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The Standardization of Digitalis and the Potency of American-Grown Digitalis

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THE STANDARDIZATION OF DIGITALIS AND THE POTENCY OF AMERICAN-GROWN DIGITALIS*

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This study was undertaken by us, at the suggestion of Dr. Janeway, in the endeavor to insure digitalis preparations of maximum and known effectiveness for use in the wards. These desiderata are so rarely fulfilled in any hospital that the results we have obtained seem worthy of a brief report.

METHODS OF STANDARDIZATION

Two methods of biologically standardizing digitalis preparations are commonly employed: the so-called "frog" method, and the so-called "cat" method. After a number of preliminary experiments it was found that the frog method was less reliable for the standardization of the infusion than the cat method: the latter method was therefore exclusively employed in this work. The technic followed by us was suggested by Hatcher and Brody, and is somewhat similar to that described by them, and consisted in determining the minimal fatal dose per kilogram weight of cat, the drug being injected slowly into the femoral vein. Our procedure was briefly as follows:

A healthy cat was anesthetized with ether, and a cannula inserted into a femoral vein, subsequently a minimum amount of ether being administered, just sufficient to keep the animal

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*From the Medical Clinic of the Johns Hopkins Hospital, and Pharmacological Laboratory of the Johns Hopkins University.
1. It is advisable to make three toxicity experiments with each preparation and to take the average. As a rule wide variations are not encountered.
Ten c.c. of the infusion of digitalis were slowly injected into the vein in the course of five minutes, and thereafter 1 c.c. every two minutes until the death of the animal. The total amount of the drug injected divided by the weight of the animal gave the strength of the preparation in terms of so-called “cat units.” The following protocol will serve as an illustration:

Experiment, April 30, 1915. Cat weighing 2.6 kg. Cannula in left femoral vein, light ether anesthesia.
3:20 p.m. experiment begins. Pulse 160 per min.
Slow injection of infusion digitalis.

<table>
<thead>
<tr>
<th>Time</th>
<th>Action</th>
<th>Drug</th>
<th>Pulse</th>
<th>Respiration</th>
</tr>
</thead>
</table>
| 3:25 | Finished injection of 10 c.c. | Pulse 140 per minute
| 3:27 | Injected 1 c.c. | | 120 |
| 3:29 | Injected 1 c.c. | | 100 |
| 3:31 | Injected 1 c.c. | | 72 (rapid) |
| 3:33 | Injected 1 c.c. | | 72 (vomits) |
| 3:35 | Injected 1 c.c. | | 72 |
| 3:37 | Injected 1 c.c. | | 60 |
| 3:39 | Injected 1 c.c. | | 148 |
| 3:41 | Injected 1 c.c. | | 160 |
| 3:43 | Injected 1 c.c. | | 160 |
| 3:45 | Injected 1 c.c. | | 180 |
| 3:47 | Injected 1 c.c. | | 168 |
| 3:49 | Injected 1 c.c. | | 240 |
| 3:51 | Injected 1 c.c. | | 240 |
| 3:53 | Injected 1 c.c. | | 240 |
| 3:55 | Injected 1 c.c. | | Irregular, very rapid |
| 3:57 | Injected 1 c.c. | | Irregular, very rapid |
| 3:59 | Injected 1 c.c. | | Pulse dead: heart in systole |

Total amount of infusion = 26 c.c.
Therefore lethal dose = \[ \frac{26}{2.6} = 10 \text{ c.c. per kg.} \]

By this method different infusions of digitalis prepared from two batches of Allen’s English leaves were assayed: the one from the stock of the pharmacy of the Johns Hopkins Hospital, the other an infusion procured from a well-known pharmacy in New York. The lethal dose of the former was found to be 13.5 c.c. per kilogram, that of the latter, 7.5 c.c. per kilogram. This difference in potency could be accounted for only in two ways: either by differences in the method of preparation or by variations in the intrinsic quality of the leaves.

DIFFERENCES IN POTENCY DUE TO METHOD OF PREPARATION

A comparison was made between a New York infusion of digitalis and an infusion from the same stock of leaves prepared by our own pharmacist. The lethal dose of the New York preparation was 6.6 c.c. per kilogram. The lethal dose of our own infusion from
the same leaves was 9 c.c. per kilogram. Four days later the same preparations, having been kept on ice, were restandardized, and gave the lethal doses of 6.8 c.c. and 9 c.c. per kilogram, respectively, showing that the preparation did not deteriorate rapidly on standing, a fact which has been pointed out recently by Hatcher.

