horehound in the manufacture of cough drops or other medicinal preparations. It has, however, an agreeable odor and may possibly be a desirable material for use in the manufacture of confectionery. Its similarity in odor to true horehound seemed so striking that for purposes of comparison a small amount of candy was prepared from an infusion of the material. The flavor was not at all unpleasant and very closely resembled that of a candy similarly prepared from genuine horehound.

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THE CULTIVATION OF MEDICINAL PLANTS.*

BY GEORGE P. KOCH.

War with all its horrors, and terrible as the results may be, does produce some good. It stimulates production, compels efficiency, and teaches us to be more self-reliant.

This applies to every phase of our national life, and one of the results of the great world war has been to teach the United States how it may produce the supply of medicinal drug plants necessary to its health and life.

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Before the war most of the crude drugs used in this country were imported and many were supposed to be unsuitable to our climate and soil conditions.

War rendered importation impossible and compelled us to learn how to grow these drug plants in this country, whether conditions were suitable or not.

This has been done, and the United States is now able to grow the more important drug plants within its own borders, in large quantities and at a commercial profit.

Cultivation of medicinal herbs is reported as early as the middle of the sixteenth century, when plants used for medicine were grown in Italian gardens. About sixty years later, a large tract of land was set aside in Paris for a botanical garden, a portion of which comprised the "Jardin Botanique de la Faculty de la Medicine." Then other nations began to devote their attention to the cultivation of medicinal herbs. Medicinal plants have been grown in the United States for the last two centuries, and for many years were termed "healing herbs." Their crude products formed the remedy used. As soon as commercial preparations appeared on the market, many small, private gardens of healing herbs were discontinued, as it was cheaper and more convenient to buy the more standardized preparations than to grow and use the plants. Thus, individuals, companies and corporations devoted their interests to collecting medicinal plants and preparing commercial drugs. There are, however, still many medicinal plants that are grown in a small way in private gardens. These plants are used in cookery, for decorative purposes and, to a small extent, for their medicinal value.

There is a great variety of plants used for medicinal purposes, but the amount of them is very small compared with staple crops, such as corn, wheat and potatoes. Many of the drug plants grew wild, and their leaves, roots or barks were collected and sold to those interested in manufacturing.

As more and more of the wild and virgin soil was brought under cultivation, there was less area for these wild growing herbs. Consequently, as the wild plants disappeared, the prices steadily advanced. With the advance in price to the point where cultivation was profitable, individuals began growing these plants under commercial conditions.

As the cost of production of medicinal plants was considerably less in foreign countries than in the United States, the greater amount of the crude drugs was imported. Hence, drug culture never became a very important phase of agriculture in the United States. The only medicinal plants that were cultivated were small crops yielding volatile oil, and various species of medicinal plants grown by pharmaceutical departments of universities, principally for class work. A few large companies engaged in the manufacture of drugs were carrying on experiments concerning the culture of a few plants. It was not until 1914, when the importation of crude drugs was checked, that we began to realize how dependent the United States was upon other countries for these products. With the steady increased demand for crude drugs and a continued lack of supply, prices advanced rapidly. These high prices furnished a great stimulus for drug raising in the United States. Making easy money by raising drugs, for a time, was a popular newspaper story. Several of the large drug manufacturing houses, State experiment stations and pharmaceutical departments of the large universities, began

extensive experiments to determine to what extent medicinal plant culture could be successfully and profitably carried on in the United States.

The cultivation of some medicinal plants is no more difficult than that of some agricultural plants. The principal objection found in propagating these plants in this part of the country is that it requires considerable hand labor. Hence, as the wages paid are high, the cost of production is usually rather expensive. Thus it was desirable to perfect methods, wherever possible, so that the highest standard of quality of the product in question was always obtained and the most effectual labor-saving methods employed, as by the utilization of machinery.

