# SCIENTIFIC SECTION

## BIOASSAY OF ACONITE AND ITS PREPARATIONS. 2. THE PHARMACOLOGY AND PHARMACOGNOSY OF VARIOUS SPECIES OF ACONITUM.*

BY JAMES C. MUNCH AND H. H. CROSBIE.

The therapeutic use of aconite dates from the report of Störck (20) in Vienna in 1763. It was made popular by Fleming in London 75 years later (8). Clinical reports have shown (19) that aconite is of value in slowing the heart in sthenic fevers and as a peripheral stimulant in neuralgia and rheumatism. However, reports in the literature do not indicate which of large number of varieties of aconite have been employed. Investigations by pharmacologists and chemists have shown that different varieties differ in physiological action and chemical composition. The International Protocol (14) has specified *Aconitum Napellus* L. as the official variety for international use and most of the National Pharmacopœias have adopted this variety.

U. S. Pharmacopœia X gives a pharmacognostic description of aconite root (15). Our experience has shown that this is very inadequate in several particulars. It leaves us in doubt regarding the characteristics of "modified endodermis." We have been wondering how this would appear? We have also been wondering whether anyone has ever seen authentic *Aconitum Napellus* which is truly fusiform? Such a sample has never come to our attention. Products which by a strict interpretation of the Pharmacopœial description would be passed, in reality should be rejected. Some of the pharmacognostic characteristics of *Aconitum Napellus* are wanting and pharmacologically many products are inferior. The U. S. Pharmacopœia X description will exclude Indian and Japanese aconites without difficulty but a more precise description is necessary to keep out some European aconites. In a recent shipment of 1300 pounds of "Aconite" which was invoiced as "Aconitum Napellus" we were able to select a number of tubers which differed in gross appearance from the bulk of the shipment. These selected tubers had no physical characteristic which greatly disagreed with U. S. Pharmacopœia description. Physiological assay showed the average potency of the entire shipment to be twice the U. S. Pharmacopœia X minimal requirement (that is to say, the M. L. D. was 20 mg. per Kg. when injected subcutaneously into guinea-pigs, whereas the U. S. Pharmacopœia X standard for toxicity is 40 mg. of aconite root per kilogram (15)). The selected parent and daughter tubers were each one-third of this strength (the M. L. D. was 60 mg. per kilogram). As a further precaution roots were separated into those having light and dark fractures. No difference in physiological activity was found in any sample; the M. L. D. was 60 mg. per kilogram.

Figures 1 and 2 show at once that these selected tubers are not normal *Aconitum Napellus*. A cross section of the daughter root is shown in Fig. 3. An almost perfect circular cambial zone is noted. Had U. S. Pharmacopœia IX (16)

* Scientific Section A. PH. A., Rapid City meeting, 1929.

been in force this product would have been excluded. U. S. Pharmacopœia X (15) permits "in the cambium zone a 2- to 4-rayed collateral vascular bundle at each angle or a number of small bundles in an irregular circle." A cross section of the weak mother root is shown in Fig. 4 where the same circular cambial zone

Fig. 1.—Weak daughter tubers, half size.

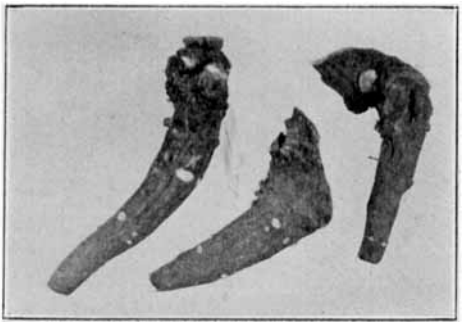

Fig. 2.—Weak parent tubers, half size.

is apparent. Smaller auxiliary bundles are noted between the main bundles which have the "Gestrechte V" (21) form that seems to characterize all aconites. For comparison Fig. 5 shows the cross section of what we take to be a sample of normal *Aconitum Napellus* with a most distinctly stellate cambial zone. There

