# THE DETERIORATION OF DIGITALIS EXTRACTS.

BY HERBERT C. HAMILTON.

A recent publication on this subject by Pittenger and Mulford Jr.[1] is so revolutionary in character that while it would require a rather long series of experiments to cover the ground fully, a preliminary note on the subject seems called for because these results would lead one to infer that the tincture is practically worthless.

It is a well-known fact that digitalis has not yet been prepared in any absolutely stable form adapted to clinical use. The reason for this instability is still a matter of conjecture. Bourquelet[2] and Choay[3] recognizing the presence of enzymes in the fresh leaves considered them to be the cause of the deterioration, because of enzyme action on the glucosides. The remedy suggested was that of exposing the crude drug before drying, to the action of strong alcohol vapors which killed the enzymes, dehydrated the drug and hastened the drying process, all of which are undoubtedly valuable but also more or less impracticable steps. That this is not the remedy, however, is demonstrated by the deterioration of the fluidextract, the tincture and the extract which have been extracted with alcohol strong enough to kill or to precipitate any enzymes present in the drug.

Some experiments in this laboratory carried over a number of years indicate that the presence of certain constituents of unknown character are largely but not entirely responsible for the observed instability. This, however, is reserved for publication later.

The object of this preliminary note is to call attention to data either already published or accumulated through years of close association with the extraction and testing of digitalis and to pave the way for a further publication of fresh data bearing directly on the point at issue, namely, whether digitalis is really as unstable as these results would indicate. If it were true that this valuable agent is so unstable, in many cases it would be practically worthless before it reaches the shelves of the druggist. This however is inconceivable since clinically the tincture is considered as valuable as any of the digitalis preparations.

Summarizing the data submitted by Pittenger and Mulford Jr., their results are shown in the following table:

| Menstruum | 50% alcohol. | 50% alcohol. | 80% alcohol. |
|---|---|---|---|
| Character of drug | Not defatted. | Fat-free. | Fat-free. |
| Average loss on 5 samples in 8 months | 47.8% | 22.8% | 40.7% |

NOTE: These percentages of loss are based on the original assay.

From this one might conclude that a tincture is of little value unless made by extracting fat-free leaves with 50 percent alcohol, since the fat-free tincture with 80 percent alcohol is apparently no more stable than that with less alcohol. It seems improbable however, that either the higher percentage of alcohol or the absence of fats is responsible for the great loss in the third series.

Hale[4] found the official fluidextracts, which are not fat-free, to have lost only an average of 6.6 percent in two years.

Roth[5] observed an average loss of activity in 7 samples of fat-free tinctures of Digitalis of 14 percent in 6 months. Of this number two showed no loss while two others suffered an exceptionally high loss.

Houghton and Hamilton[6] published the results of a series of experiments on deterioration which was summarized as follows:

LOSS OF POTENCY OF DIGITALIS PREPARATIONS WITH AGE.

| | No. sample. | Av. No. H. T. U.'s. per cc. when mfg. | Years later. | Av. No. H. T. U.'s. | Av. yearly loss, %. |
|---|---|---|---|---|---|
| Prep. Extract..... | 11 | 260 | 5 | 160 | 8 |
| Fl. Ext. U. S. P. 7th Rev..... | 8 | 72 | 6 | 55 | 4 |
| Fl. Ext. U. S. P. 8th Rev..... | 11 | 55 | 3½ | 35 | 10 |
| Tincture U. S. P. 8th Rev..... | 8 | 7 | 3 | 5 | 9 |

From the results in the above table and some other data not included the authors concluded:

1st. That a maximum average loss of 10 percent a year can be expected in tinctures or fluid extracts of digitalis.

2nd. That an alcoholic content of more than 50 percent in the extracting menstruum not only more completely extracts but also more nearly preserves the activity of digitalis.

This has been demonstrated so conclusively that the 9th Revision of the U. S. P. eliminates the low alcoholic menstruum and some manufacturers discarded it after only a short trial.

It seems improbable therefore that tinctures with this low alcoholic content would be uniformly found more stable than when extracted with 80 percent alcohol whether the drug was fat free or not. One cannot avoid the thought that perhaps each of the investigators quoted, obtained exceptional results due to certain unusual conditions; further, that no data either good or bad should be accepted as representing the average condition of digitalis after any particular period of aging.