More or less detailed experiments were made with the five species of drug plants which were most important and most likely to be adapted to the state of Pennsylvania. Practical and the scientific considerations were constantly carried on. The five plants considered were *Atropa belladonna, Hyoscyamus niger, Digitalis purpurea, Cannabis* and *Datura stramonium.*

Belladonna has probably received the greatest amount of consideration by investigators. It requires a long time for belladonna seeds to germinate, and since the growing season in the field is comparatively short, in order that belladonna growing should be successful, it is necessary that these plants be first developed under glass. The germination period for belladonna seeds may be from three to eight weeks, usually only a small percentage germinating in three weeks. Treating the seeds with acids, as shown by Sievers[7] and others, proved of no particular advantage. Some investigators have reported that freezing them hastened germination, while others have found such treatment to be ineffective.

As belladonna plants are grown for some time under glass, and infectious organisms as "damping-off" fungi must be guarded against, the sterilization of the soil to be used is to be recommended.[4] This not only destroys the destructive organisms but it kills weed seeds, which are always numerous. Sterilization, likewise, greatly increases the available constituents of the soil to be utilized by the growing plants.

Belladonna plants will make a very large growth in one season. If the proper care and conditions are given these plants, three pickings of leaves can be harvested. Besides the leaves and roots, it has been found[4] that the stems of belladonna plants can also be utilized. Since three crops of leaves are harvested, it is apparent that this is a vigorous grower, hence, a hearty feeder upon the soil. This being the case, sufficient plant food must always be available for the ready use of the plant. Schneider[6] states that with the particular soil used, no marked increase in yields was realized where fertilizers were applied. Carr[1] reports the contrary and the investigations carried out at our laboratories[4] show conclusively that applying complete fertilizer resulted in very marked increases, namely, 3 to $3^1/_2$ times the yield of those plants receiving no fertilizer treatments. Hence, the application of sodium nitrate, acid phosphate and potash is to be recommended.

When cultivating belladonna under Pennsylvania conditions, it is desirable to plant the seeds in sterile soil under glass about December 20th to January 1st. In about seven weeks plants will be sufficiently large for potting. In order that the cost of production be kept at the minimum, the plants need to be potted but once. Repotting into larger pots is not necessary. As soon as the weather and soil conditions permit, these plants are transplanted into the field.

In the cultivation of belladonna, an important consideration is to successfully control the attacks of insects. Practically all of those insects that are destructive to truck crops are destructive to these plants. Of the chewing insects, the Colorado potato beetle is by far the most destructive, while the green and pink aphids are the most harmful sucking insects.

Hydrocyanic acid fumigation is the most successful and desirable means of controlling all the insect pests while the plants are being propagated in the greenhouse. In the field, chewing insects can be controlled by the various arsenical spray mixtures.[4] The best of these are Paris green and arsenate of lead. For combating aphids, nicotine sulphate, otherwise known as "Blackleaf 40," has been found the most effective. All insect injury can be controlled if proper precautions are taken and the spray applied as soon as any of the destructive factors make their appearance.

In order that the resultant product of dry belladonna shall be of the best quality, the drying should be carried on under the most favorable conditions. Sievers[8] first air-dried samples of belladonna, after which the remainder of the moisture was driven off by drying in a hot air oven. Other investigators report various means of drying. The results which have been obtained at the Mulford Laboratories[4] indicate that in order to secure the most desirable product the leaves of belladonna should be dried at a temperature not above 55 to 60° C.

One reason why belladonna culture did not flourish a few years ago was because it was very difficult to secure viable seeds. Belladonna plants are very prolific seed producers and an average sized plant will easily produce an ounce of clean, dry seed. Hence, we can harvest several pounds of seed from a small number of plants. Most belladonna growers have now learned how and when to collect the seed. In growing belladonna, as with other medicinal plants, it is important to have a product with the active principle as high as possible. It is true that the alkaloidal content of two belladonna plants may be quite different, even if grown under identical conditions of temperature, moisture, soil, fertilizer treatments, etc. This difference is due to the individualism of the respective plants. In like manner the various parts of the same plant will vary greatly in activity. Still further, the leaves of the same plant will show a remarkable difference in percent of alkaloid. This variation, according to Sievers,[8] may be from 0.110 to 0.766 percent. Hence, it behooves us, in order to produce a final product of the highest activity, to select strains of plants producing the highest alkaloid content. These must be cultivated under the most favorable conditions and the crop harvested when the leaves have reached the size at which the most alkaloid is present in them and, at the same time, we get the largest yield possible.

