2. Rats exhibited an extremely wide variation in susceptibility to diethylene glycol. The two extremes were represented by death in 4 days from 2.5 cc. per Kg. three times daily, and survival for 60 days of daily doses of 7.5 cc. per Kg. In general, those rats which died following the administration of the glycol were found to have suffered extensive liver and kidney damage; whereas, those which survived were found to be normal when sacrificed for microscopic examination. Furthermore microscopic examinations of organs from four rats which received daily doses of 7.5 cc. per Kg. of "Elixir of Sulfanilamide-Massengill" for a period of 41 days showed no pathological changes.

3. The ingestion of 1.0% and 0.3% solutions of diethylene glycol in the drinking water for a period of 175 days had no apparent deleterious effect on growing male and female rats.

BIBLIOGRAPHY.

(1) Kesten, H. D., Mulinos, M. G., and Pomerantz, L., *J. Am. Med. Assoc.*, 109, 1509 (1937).
(2) Holck, H. G. O., *Ibid.*, 109, 1517 (1937).
(3) Geiling, E. M. K., Coon, J. M., and Schoeffel, E. W., *Ibid.*, 109, 1532 (1937).
(4) Cannon, P. R., *Ibid.*, 109, 1536 (1937).
(5) Poe, C. F., and Witt, P. C., *Proc. Soc. Exp. Biol. Med.*, 37, 559 (1937).
(6) von Oettingen, W. F., and Jirouch, E. A., *J. Pharm. and Exp. Therap.*, 42, 355 (1931).
(7) Lepkovsky, S., Ouer, R. A., and Evans, H. O., *J. Biol. Chem.*, 108, 431 (1935).
(8) Haag, H. B., and Ambrose, A. M., *J. Pharm. and Exp. Therap.*, 59, 93 (1937).

STUDIES OF NATIONAL FORMULARY DRUGS.*

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LAPPA.

The purpose of this investigation was to examine the botanical and pharmacognostical portions of the monograph on Lappa in the sixth edition of the National Formulary in order to ascertain whether the facts therein set forth were scientifically correct and to make recommendations to the Revision Committee wherever changes were found necessary.

History.—Lappa or Burdock Root was first introduced into the U. S. P. in 1850 where it appeared in the secondary list under the title of Lappa, and was there defined as "The root of *Lappa minor*, De Candolle." (*Lappa minor* is now known as *Arctium minus*, Bernh.). It remained in the same list with the same definition in the pharmacopœias of 1860 and 1870. In the sixth revision of the pharmacopœia of 1880 it was transferred to the primary list and defined as "The root of *Lappa officinalis*, Allioni (nat. ord. *Compositæ*)." (Allioni's concept for this species now includes *Arctium minus*, Bernh. and *A. Lappa*, L.). The seventh revision of the U. S. P. of 1890 defines it as the root of *Arctium Lappa*, L. and of some other species of *Arctium* (nat. ord. *Compositæ*). In the eighth revision of the U. S. P. (1900) the definition was changed to "The dried root of *Arctium Lappa*, Linné or of other species of *Arctium* (Fam. *Compositæ*) collected from plants of first year's growth."

Lappa was dropped from the ninth revision of the U. S. P. (1910) and admitted into the fourth edition of the National Formulary (1916) with the same definition as appeared in the

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U. S. P. of 1900. The drug has continued to be recognized as official in the National Formulary although its definition was changed in the fifth edition of 1926 of this work to read, "The dried first-year root of *Arctium Lappa*, Linné or of *Arctium minus*, Bernhardi (Fam. *Compositæ*)." In the present sixth edition this definition is continued unchanged.

Burdock Root has been used in domestic and regular medicine for ages as a remedy for the treatment of gout, chronic skin diseases and syphilitic disorders. It was known to Dioscorides and Galen as "*Arkteion*," from whence the Linnean genus name "*Arctium*" was derived. More recently Leconte and Burnier (1927) report successful results from the use of an aqueous extract of this drug externally and pills of the powdered root internally in the treatment of the inflammation of furunculosis (1).

The exact action of Burdock is not completely understood at present owing to the want of pharmacodynamic evidence. Various phases of the chemistry of Burdock Root have been investigated by Weckler (2), Henderschott (3), Trimble (4) and Donaldson (5). Weckler found 8.21% of moisture and 3.67% of total ash. He obtained 0.4% of a fixed oil of an orange color with petroleum benzin (0.5% with ether) which was soluble in absolute alcohol and which turned reddish brown with HNO_3, also 3.25% alcoholic extract, 18.60% water extract, 4% of mucilage with little albumen, 0.965% of resins; inulin, cellulose and lignin. Both Henderschott and Trimble report the presence of a bitter, crystalline glucoside, while Donaldson found 8.6% of a yellow fixed oil. Burnier (*Presse Med.*, 1918) states that Burdock Root must be gathered in the spring, that collected in the fall being inert.