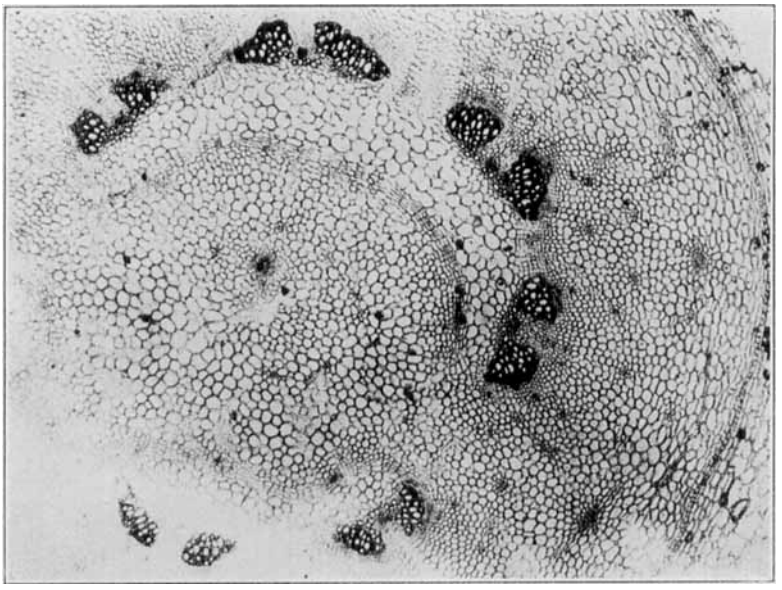

Fig. 3.—Weak daughter tubers, cross section.

seems to be no doubt that aconite is coming into the American market as a mixture of species and that even unskilled workmen can pick out weak roots by their outward appearance. However, the official description is so indefinite that these weak products cannot be rejected on the ground that they are "not U. S. P."

This is by no means an isolated case. Figure 6 shows another aconite which obviously is not normal *Aconitum Napellus*. The microscopic structure as shown

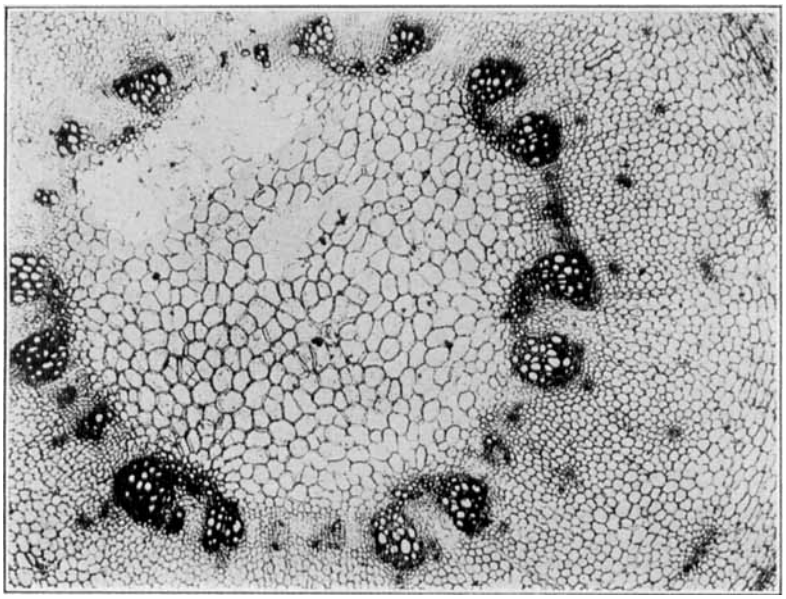

Fig. 4.—Weak parent tubers, cross section.

in Fig. 7 is widely different from *Aconitum Napellus*. Among other amazing features the presence of bast fibres is noted. This particular sample assayed 180%