These figures indicated clearly a difference in potency due to the method of preparation. The New York technic for preparing the infusion was then ascertained\(^3\) and applied to our own stock of English leaves. The lethal dose of this infusion was found to be 11.1 c.c. per kilogram of cat. An infusion made from the same leaves by the method formerly employed by our pharmacist gave a lethal dosage of 13.5 c.c.

In order to ascertain still further how great a difference in potency of infusions may result from variations in the methods of preparing them, our pharmacist, Dr. Wahl, prepared three infusions from the same lot of Allen's English leaves, by slightly different pharmacutic methods. Infusion 1 was prepared according to the U. S. Pharmacopeia.\(^4\) Infusion 2 was made by macerating the leaves with water plus 10 per cent. dilute alcohol, instead of adding the alcohol to the finished product as directed in the U. S. Pharmacopeia. Infusion 3 was prepared by macerating the leaves with boiling water in a closed flask, and gently beating the contents of the flask during the whole process of extraction. The lethal dose of Infusion 1 was found to be 11.4 c.c., that of Infusion 2, 9.5 c.c., and that of Infusion 3, 10.6 c.c. per kilogram weight of cat. Thus it will be seen that a considerable variation in the potency of an infusion of digitalis may result from differences in methods of preparation.

**VARIATIONS DUE TO THE SOURCE OF THE LEAVES**

The difference in the potency between the New York infusion and our infusions just described could not be entirely explained by variations in the method of preparation, but were also obviously due to differences in

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3. The method of preparing the infusion employed at Johns Hopkins is the official method of the U. S. P. The New York technic differed from this in some details which need not be gone into in this place.

4. Although the U. S. P. gives specific direction for preparing the infusion of digitalis, we have good reason to believe that those directions are not always followed. Compare Alpers: Jour. of Am. Pharmaceut. Assn., June, 1915, p. 715.
the inherent qualities of the leaves used. The next step in the investigation was therefore to assay infusions of digitalis prepared by a uniform method from various lots of digitalis leaves obtained from various sources. Great variations in the strength of the products were noted.

It was found that an infusion prepared according to the U. S. Pharmacopeia from our stock of English leaves yielded a product with the lethal dose of 13.5 c.c. That of an infusion from another lot of English leaves was found to be 9.6 c.c., while still another lot of English leaves yielded an infusion, the lethal dose of which was 8.7 c.c. per kilogram. An infusion prepared from some German digitalis leaves found in the hospital pharmacy proved very inferior in quality, giving a lethal dose of 19 c.c. per kilogram weight.

**POTENCY OF AMERICAN LEAVES**

It was especially interesting to find that certain American grown digitalis leaves yielded a product of a very high quality. Two lots of American leaves were assayed by us. One was a supply of Wisconsin leaves kindly presented by Dr. George B. Roth of the Hygienic Laboratory in Washington. The second was obtained from Dr. E. Kremers of the Pharmaceutical Experiment Station, University of Wisconsin. The first yielded an infusion with a lethal dose of 7.6 c.c., and the second an infusion with a potency of 7.8 c.c. per kilogram weight of cat. It is evident that both infusions made from the American grown leaves were superior in potency to those made from our stock English and German leaves, and in fact superior to all other leaves assayed by us. We have in America, therefore, a digitalis which is unsurpassed. Through the kindness of Dr. Kremers a supply of Wisconsin leaves was secured and is now being used exclusively in the wards of the Johns Hopkins Hospital.

**THE MORAL.**

These investigations strikingly emphasize the need of standardization of digitalis. Variations in lethal dose from 6.6 to 19 c.c. per kilogram weight—approximately 300 per cent.—were found in infusions prepared from these various leaves. Certainly this is greater than should be tolerated by the profession.
Yet in all probability still greater variations exist in leaves purchased in the open market.

Standardization reveals the strength of the digitalis preparation and permits of graded dosage — more or less — according to the potency of the preparation. The physician’s duty to his patient does not end with the prescribing of digitalis. Plainly it is incumbent on him to secure digitalis effects if the case is a suitable one. This is more likely to be accomplished if the potency of the preparation is known.

We are also brought face to face with another fact, that the name of this or that firm does not always insure potency or digitalis effect. As we have shown, American leaves can be secured which are unsurpassed. The answer to the question of potency is to be found in standardization, which is essential to the best treatment.