Most of the Burdock Root used in this country is obtained from Belgium and France. Smaller amounts are gathered for the market in this country chiefly from *Arctium minus* and *Arctium Lappa*.

Nomenclature.—The official Latin and English titles "Lappa" are justified on the basis of the custom of naming most drugs after either the genus or specific epithet of the plant representing the source or main source. The U. S. P. of 1850, the first American work on drug standards to adopt that title, recognized De Jussieu's Genus *Lappa* in his Genera Plantarum of 1789, page 173. Linnaeus in his Systema Naturæ of 1753 had previously placed the Burdocks in the genus *Arctium* and in his Species Plantarum named and briefly described the present leading source of the drug, *Arctium Lappa*. Arctium could be used as the official title but we see no sufficient reason for changing a name of such long standing in pharmaceutical literature as Lappa. The botanical origin, *Arctium Lappa*, Linné or *Arctium minus*, Bernhardi are correct names according to the International Rules for the sources of the greater bulk of the drug of commerce.

Both species are native to Europe and Asia and are naturalized and widely distributed in the United States. Since the Formulary recognizes only the first-year root of either species, and since during the first year both species being biennials produce a similar root system and rosette of leaves which cannot readily be distinguished by collectors, therefore, until chemical or pharmacological evidence of the superiority of one over the other shall be forthcoming, we would not recommend any change in the botanical source of Lappa. To limit the source to *Arctium Lappa* would be unwise owing to the fact that *Arctium minus* or Lesser Burdock appears to be more abundant in the United States than *Arctium Lappa* or Great Burdock.

Materials.—The materials employed in this investigation consisted of freshly dug root systems and aerial portions of first- and second-year plants of *Arctium minus* collected in Boston and Worcester, Massachusetts during the fall of 1937 and of herbarium specimens of *Arctium Lappa* and *Arctium minus* in the Herbarium of the Massachusetts College of Pharmacy and Gray Herbarium, also a number of samples of commercial drug obtained from the drug market.

Time of Collection.—In order to ascertain whether the drug should be limited to roots of first-year plants, extraction tests were conducted on samples of roots of both first- and second-year *Arctium minus* collected in Boston in September 1937. The roots were cleaned, and dried at a temperature of 80° C. in the hot air oven, ground and extracted in a continuous extraction apparatus with 95% alcohol for five hours, the extract evaporated to dryness and the residue dried to constant weight at 100° C. and weighed. The second-year root yielded 2.71% and the first-year root 8.61% extract soluble in 95% alcohol.

Purity Rubric.—The N. F. VI limits the percentage of attached leaf bases to not more than 5 per cent. Four determinations of attached leaf bases gave the following percentages:

0.03, 3.55, 6.97, 3.09 (average 3.18%). A change is suggested on the basis of these figures to not more than 4 per cent.

