SUMMARY

Briefly summarizing, it would appear that: The cat unit for the digitalis preparations examined is, on the average, considerably higher if chlorobutanol anesthesia is substituted for ether in the performance of the assay by the cat method of Hatcher and Brody.

The cat unit, as determined on cats under the influence of chlorbutanol anesthesia, is practically identical with that obtained by the use of animals under dial-urethane anesthesia.

Profound etherization of the animals prior to administration of dial-urethane for anesthesia does not lead to a reduction of the size of the cat unit to any marked extent if a non-volatile anesthetic, dial-urethane, is subsequently given in dose sufficient to prevent struggling.

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# The U. S. P. XI Digitalis Standard

*By Orlo F. Swoap and Marvin L. Pabst**

The adoption in the Eleventh Decennial Revision of the United States Pharmacopœia which became official June 1, 1936, of a standard reference digitalis powder to replace ouabain as a standard for digitalis preparations naturally led to the question of whether any pronounced changes in the activity of official preparations had occurred in the transition from the U. S. P. X.

The growing confusion among physicians and others with regard to the strength of official U. S. P. XI digitalis preparations in terms of the familiar U. S. P. X standard has been recently pointed out by Wright, Fahr, and Lewis (1) in their correspondence to the editor of the *Journal of the American Medical Association*. It therefore, appears timely for us to call attention to conclusions reached in our laboratory on this matter.

We have used the U. S. P. XI Reference Digitalis Powder (No. 3057 × 915921) in this laboratory since it was obtainable. This powder carries the correction factor or relationship that 0.0745 Gm. is equivalent to 1 "U. S. P. Digitalis Unit" or 0.1 Gm. of the International Standard Digitalis Powder. We wish to call particular attention to the fact that this correction factor has always been applied in preparing extracts from the powder so that in all cases we have used a strictly U. S. P. XI Standard Tincture.

Our first tests, when we received this powder in April, 1936, indicated the U. S. P. XI Standard Tincture to be approximately 125 per cent U. S. P. X. Other laboratories (2), (3), (4) had reported that the International Standard was about 125% of the U. S. P. X standard and it was therefore considered that the digitalis standard had been raised 20–30 per cent over the U. S. P. X level. Later parallel runs between the U. S. P. XI standard tincture digitalis and ouabain indicated this value to be somewhat higher. Hence, it was decided to directly compare the U. S. P. XI standard tincture to ouabain at various times and thus by a series of comparative tests, spread over a sufficient time interval, to accurately determine the relationship between these two digitalis standards.

EXPERIMENTAL

Our method of testing these preparations has been that specified in the U. S. P. XI, pages 397–398.

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We store frogs in a refrigerator at a temperature of 5–10° C., in trays supplied with running water, and then place them in a constant-temperature tank as specified in the U. S. P. XI (temperature 20° C. ± 1.0° C.). Our refrigerator and constant-temperature equipment is that supplied by the George H. Wahmann Manufacturing Company of Baltimore, Maryland, and corresponds to that in use at the Food and Drug Administration and several other laboratories. We have found, however, that due to the tremendous variation in seasonal susceptibility of the frog (*R. pipiens*), it has been impossible to hold to the specifications of the U. S. P. XI, page 398, which state that the injected dose of diluted digitalis standard tincture shall be equivalent to not less than 0.003 cc. and to not more than 0.008 cc. of the original standard preparation per Gm. of body weight of frog (see Table I). Runs are made on groups of ten frogs for each single dose and the 50 per cent Minimum Systolic Dosages are determined from the observed mortalities by the use of Trevan's Curve (5), which has been shown by others (6), (7) to hold for digitalis preparations and ouabain. This 50 per cent M. S. D. value is then used for comparison of standard and unknown and the determination of percentage values. All runs reported in this paper have been made in parallel on both the standard tincture and ouabain.

Our work has now covered a period of two years, and during its progress other laboratories reported figures to indicate that the digitalis standard had been raised approximately 50–60 per cent in changing from U. S. P. X to U. S. P. XI (8), (9), (10). The average of our values as shown in Table I indicates that U. S. P. XI digitalis preparations are 160 per cent U. S. P. X.