Goodall[7] summarizes some results of his as follows:

"Tincture of digitalis probably retains its full activity for one year but after that period deterioration of its potency to an important extent is likely to take place." This sounds like a reasonable conclusion, which, however, may not be verified by any single set of experiments.

The following data was obtained by my colleague, L. W. Rowe, from retests of six tinctures after an average period of six and one-half months. The tinctures were in every case extracted with 70 percent alcohol and in two cases fat-free drug was used.

These assays were carried out by the M. L. D. Frog-heart Method.[6]

SUMMARY OF ASSAYS OF TINCTURE OF DIGITALIS.
(U. S. P. MENSTRUUM.)

| Number. | Drug. | 1st test. | 2nd test. | Percent loss. | Age. |
|---|---|---|---|---|---|
| A | Fat-free | St'd | 90 | 10 | 8 mo. |
| B | Not defatted | 110 | 90 | 19 | 7½ mo. |
| C | Not defatted | 200 | 130 | 35 | 5½ mo. |
| D | Not defatted | 160 | 130 | 19 | 5 mo. |
| E | Fat-free | St'd | St'd | 0 | 8 mo. |
| F | Not defatted | 140 | 80 | 43 | 6 mo. |

Average loss on 6 samples—21 percent.
Average loss on fat-free samples—5 percent.
Average loss on other samples—29 percent.

The preceding data show very clearly that:

1st. The degree of deterioration varies with different lots.

2nd. The fat-free tincture made with 70 percent alcohol—two out of six samples—is apparently less subject to deterioration than that from the original drug.

3rd. The deterioration of tincture of digitalis is not so uniformly rapid as isolated experiments would indicate.

BIBLIOGRAPHY.

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(4) Hale, *Hygienic Laboratory Bulletin* No. 74.
(5) Roth, *Hygienic Laboratory Bulletin* No. 102.
(6) Houghton and Hamilton, *Am. Jour. of Pharmacy*, Oct. 1909.
(7) Goodall, *Br. Med. Journal*, 1912, Vol. I, p. 887.

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## ESTIMATIONS OF MINUTE QUANTITIES OF EPINEPHRIN IN ANESTHETIC HYPODERMIC TABLETS.

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The chemical assay of such tablets is apt to be unsatisfactory, partly because of the small quantities involved, but mainly because the color-reactions of epinephrin are not always reliable in the presence of other substances.

A biologic assay is much more rapid, and possesses very fair accuracy. The most suitable quantitative method for this purpose consists in the intracutaneous injection of a dilute solution into the skin of the human forearm. The quantity of epinephrin is judged by the extent, intensity and duration of the blanching, as compared with the effects of a known solution, injected at the same time. If the solution contains an anesthetic, the quantity of epinephrin may also be judged by the duration of the anesthesia. This is a useful check on the blanching.

The solution should be very dilute. In my experiments I employed a dilution of epinephrin of 1 : 800,000. This was easily distinguishable from a dilution of 1 : 1,600,000. Other skins may do better with somewhat different concentrations. The dilutions should be made with a boiled 1 percent solution of sodium chloride.

The method of injection is simple. One or 2 Cc. are drawn into a Luer syringe, having a very fine needle. The skin of the inner surface of the forearm is cleansed with a pledget of cotton moistened with alcohol. The point of the needle is thrust *into*, not under, the skin, holding the needle at a very slight angle. Enough of the solution (about 0.2 to 0.4 Cc.) is injected to raise a wheal of about 7 mm. diameter—the exact quantity or size of the wheals is not very important, if all are made nearly alike. Three injections are made of each solution, across the arm. The next solution is then injected in the same manner, about an inch distant. The sensation is tested with a bit of cotton, twisted to a point. A sketch is made of the area of blanching. The observations are repeated at intervals first of 5 minutes, later of 10, 20 and 30 minutes, until a fair comparison is secured. It is advisable to make one of the known solutions of the same strength as the sample to be tested, and another of one-half this strength.

The injections are practically painless, but the skin may remain slightly swollen and hardened for some days.

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