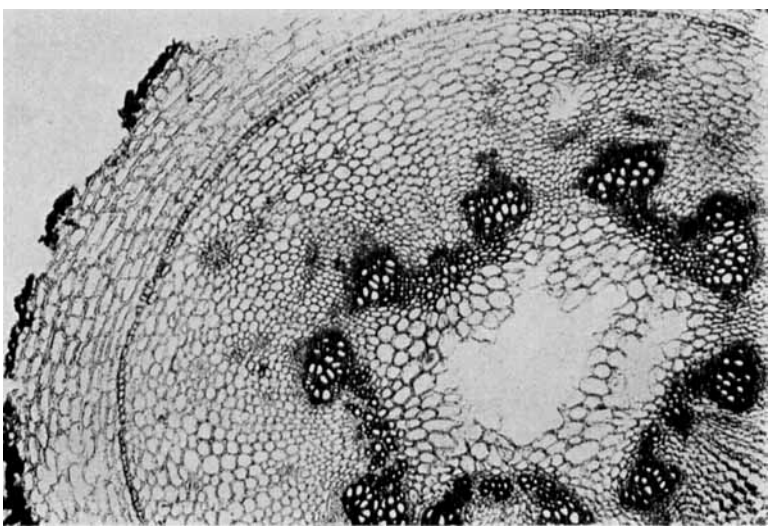

Fig. 5.—Aconitum Napellus, cross section.

physiologically. Another type of structure is shown in Fig. 8 which discloses two concentric rings of tracheal bundles, the main ones being connected radially.

The presence of bast fibers in the bundles is shown in greater detail in Fig. 9. The British Codex requirement (2) that bast fibers be absent might be worth considering in the official description.

Yet another variety from Italy, offered as *Aconitum Napellus*, is shown in Fig. 10. Here we see clusters of daughter tubers, a characteristic which is most distinctly not normal for *Aconitum Napellus*. Tschirch (21, page 579) indicates that *A. Störckianum* Rchb. has this peculiarity. This sample also contained long, slightly tapering tubers, most emphatically not normal in shape.

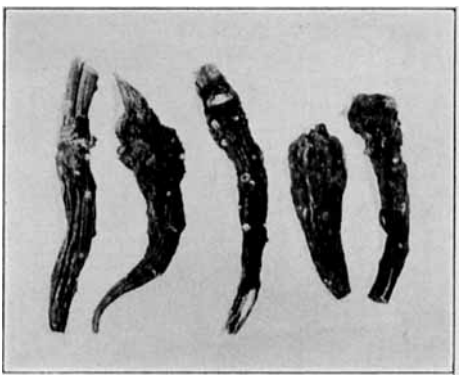

Fig. 6.—Aconite of abnormal structure, half size.

All of our sections were taken from the same region in each tuber where the diameter was about 5 mm. We chose this particular region as it was most convenient for photographic purposes.

The samples of aconite depicted represent material which is found in shipments invoiced as "Aconitum Napellus." It appears evident that species other than *Napellus* are being offered in contravention of U. S. Pharmacopœia and International Protocol requirements or that we are dealing with hybrids. If we study

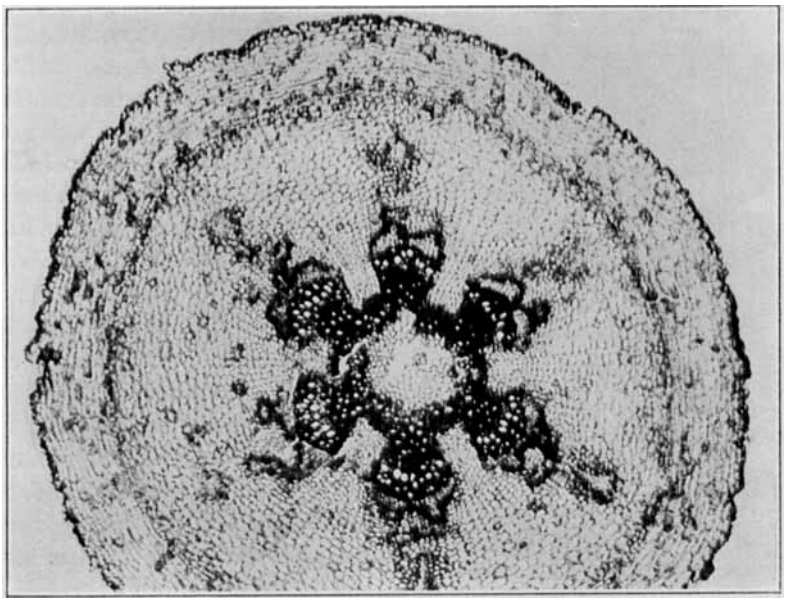

Fig. 7.—An Aconite with bast fibres, cross section.