Table I.—Comparison of U. S. P. XI Standard Tincture Digitalis to Ouabain Using the U. S. P. One-Hour Frog Method

| | U. S. P. XI Standard Tincture Digitalis | | | Ouabain | | | |
|---|---|---|---|---|---|---|---|
| Date | Dose Cc./ Gm. | Mortality Per Cent | 50 Per Cent M. S. D.[a] Cc. | Dose Mg./ Gm. | Mortality Per Cent | 50 Per Cent M. S. D.[a] Mg. | Per Cent XI of X |
| 3–15–37 | 0.0045 | 70 | 0.00414 | 0.00060 | 40 | 0.000637 | 185 |
| 3–15–37 | 0.0040 | 60 | 0.00384 | 0.00065 | 40 | 0.000690 | 216 |
| 3–22–37 | 0.0040 | 45 | 0.00412 | 0.00070 | 50 | 0.000700 | 204 |
| 3–22–37 | 0.0040 | 50 | 0.00400 | 0.00070 | 50 | 0.000700 | 210 |
| 3–24–37 | 0.0040 | 40 | 0.00424 | 0.00070 | 60 | 0.000672 | 190 |
| 4–28–37 | 0.0040 | 50 | 0.00400 | 0.00070 | 30 | 0.000790 | 237 |
| 8–10–37 | 0.0090 | 50 | 0.00900 | 0.00080 | 30 | 0.000903 | 120 |
| 8–10–37 | 0.0090 | 40 | 0.00954 | 0.00090 | 40 | 0.000954 | 120 |
| 9–24–37 | 0.0085 | 30 | 0.00959 | 0.00075 | 40 | 0.000795 | 100 |
| 9–24–37 | 0.0095 | 40 | 0.01008 | 0.00080 | 60 | 0.000767 | 91 |
| 9–28–37 | 0.0095 | 50 | 0.00950 | 0.00075 | 20 | 0.000929 | 117 |
| 9–28–37 | 0.0095 | 40 | 0.01008 | 0.00090 | 40 | 0.000954 | 114 |
| 11– 9–37 | 0.0075 | 60 | 0.00719 | 0.00080 | 40 | 0.000848 | 141 |
| 11– 9–37 | 0.0070 | 50 | 0.00700 | 0.00085 | 50 | 0.000850 | 146 |
| 12–17–37 | 0.0050 | 40 | 0.00531 | 0.00070 | 50 | 0.000700 | 158 |
| 12–23–37 | 0.0050 | 50 | 0.00500 | 0.00070 | 50 | 0.000700 | 168 |
| 12–23–37 | 0.0050 | 30 | 0.00564 | 0.00070 | 40 | 0.000743 | 158 |
| 12–28–37 | 0.0050 | 50 | 0.00500 | 0.00070 | 40 | 0.000743 | 178 |
| 12–28–37 | 0.0050 | 40 | 0.00531 | 0.00075 | 40 | 0.000795 | 180 |
| 1–13–38 | 0.0050 | 40 | 0.00531 | 0.00070 | 50 | 0.000700 | 158 |
| 1–13–38 | 0.0055 | 40 | 0.00583 | 0.00070 | 40 | 0.000743 | 153 |
| 1–26–38 | 0.0050 | 40 | 0.00531 | 0.00070 | 30 | 0.000790 | 179 |
| 1–26–38 | 0.0055 | 40 | 0.00583 | 0.00080 | 50 | 0.000800 | 165 |
| 2– 8–38 | 0.0050 | 50 | 0.00500 | 0.00080 | 40 | 0.000848 | 203 |
| 2– 8–38 | 0.0050 | 30 | 0.00564 | 0.00085 | 50 | 0.000850 | 181 |
| 2–10–38 | 0.0055 | 50 | 0.00550 | 0.00085 | 40 | 0.000902 | 197 |
| 2–10–38 | 0.0055 | 40 | 0.00583 | 0.00090 | 80 | 0.000795 | 164 |
| 2–25–38 | 0.0055 | 50 | 0.00550 | 0.00085 | 50 | 0.000850 | 185 |
| 2–26–38 | 0.0055 | 80 | 0.00486 | 0.00085 | 40 | 0.000902 | 222 |
| 3– 3–38 | 0.0050 | 80 | 0.00442 | 0.00085 | 40 | 0.000902 | 245 |
| 3–25–38 | 0.0060 | 60 | 0.00576 | 0.00095 | 60 | 0.000911 | 190 |
| 4– 1–38 | 0.0055 | 50 | 0.00550 | 0.00090 | 50 | 0.000900 | 196 |
| 4– 1–38 | 0.0055 | 50 | 0.00550 | 0.00090 | 40 | 0.000954 | 208 |
| 4–27–38 | 0.0065 | 70 | 0.00598 | 0.00095 | 70 | 0.000875 | 176 |
| 4–27–38 | 0.0060 | 50 | 0.00600 | 0.00090 | 30 | 0.001017 | 203 |
| 5– 3–38 | 0.0060 | 60 | 0.00576 | 0.00095 | 60 | 0.000911 | 190 |
| 5– 3–38 | 0.0060 | 60 | 0.00576 | 0.00095 | 50 | 0.000950 | 198 |