In considering the requirement of the United States Pharmacopoeia for belladonna, a word may be said with regard to the utilization of the stems of this plant in conjunction with the leaves. Since the United States Pharmacopoeia calls for the admixture of no more than 10 percent foreign matter, which might be stems, this will not permit the utilization of all the stems in conjunction with the leaves as they exist on the plant under field conditions, as this ratio is approximately two parts of leaves to one of stems. Investigation of this matter[4] has revealed the fact that the alkaloidal content of belladonna leaves and stems used collectively in their proportion as grown in the field was considerably above the

United States Pharmacopoeia requirement. This is an important factor for practical as well as scientific consideration. It would bring into use the stems, and further, it would facilitate the harvesting, cutting and drying the crude material, and thus reduce the cost of production.

The same method of propagation under glass, germination, potting, planting, fertilization and growing in the field, which were employed in belladonna culture, can be applied in the cultivation of henbane, or *Hyoscyamus niger*, another member of the nightshade family. As henbane is more delicate, it requires a little more skill and caution than belladonna. However, if proper precautions are always taken, from a cultural standpoint, henbane can be grown as successfully in Pennsylvania as belladonna. As with all the other medicinal plants here to be considered, only one year's growth of henbane can be obtained, hence the annual variety is cultivated.

A few of the most important phases may be mentioned in the propagation and treatment of henbane. The plants should have attained considerable size—about 3 inches—before potting. Great care must be exercised when transplanting into the field as the plant should have attained a fair size. This plant does not have the massive root structure which belladonna has, consequently it is more delicate. Similar to belladonna, henbane is a vigorous feeder, hence it is most desirable to have sufficient plant food available for it during the growing season. Insects, especially the potato beetle, are very destructive to henbane. Stockberger[9,10] well expresses it when he says that "leaves of henbane usually suffer severely from attacks of the potato beetle during the first year." We[3] have found that by careful spraying of henbane plants with arsenate of lead (5 pounds to 100 gallons) the plants were able to withstand the attack of these beetles. Paris green applied in all of the ordinary concentrations proved destructive to the plant.

Henbane, like belladonna, produces many seeds. One large plant would produce sufficient seed to plant two or three acres.[3] The mydriatic alkaloid content of the leaves of the annual variety of *Hyoscyamus niger*, which was cultivated at Glenolden,[3] was 0.073 to 0.120 percent, while analysis of the roots and stems was 0.081 percent. These results compare very favorably with the United States Pharmacopoeia requirement, which is 0.065 percent.

Digitalis purpurea is a perennial plant, which was grown rather extensively in European countries and has long been grown in flower gardens in the United States as an ornamental plant. Digitalis grows wild over a very large area of western Washington and Oregon. Up to three years ago this wild plant was considered a very destructive weed, especially in pasture land, and land owners treated it as a weed, pulling out the immense stalks at blooming time, thus preventing its spreading. With the curtailment of the normal supply from abroad, and the advance in market prices paid for digitalis, this weed of the far west was carefully collected and placed upon the market.

Digitalis can be successfully grown in Pennsylvania.[5] Open, well drained soil is preferable, as it is the most natural medium for this plant, and it makes possible early planting in the field. A good crop of digitalis can be grown on a heavy clay loam soil, if sufficient plant food is available.

Probably the most important factor, in growing a successful crop of digitalis, is securing plants. Direct field sowing has not proven satisfactory.[5] Even though

the seeds of digitalis germinate rather quickly, weeds usually get the upper hand. Consequently, it is quite difficult to separate the weeds from the small digitalis plants.

