SCIENTIFIC SECTION

THE QUALITY OF ACONITE.

BY H. B. HAAG AND L. W. HAWKINS.

About fifteen or more years ago a series of articles appeared from this and other laboratories bearing upon the variability in physiological activity of the then available supply of aconite preparations. That the physiological potency of one specimen might be seven times that of another was shown by Haskell (1), and his co-workers (2, 3, 4), although all of the preparations in a series might assay practically within the official chemical requirements of the Pharmacopœia then in force. Similar findings were characteristic of most of the papers concerned with the subject (5, 6). Because the majority of investigators found the chemical method of assay to be an unreliable index as to physiological activity, this procedure was discarded in the tenth revision of the United States Pharmacopœia in favor of the bio-assay test, employing guinea-pigs. The value of this method of standardizing aconite has been quite definitely established by several groups of workers (7, 8, 9, 10, 11).

It has been known for some time that aconitine, by far the most active principle in aconite, is rather unstable, and it has also been shown that preparations of aconite, unless prepared in acidulated media, readily undergo deterioration (12, 13, 14, 15). However, reasoning on the basis that adoption of the guinea-pig method of assay renders standardization of aconite more accurate, the impression is held in some quarters that the activity of the tincture now on the market is probably more uniform than it was when the preparation was assayed according to its aconitine content, as outlined by earlier pharmacopœias.

During the course of another investigation our attention was called to the great variation in activity which existed between two specimens of tincture of aconite submitted to this laboratory for examination. Hence, it was thought that it might prove of interest to compare the quality of the tinctures of aconite now available for clinical use with that of preparations examined in this laboratory when the U. S. P. VIII was in force; and, in light of the recent work of Swanson, *et al.* (12, 13, 14), with special reference to the hydrogen-ion concentration of the various tinctures.

Four specimens of tincture of aconite manufactured under the names of well-known pharmaceutical houses were obtained from local jobbers. It is interesting to note that, although the present Pharmacopœia has been official for over four years, the product of one prominent manufacturer bore a label stating that the drug had been standardized chemically. This is possibly explained upon the assumption that the local dealer had not renewed his supply for quite some time; nevertheless this is an indication of laxness from some source. This is to be deplored, not that it is particularly important in the case of the almost therapeutically ostracized aconite, but because the same indifference might be employed with other much more important drugs, such as digitalis preparations, which are liable to deterioration. It might be stated at this point that this particular preparation showed the lowest activity of any tested. A fifth specimen was obtained

from the Practice Drug Store of the School of Pharmacy of this institution, and although it had been presented as a museum specimen, and hence probably not intended for clinical use, it was far more active than the one mentioned above, which was being offered for distribution to the dispensing pharmacists. Because of the inability to obtain a specimen of tincture of aconite manufactured by one of the larger pharmaceutical houses from local jobbers, the sixth specimen was obtained directly from the manufacturer (listed as specimen number one in tables).

The assays were made upon guinea-pigs as directed by the U. S. P. X, the M. L. D. being taken as the smallest amount, injected subcutaneously, which would cause death in two out of three guinea-pigs in six hours. The following table illustrates the results obtained:

TABLE I.

Specimen number.	M. L. D. (cc. × Gm. bodyweight).	Per cent below minimal U. S. P. requirements.
1.	0.00045	0.0
2.	0.00045	0.0
3.	0.0005	10.0
4.	0.0006	25.0
5.	0.00075	40.0
6. plus	0.0045 plus	90.0 *

The label on specimen number three bore the statement that the minimal lethal dose (M. L. D.) was 0.0004 cc. × Gm. bodyweight (which is the mean between the upper and lower limits of the Pharmacopœia), that on number one and four stated that to overcome deterioration, acid had been added, number five was the museum specimen, while number six was the one bearing the lable indicating that it had been standardized upon its aconitine content. Judging from the statement on the labels, the alcoholic content was about the same for all of the specimens. Inasmuch as number five was a museum specimen and consequently never would have been offered for dispensing, this tincture should not be considered so seriously as the others. The criticism might be raised that whereas number six was probably prepared prior to the present pharmacopœial requirements, it should likewise not be considered in this analysis. However, we were concerned with the supply of aconite which was being offered to pharmacists for use by them in prescription work, and there is no doubt but that this was being sold to these dispensers. Whereas guinea-pigs tolerated well ten times the maximum U. S. P. dose no further attempt was made to determine the exact toxicity of number six; this would have required evaporation of the tincture, thus bringing in questionable factors. The table shows that of the preparations only two assayed, and then only barely, within the pharmacopœial requirements, which state that the M. L. D. should be between 0.00035 and 0.00045 cc. of the tincture per Gm. bodyweight when tested upon guinea-pigs. This is no indictment against the guinea-pig method of assay, but rather shows that (*a*) proper procedures should be utilized to stabilize the preparation, and (*b*) manufacturers should see to it that their agents exercise more judgment in the care of their stocks to the end that the products offered for sale be of sufficiently recent manufacture to indicate that when made at least, they conformed to the latest revision of the pharmacopœia.