Table I.—(*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5-13-38 | 0.0060 | 30 | 0.00667 | 0.00095 | 50 | 0.000950 | 168 |
| 5-13-38 | 0.0070 | 40 | 0.00743 | 0.00095 | 80 | 0.000839 | 136 |
| 5-25-38 | 0.0090 | 70 | 0.00828 | 0.00100 | 80 | 0.000884 | 128 |
| 6-16-38 | 0.0080 | 50 | 0.00800 | 0.00095 | 70 | 0.000875 | 131 |
| 6-16-38 | 0.0080 | 40 | 0.00848 | 0.00090 | 50 | 0.000900 | 127 |
| 7- 7-38 | 0.0085 | 60 | 0.00815 | 0.00090 | 80 | 0.000795 | 117 |
| 7- 7-38 | 0.0085 | 60 | 0.00815 | 0.00080 | 40 | 0.000848 | 125 |
| 7-12-38 | 0.0085 | 70 | 0.00782 | 0.00085 | 50 | 0.000850 | 130 |
| 8-16-38 | 0.0095 | 35 | 0.01039 | 0.00090 | 40 | 0.000954 | 110 |
| 8-16-38 | 0.0100 | 60 | 0.00959 | 0.00095 | 30 | 0.001073 | 134 |
| 9- 8-38 | 0.0085 | 50 | 0.00850 | 0.00090 | 70 | 0.000828 | 117 |
| 9- 8-38 | 0.0085 | 60 | 0.00815 | 0.00080 | 50 | 0.000800 | 118 |
| 9-20-38 | 0.0080 | 40 | 0.00848 | 0.00080 | 70 | 0.000737 | 104 |
| 9-20-38 | 0.0085 | 40 | 0.00902 | 0.00075 | 40 | 0.000795 | 106 |
| 11-17-38 | 0.0070 | 80 | 0.00618 | 0.00075 | 50 | 0.000750 | 146 |
| 11-17-38 | 0.0060 | 50 | 0.00600 | 0.00075 | 60 | 0.000719 | 144 |
| 11-29-38 | 0.0050 | 30 | 0.00564 | 0.00070 | 60 | 0.000672 | 143 |
| 12-21-38 | 0.0045 | 40 | 0.00477 | 0.00065 | 60 | 0.000623 | 156 |
| 12-21-38 | 0.0050 | 50 | 0.00500 | 0.00065 | 50 | 0.000650 | 156 |
| 1-11-39 | 0.0045 | 30 | 0.00508 | 0.00065 | 30 | 0.000734 | 173 |
| 1-31-39 | 0.0045 | 30 | 0.00508 | 0.00070 | 70 | 0.000644 | 152 |
| 1-31-39 | 0.0050 | 70 | 0.00460 | 0.00065 | 50 | 0.000650 | 170 |
| 2-15-39 | 0.0045 | 60 | 0.00432 | 0.00065 | 60 | 0.000623 | 173 |
| | | | | | | Average | 160 |

[a] As calculated from Trevan's Curve (5).

An examination of this table shows a tremendous divergence of results from the low value of 91 per cent X to the high value of 245 per cent X. These variations far exceed experimental error and appear to have a bearing on the time of year that the comparisons were made. By plotting the daily average percentage values U. S. P. X for the standard tincture, it is easily seen that this appears to be in the nature of a seasonal variation. Further work on this matter is being continued.

Our work thus shows that in order to arrive at any definite comparison of the U. S. P. X and XI standards for digitalis, observations must be made over a relatively long period of time. Our indication that the U. S. P. XI standard tincture digitalis is 160 per cent U. S. P. X is in excellent agreement with that of Rowe and Pfeifle (10), who have reported a value of 151 per cent U. S. P. X covering a one-year period. It is interesting to point out that our work was started at a point where Rowe and Pfeifle left off and had been in progress a year before the details of their work were published. If their values in Table I of their paper (10), page 183, were plotted against time, it would appear that our curve is a direct continuation of their curve.