these cross sections we must admit either that we are dealing with different species or that the microscopic study of structure is a waste of time. A study of the literature leaves one with the impression that the contradictions found there are caused

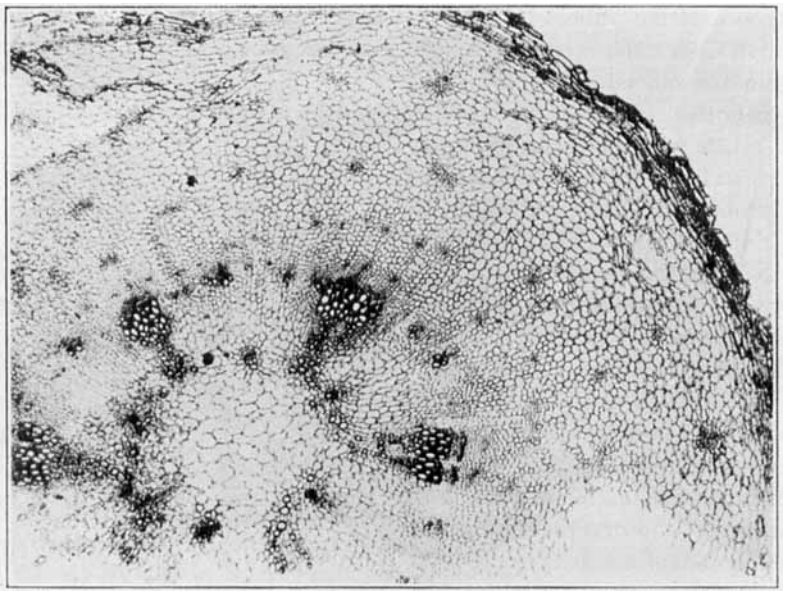

Fig. 8.—Aconite sold as Napellus, cross section.

by neglecting to identify the species used. To obtain definite and authentic information on this subject the authors believe that the pharmacognosy and pharmacology of an authentic specimen of *Aconitum Napellus* should be followed under carefully controlled conditions, starting from the seed. Material should be collected in the flowering stage when identification is certain and a thorough microscopic examination should be made, as well as a pharmacological study.

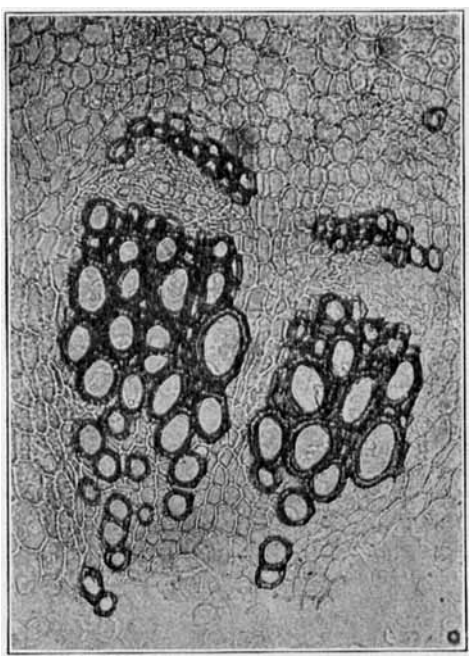

Fig. 9.—Aconite: vascular bundle, showing bast fibres.