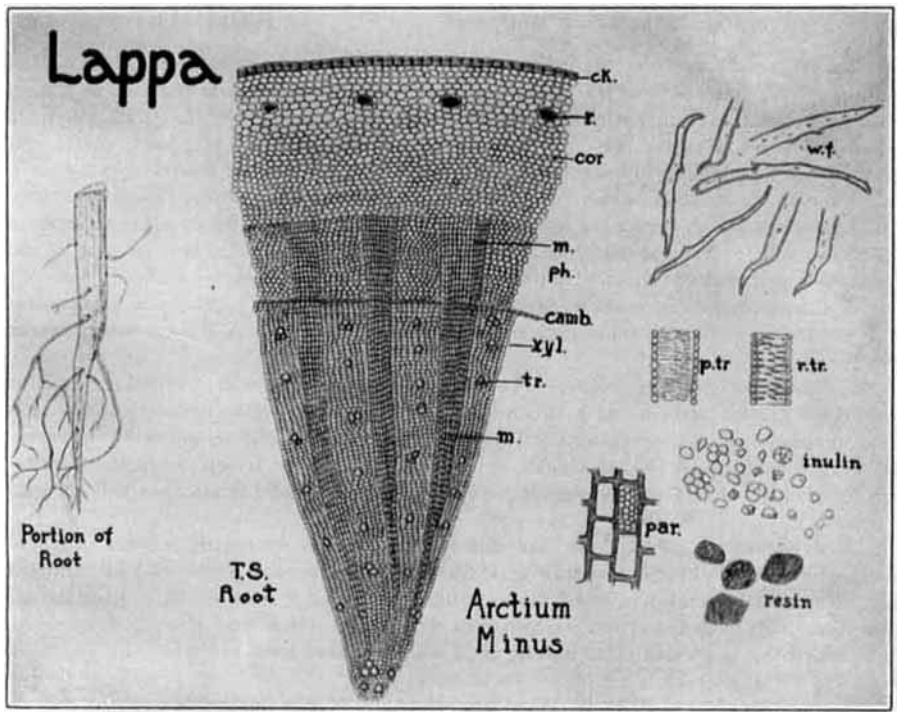

Fig. I.—First-year root of *Arctinum minus*, the chief American source of Lappa. *ck.*, cork; *r.*, resin cells; *cor.*, cortex; *ph.*, phloem; *camb.*, cambium; *xyl.*, xylem; *tr.*, trachea; *m.*, medullary (vascular) ray. On right, elements of powdered root; *wf.*, wood fibers from crown; *p. tr.*, portion of pitted trachea; *r. tr.*, portion of reticulate trachea; *par.*, parenchyma.

The N. F. VI limits the acid-insoluble ash of Burdock to not more than 2%. Duplicate tests made on 2 samples of Burdock Root collected by us in Boston and Worcester, washed and dried before ashing gave the following:

Sample 1	A 0.33%	Sample 2	A 0.93%
	B 0.28%		B 1.17%

Duplicate tests made on 4 commercial samples gave the following results:

Sample 1	A 1.95%	Sample 2	A 2.99%
	B 2.02%		B 2.04%
Sample 3	A 3.37%	Sample 4	A 3.76%
	B 3.89%		B 3.44%

The acid-insoluble residue in each of the commercial samples was of a reddish color and consisted of dirt and tiny pebbles. The average acid-insoluble ash in the six samples was 2.17%. The average acid-insoluble ash in the commercial samples was 2.93%. On the basis of these determinations a change is suggested from 2% to 3%.

Description and Physical Properties.—Unground Lappa: Examination was made of 6 samples of the commercial drug and comparisons made with this portion of the present N. F. monograph. The following variations from the present text were observed.

Burdock Samples.	N. F. VI.
Length: Up to 14.5 cm.	Variable
Diameter near crown: 4 to 18 mm.	5 to 20 mm.
Fracture: Sharp, short and horny	Somewhat horny

Histology.—Microscopic examination was made of first- and second-year roots of *Arctium minus* and of segments of first-year and second-year roots of commercial Burdock in transverse, longitudinal-radial and tangential-longitudinal sections. As a result of this work, the inclusion of a paragraph on structure of first-year root is recommended essentially as follows:

Cork of 1 to 3 layers of brownish, tangentially-elongated cells separated from the cortex by cork cambium; cortex about 30 layers in depth and composed of thin-walled parenchyma containing glistening, amorphous masses of irregularly-angled inulin crystals, the outer region with larger, thick-walled cells containing a yellowish resin; phloem consisting of a narrow zone of phloem strands composed of sieve tubes and of phloem cells rich in inulin, separated by broad phloem rays; xylem of elongated, slender wood wedges and broad wood rays up to 13 cells in width; tracheæ mostly occurring singly and possessing walls with elliptical pits; wood fibers absent, except in crown portion.

Examination of Crown of Root.—The crown portion of a root was prepared for examination in water and in phloroglucin and hydrochloric acid reagent by Schulze's maceration process, resulting in the following observations: There were present thin-walled, uniseriate hairs up to 4 cells in length and up to 140μ in length, spiral tracheæ from leaf bases, pitted tracheæ, beaded parenchyma cells; elongated, non-lignified, wavy, wood fibers with partially beaded walls and slit-like pores.

A portion of the root cut one-half inch from the crown treated by Schulze's process and examined microscopically, did not show wood fibers. Reticulate and pitted tracheæ and tracheids either isolated or imbedded in wood parenchyma were noted. However, at a distance of one-fourth of an inch from the crown, certain cells were noted which were elongated, up to 200μ in length, and which possessed thin, non-lignified walls. These were probably the beginnings of wood fibers.