The work of both laboratories, covering a three-year period, would therefore indicate that, in changing from U. S. P. X to U. S. P. XI, the potency of official digitalis preparations has been increased 50 to 60 per cent.

During the course of the experiments here described, the U. S. P. XI Standard Reference Digitalis Powder No. 3057 × 915921, the Canadian Standard Digitalis Powder No. 1135, and the International Standard Digitalis Powder (1936) were compared using their appropriate factors.

Table II.—Comparison of Official Digitalis Standards

| Date | Preparation | Per Cent International Tincture | |
|---|---|---|---|
| 9-28-37 | International Standard Tincture Digitalis | 100 | |
| | U. S. P. XI Standard Tincture Digitalis | 106.1<br>105.3 | av. 105.7 |
| | Canadian Standard Tincture Digitalis | 100.0<br>106.1 | av. 103.1 |

The results given in Table II, based on two comparisons made on the same day, indicate that the present U. S. P. and Canadian Digitalis Standards are approximately equal to the International Standard.

Ouabain was also included in the above test permitting the comparison in terms of U. S. P. X values. At the date of this assay, the International Standard Powder (1936) was found to be 109 per cent U. S. P. X, the U. S. P. XI Standard Powder 116 per cent U. S. P. X, and the Canadian Standard Powder (No. 1135) 113 per cent U. S. P. X. These values again show the equality of the three Digitalis Standard Powders. The low U. S. P. X values have been explained in the first part of this paper (see Table I).

The limited results as shown in Table II are in agreement with the U. S. P. XI statement that the present U. S. P. and International Digitalis Standards are identical in potency. This would indicate that the International Standard, at the time of its adoption, was set at a much higher level than previously accepted clinical standards.

SUMMARY

The U. S. P. XI Digitalis Standard has been compared to the U. S. P. X Digitalis Standard in a series of parallel runs extending over a period of two years.

The results show that the U. S. P. XI Digitalis Standard averages about 50 to 60 per cent stronger than the U. S. P. X Digitalis Standard.

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# A Recent Substitute for Jalap*

*By Heber W. Youngken*

A little more than a year ago the writer received a sample of a root from a pharmaceutical manufacturer who claimed to have purchased it as "Jalap," but which after having been made into a preparation yielded a product so unlike that which the manufacturer was accustomed to recognizing as the Jalap preparation that his suspicions were aroused. Never before had Jalap been found to yield so low a percentage of resin.

The sample forwarded for identification consisted of transverse segments of a root, the cut surfaces of which possessed a dirty white to pale brown color and exhibited concentric rings of bundles. The segments were lighter in weight than Jalap cut similarly. A cursory examination with a hand lens failed to disclose any evident resin cells.

Cross and longitudinal sections were prepared from it and examined in water, chloral and in phloroglucin-HCl mounts. These showed it to possess a starch- and crystal-bearing parenchyma imbedded in which were a concentric series of open collateral bundles. Typical resin cells, closely arranged, tracheæ with bordered pores, rosette aggregates of calcium oxalate and characteristic starch grains such as Jalap possesses were absent. It differed from Poke, Beet, Amaranthus, Levant and Mexican Scammony, Turpeth Root, Piptostegia and other roots exhibiting concentric circles of bundles with which the writer was familiar. The only tangible clues from a microscopic examination of its structure were the presence of numerous raphides of calcium oxalate, many of which occurred in bundles within crystal cells of the parenchyma, and its possession of a concentric series of secondary collateral bundles.

A search of the literature of pharmacognosy failed to reveal anything recorded which corresponded with this sample.

A possible clue remained. If this material was marketed as "Jalap," it may have been shipped from Jalap-producing Mexico. In thinking of some of the plants commonly found growing there, *Mirabilis Jalapa* flashed to mind. Upon looking up the literature on the anatomy of the axis of this plant, I came upon a brief reference in Solereder's Systematic Anatomy of the Dicotyledons (1). Raphides of calcium oxalate and the concentric series of bundles were there mentioned as occurring in *Mirabilis* species. I obtained some roots of *M. Jalapa* from the Medicinal Plant Garden of the University of Minnesota through the kindness of Professor Fischer. Upon sectioning one of these and comparing its histology with that of the

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