Pharmacological information does not indicate whether hybrids of *Aconitum Napellus* may be safely substituted for the true strain, even if the International Protocol permitted this to be done. Fraser (10) states that only two or three of the 150 species of aconite have been studied pharmacologically. He reports observations upon two Indian species, *A. Heterophylloides* and *A. Nagarum*. The predominant alkaloid in both was pseudoaconitine which Wright (22, 24) and Dunstan and Carr (6) have shown to predominate in *A. Ferox*. *A. Lycoctonum*, a yellow blooming variety from middle Europe, contains lycaconitine (4, 12) and myocto-

nine (18). *A. Septentrionale*, from northern Norway, contains lappaconitine, septentrionaline and cynoctonine (17). Apparently all of these varieties resemble pseudoaconitine in their physiological action. The principal action is exerted upon respiration and death is due to respiratory depression (3, 9).

*A. Napellus* is the source of aconitine (3, 7, 23). The Japanese variety, *A. Japonicum* Fisheri, yields japaconitine (13, 22, 24). The Indian variety, *A. Chasmanthum*, yields indaconitine (5). *A. Spicatum* Stapf from India contains bikhaconitine (1, 5) which resembles indaconitine but is somewhat more toxic. Japaconitine, indaconitine and bikhaconitine appear to resemble aconitine physiologically, the predominant action being depression of the heart and death resulting from circulatory failure (9). Gray (11) lists only three varieties growing in America. These three are reported as *A. Noveboracense* Gray, growing in New York and Ohio; *A. Reclinatum* Gray, growing in Virginia and the southwestern Alleghenies; and *A. Uncinatum* L. reported in Pennsylvania and Wisconsin. In addition, several other varieties have been listed in pharmacognostic literature. However, no reports of pharmacological studies upon any of these varieties have been found. The data given by Boehm (1) have been consolidated in the following table. The figures represent lethal doses in milligrams per kilogram. The methods of administration are not given but it is assumed that injections were made intravenously into rabbits and cats, subcutaneously into guinea-pigs and into the lymph sacs of frogs.

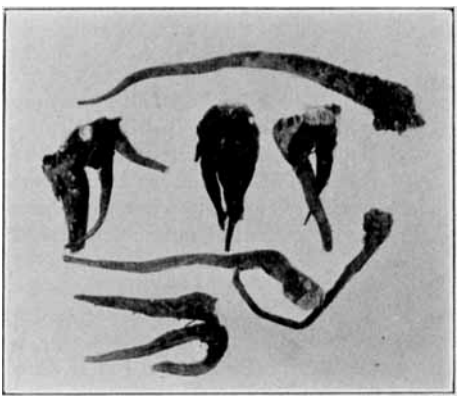

Fig. 10.—Abnormal Aconite from Italy, half size.

| | M. L. D. in milligrams per kilogram. | | | |
|---|---|---|---|---|
| Product. | Rabbits. | Cats. | Guinea-pigs. | Frogs. |
| Aconitine | 0.085–0.011 | .. | 0.11 | 0.075–1.15 |
| Japaconitine | 0.065–0.105 | .. | 0.10 | 0.55 –1.0 |
| Pseudoaconitine | 0.038–0.046 | .. | 0.045 | 0.11 –1.2 |
| Indaconitine | 0.12 | .. | ... | 1.2 –1.25 |
| Bikhaconitine | 0.087 | .. | ... | 1.25 |
| Lycaconitine | ... | 12 | ... | 200 –400 |
| Lappaconitine | ... | 16 | ... | 8 –16 |
| Septentrionaline | 23. | .. | ... | ... |

Information is not given stating the quantity of alkaloid in each crude drug, so the comparative toxicities of the crude drugs cannot be calculated.

Until identified material is available for pharmacological investigation it would appear advisable to rigidly comply with that specification of the International Protocol, which has been embodied in U. S. P. X, and use only *Aconitum Napellus*.

## CONCLUSION.

1. Many shipments of material labeled "Aconitum Napellus" are adulterated with other species which are less active physiologically.

2. The pharmacognostic description of aconite root in U. S. Pharmacopœia X is somewhat indefinite in several particulars and fails to exclude these adulterants.

3. A fundamental research should be undertaken upon authentic aconite grown under controlled conditions and collected at the time of flowering in order to draft a correct and comprehensive description of this drug. Pharmacological studies should be made simultaneously to determine the true physiological activity at various stages of growth.