In a paper having the same title as the present one, Haskell in 1916 (1) included

the following table which gives an index to the quality of the preparations then on the market. For purposes of comparison the results of the present investigation are also tabulated again. Identical numbers in each of the series do not necessarily indicate that the tinctures were obtained from the same sources.

TABLE II.

1916.		1929-1930.	
Specimen number.	M. L. D. (cc. × Gm. bodyweight).	Specimen number.	M. L. D. (cc. × Gm. bodyweight).
1.	0.00033	1.	0.00045
2.	0.00065	2.	0.00045
3.	0.00065	3.	0.0005
4.	0.00150	4.	0.0006
5.	0.00240	5.	0.00075
6.	0.00240	6.	plus 0.00450

While the average activity of the specimens available in 1929–1930 is somewhat greater than that of the 1915 specimens, the range of variation is even greater than in the older series. Omitting the last two specimens in the 1929–1930 table, the average then obtained is somewhat encouraging, although even then the figure is below the U. S. P. minimum requirements.

The publications of Swanson and others (12, 13, 14) clearly indicate that deterioration of aconite preparations depends upon acidity of the finished product. Tinctures prepared with an acidulated menstruum are stable, and those acidulated after ordinary manufacture show much less deterioration than those prepared according to the U. S. P. X. It has also been demonstrated that for preparing a stable tincture or fluidextract of aconite the finished product should have an acidity corresponding to a p_H value of from 2.5 to 3.0. This led us to examine the hydrogen-ion concentration of the samples which we had tested biologically. In determining this, the quinhydrone method was employed, the tincture being diluted with an equal volume of double-distilled water which had been brought to boiling immediately prior to use. The determinations were made at room temperatures.

Table III gives the results, along with the table showing activity.

TABLE III.

Specimen number.	p_H.	M. L. D. (cc. × Gm. bodyweight).
1.	3.1	0.00045
2.	3.13	0.00045
3.	4.15	0.0005
4.	4.28	0.0006
5.	4.49	0.00075
6.	4.57	plus 0.00450

Lack of information as to the age of the various specimens detracts somewhat from the importance of these results. However, it is significant that those preparations having the greatest hydrogen-ion concentration also possessed the greatest physiological activity. Assuming that all were of approximately the same activity when manufactured, these findings emphasize the importance of Swanson's suggestion (14) that to insure stability, the product should have a numerical p_H value of not more than 3.00.

SUMMARY AND CONCLUSIONS.

1. From this study it appears that although the guinea-pig method of assay is now official, tinctures of aconite now offered for clinical use still show great variation in physiological activity.

2. There exists a close relationship between stability and hydrogen-ion concentration, as had previously been shown by Swanson. In view of this it would seem highly desirable that, if the preparation is to be retained in the Pharmacopœia, the product should be adjusted to the proper p_H as recommended by Swanson.

3. As in the case of all drugs subject to deterioration, a statement should be made on the labels of these preparations giving the date of manufacture and the time limit, if possible, beyond which the drug should not be used.

4. Inasmuch as it has been shown that digitalis leaf is far more stable than any of its liquid preparations (16) it would seem desirable that studies be made to ascertain whether the same holds true for aconite.

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THE HYDROLYSIS OF ARSENOUS IODIDE.*,**

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Reference books differ in their statements regarding the rate and extent of hydrolysis of arsenous iodide in aqueous solution. Hager's "Handbuch" (1) states that the aqueous solution is neutral, and that on long standing, or more rapidly on heating or in concentrated solution, hydriodic acid and arsenous acid appear in the solution. According to the U. S. P. (2), "one Gm. of arsenous iodide is soluble in about 12 cc. of water at 25° C. with partial decomposition" and "a freshly prepared aqueous solution of the salt is colorless, but upon standing, it

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