Seeding small $1^3/_4$ inch pots with 6 to 8 viable seeds and allowing the plant from these to grow under glass for 7 to 8 weeks, then planting them in the field when they are from 2 to $3^1/_2$ inches high, has been found to be a most successful method. They make a very vigorous leaf growth, so that at harvesting time, which is just before the heavy frosts, a crop of from 500 to 700 pounds of dry leaves per acre can be collected, and this would be considered a satisfactory yield. Since the winters are usually quite severe in Pennsylvania—at least the soil is frozen to some depth—no attempt is made to grow digitalis as a biennial or a perennial plant. Formerly it was thought that the leaves of the second year's growth were the only ones that could be utilized in the manufacture of drugs. Experimental evidence has demonstrated the fact that the first year's growth of leaves is as active in medicinal principle as the second, hence, they are now used.

The drug plant cannabis, or *Cannabis Indica*, formerly imported, is now successfully grown here on a commercial scale. Imported Indian Cannabis was formerly thought to be the only variety suitable for use in the preparation of medicines. However, cannabis grown by scientific methods in the United States is now extensively used by American drug manufacturers. As with the other medicinal plants, the climate, season and conditions of growth affect the quality of cannabis.

Thus technical skill is necessary in order to produce cannabis of quality. Most of the cannabis culture in the United States is carried on in the Southern states, principally Kentucky and South Carolina. It can be very successfully grown in Pennsylvania. Grown under well cultivated conditions, and with plenty of available plant food, cannabis attains a remarkable height. It was not uncommon to find cannabis stalks on the Mulford Drug Farm from 9 to 10 feet in height. Harvesting such a forest of material would seem, at the outset, a somewhat difficult operation. This difficulty has, however, been conquered. The male plants are first removed, then with an ordinary corn binder the female plants are cut off as high as possible from the ground. The upper one-fourth to one-third of the female plants is then cut into small pieces with an ensilage cutter. By adopting these methods the cost of producing cannabis has been greatly reduced.

Stramonium (*Datura Stramonium*) grows as a weed in nearly all parts of the United States. While as a weed it makes considerable growth, it produces much better under cultivation. It thrives remarkably well on a heavy clay loam soil which is well supplied with manure. Under conditions of cultivation, after planting the seeds, no special care is necessary, other than occasional cultivation, before the plants have attained a too rank growth. Since it has been found[2] that the stems of stramonium, which are very pulpy and succulent, can be employed in conjunction with the leaves, and the alkaloid requirement of the U. S. P. still easily met, it has greatly facilitated the handling of this crop. The plants can be mowed with a mowing machine, ground in an ensilage cutter and then dried.

After we have carefully worked out the methods for the cultivation of these various medicinal plants, the question still presents itself, does it pay to grow these plants? First of all, in growing any crop commercially, whether it is wheat,

potatoes, apples or medicinals, there must be a market for the produce. The next factor to consider is, from which crop can we realize the greatest returns for the capital invested? Hence the grower must first acquaint himself with the market conditions and then, after careful calculation, determine which crop will be most profitable. If medicinal plants have been decided upon as the crop to be grown, and all the prerequisites, capital, market, satisfactory market price, skill, equipment, proper soil, etc., are at hand for the production of such a crop, then the grower must take into further consideration that if too many individuals engage in growing the same crop, the market price will drop below the figures on which he based his profits, and a financial loss will be the result. Under commercial conditions in order to warrant the cultivation of medicinal plants they must yield a greater return than other agricultural crops.

Five medicinal plants have been considered in this paper. Prices for the crude drug of two of them, namely, belladonna and hyoscyamus, are to-day lower by half than those paid for them in December, 1917, at which time the prices for crude drug materials had reached the high mark. We have not been importing any of these five drug plants within the last year, and our consumption—hence the demand—has been much greater than a year and a half ago. This clearly demonstrates that the United States has met the original so-called possible crude drug crisis, and all the demands have been and are being met, by products from plants grown here on a commercial scale.

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THE PREPARATION OF PHENYLCINCHONINIC ACID.*

BY EDWARD D. DAVY.

The cancelling of patent rights on synthetic preparations made in Germany and the issuance of licences to American manufacturers able to produce these

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