## BIBLIOGRAPHY.

(1) R. Boehm, "Die Aconitingruppe," in A. Heffter, "Handbuch der Experimentallen Pharmakologie," 2 (1920), 283–314.

(2) British Pharmaceutical Codex, "Aconiti Radix, B. P." (1923), 62–64.

(3) J. T. Cash and W. R. Dunstan, "The Pharmacology of Pseudaconitine and Japaconitine considered in relation to that of Aconitine," *Phil. Trans.*, 195 (1903), 39.

(4) Dragendorff and Spohn, "Die Alkaloide des Aconit. Lycoctonum," *Pharm. Zeitschr. f. Russland* (1884), No. 20–24, through (1).

(5) W. R. Dunstan and A. E. Andrews, "Contributions to Our Knowledge of the Aconite Alkaloids. Part XVI. Indaconitine, the Alkaloid of Aconitine Chasmanthum," *J. C. S.*, 87 (1905), 1620–1636.

(6) W. R. Dunstan and F. H. Carr, "Contributions to Our Knowledge of the Aconite Alkaloids. Part XIV. On Pseudoconitine," *J. C. S.*, 71 (1897), 350–359.

(7) Duquesnel, *Compt. Rend.*, 73 (1871), 207.

(8) A. Fleming, "An Inquiry into the Physiological and Medicinal Properties of the Aconitum Napellus," London (1845).

(9) T. R. Fraser, "Note on Aconitine and Pseudoaconitine," Report 7th Brit. Assn. Science (1873), 128.

(10) T. R. Fraser, "A Contribution to the Pharmacology of Aconitum Heterophylloides, A. Nagarum and A. Napellus," *J. Pharm. Exp. Ther.*, 9 (1916), 43–56.

(11) Asa Gray, "A Handbook of the Flowering Plants and Ferns," Article on "Aconitum," 7th Edition (1908), 406–407.

(12) Jacobowsky, "Beiträge zur Kenntnis der Alkaloide des Aconit. Lycoctonum. I. Lycaconitin," Diss. Dorpat. (1884), through (1).

(13) Paul and Kingzett, "The Alkaloids from Japanese Aconite," *Pharm. J. and Trans.*, 8 (1877), 172–174.

(14) The Pharmacopœia of the United States of America, Tenth Decennial Revision (1925), XLIX.

(15) *Ibid.*, 31.

(16) The Pharmacopœia of the United States of America, Ninth Decennial Revision (1915), 29.

(17) H. V. Rosendahl, "Pharmakologische Untersuchungen über Aconitum Septentrionale Koelle," *Arb. pharmakol. Instit. Dorpat*, XI–XII (1895), through (1).

(18) Salmonowitz, "Beiträge zur Kenntnis der Alkaloide des Aconit. Lycoctonum. II. Myoctonin," Diss. Dorpat. (1884), through (1).

(19) Torald Sollmann, "A Manual of Pharmacology," 3rd Edition (1927), 546.

(20) Antonius Störck, "Libellus, quo demonstratur, Stramonium, Hyoscianum, Aconitum non solum tuto posse exhiberi usu interno hominibus," *Vindobonae* (1762).

(21) A. Tschirch, "Angewandte Pflanzen-Anatomie," 1 (1889), 415. Handbuch der Pharmakognosie, Tuber et Folium Aconiti, III, 1 (1923), 573.

(22) C. R. A. Wright and A. P. Luff, "The Alkaloids of the Aconites. Part II. On the Alkaloids Contained in Aconitum Ferox," *J. C. S.*, 33 (1878), 151–174.

(23) C. R. A. Wright, "The Alkaloids of the Aconites. Part I. On the Crystallizable Alkaloids Contained in Aconitum Napellus," *J. C. S.*, 31 (1877), 143–156.

(24) C. R. A. Wright and A. P. Luff, "The Alkaloids of the Aconites. Part IV. The Alkaloids of Japanese Aconite Roots," *J. C. S.*, 35 (1879), 387–399.