Second-year Roots.—Examination of transverse and longitudinal sections of this root as well as material prepared by Schulze's process showed that this root differed chiefly from first-year root by the presence of wood fibers throughout the greater portion of its length and a considerably reduced parenchymatous area. The wood fibers were elongated, tapering, up to 688μ in length, averagely 475μ, and up to 24μ in width. The walls were thin, averagely 4μ, the lumen broad, up to 16μ. The fibers were irregular in shape, some showing one or more protuberances on the side walls; others were scythe-shaped with hooked or forked ends. Some of them had oblique pores in their walls which were usually aggregated in groups of 2 to 4 pores; others showed radiating pore canals, visible only partly around the fiber. These fibers occur only in second-year roots and in the crown portion of first-year roots. If more than a very few fibers occur in a sample of Burdock Root, other structures being normal, the presence of second-year root is indicated. As a means of restricting the official drug to first-year roots the introduction of a crude fiber standard into the Purity Rubric paragraph is recommended.

Powdered Drug.—Examination of powdered authentic materials separately in water, alcohol, phloroglucin and hydrochloric acid, and cyanin solution mounts revealed the following variations from the N. F. VI description:

No sphaero-crystals of inulin were found but rather amorphous masses of irregularly-angled inulin crystals, occurring singly or in aggregates, the individual crystals being glistening and rarely up to 10μ in diameter.

It is suggested that "or sphaero-crystals" be deleted from the present N. F. paragraph on the powdered drug and "up to 10μ in diameter" be added after "inulin," also that "few wood fibers" be changed to read "very few wood fibers."

SUMMARY.

1. The National Formulary VI monograph on Lappa has been investigated and suggestions for its improvement have been offered, including changes in the purity rubric and description and physical properties paragraphs.

2. A history is given of the drug and its sources in former editions of the U. S. P. and National Formulary.

3. The second-year root can be distinguished from the first-year root by the presence of characteristic wood fibers throughout the entire root, whereas the first-year root possesses these only in its crown region.

4. The structure of the first-year root has been described.

5. It is recommended that the drug continue to be restricted to the root of first-year plants of *Arctium Lappa* and *Arctium minus*. This recommendation is based upon extraction tests here recorded.

6. It is suggested that a crude fiber standard be introduced into the purity rubric paragraph of the Lappa monograph as a means of eliminating the second-year growth.

REFERENCES.

(1) Kroeber, *Das neuzeitliche Krauterbuch. Leipzig*, 202 (1934).
(2) Weckler, G. A., *Am. J. Pharm.*, 59, 393 (1857).
(3) Henderschott, J., *Proc. Mich. Pharm. Assoc.*, 121 (1887).
(4) Trimble, H., *Pharm. Era*, 133 (1888).
(5) Donaldson, T., *Am. J. Pharm.*, 62, 123 (1890).

CONVALLARIA.

Convallaria majalis or Lily-of-the-Valley has been used as a medicine in certain specific cardiac conditions and in the treatment of dropsy for several centuries. Its use by the Germans is discussed by Dr. Pietro Matthioli in Commentaries on the Materia Medica of Dioscorides, Venice, 1621. Lloyd (1) states that, in Russia, it was investigated by the medical profession as early as 1880, having long been used in dropsy by the people. It was introduced into the U. S. P. of 1890 under the title of "Convallaria" where it was defined as "the rhizome and roots of *Convallaria majalis* (nat. ord. *Liliaceæ*)" and again became official in the U. S. P. of 1900. It was deleted from the U. S. P. of 1910 and admitted into the fourth edition of the National Formulary of 1916 which recognized it under the title of "Convallaria Radix." This edition also made the dried inflorescence of Lily-of-the-Valley official under the title of "Convallaria Flores." Both of these drugs were retained in the fifth edition of the National Formulary but Convallariæ Radix alone was recognized in the sixth edition of 1936.

The histology of the drug has been described by Youngken (2). Crosbie (3), in commenting upon the structure of the rhizome and root, failed to find the collenchyma in the hypodermis of the rhizome mentioned in the N. F. V.

The purpose of this study was to investigate the accuracy of the statements in the present N. F. monograph and more especially the pharmacognostic aspects of the monograph.

Materials.—The materials used in this investigation consisted of entire plants gathered at Arlington, Mass. by the senior author and of a number of samples of commercial drug collected from the market during 1936, 1937 and 1938 and botanically authenticated.

Nomenclature.—The Latin title, "Convallariæ Radix" and the corresponding English title, "Convallaria Root" and the synonym, "Lily-of-the-Valley Root" are found to be scientifically incorrect since the drug consists of the rhizomes and roots, not merely the roots alone. In fact the rhizome portion represents the greater bulk of this drug. We suggest that the Latin and Eng-