

STANDARDIZATION OF DIGITALIS—A PRELIMINARY REPORT.*

BY ROBERT A. HATCHER, M.D.

Some of those present will remember that Apocynum and Euonymus were dismissed from the Pharmacopoeia because it was held that no safe and effective dose could be given. Oral doses of these drugs equal to many times the fatal vein dose may be administered to animals without inducing any effects in many cases. Convallaria behaves similarly. The absorption of strophanthus and strophanthin is also imperfect; if the single daily of strophanthus—0.06 Gm. every four hours—were absorbed promptly it would prove almost immediately fatal, in fact, one could not administer it every four hours for an entire day, as that would be equal to about twice the average fatal vein dose for a man if his susceptibility is equal to that of the cat.

The daily proof of the poor absorbability of strophanthus is had in the fact that the dose given in the Pharmacopoeia for it is the same as that for digitalis, though the Pharmacopoeia requires that strophanthus shall be just one hundred times as active as digitalis. In other words, if one gives an effective dose of strophanthus he must give far more than the patient could possibly withstand should absorption occur.

Experience has taught us the danger of administering strophanthus by the mouth, and certain clinicians no longer use strophanthus orally. I am firmly convinced that many patients have died from the immediate effects of strophanthus, death being attributed to cardiac disease.

So, there is a firm basis for the continued belief in the superiority of digitalis among the more careful clinical observers, since it shows the *most nearly* uniform absorption and clinical effects of any of the drugs of the group. It is not my purpose to undermine the confidence in an old friend, but rather is it my purpose to show that Digitalis is a sort of Jekyll and Hyde, inasmuch as its constituents are not all of the readily absorbable type.

During the course of an investigation undertaken at this time for another purpose I hit upon an extremely simple and easy method of separating the digitalis principles into two groups. One of these may be termed, for convenience, the Chloroform-soluble group, and the other the Water-soluble group. The best method of separating them has not been worked out in all its details, and it presents a number of minor problems, but it may be described as follows: The digitalis in powder is exhausted with water on a water bath, the infusion is filtered, the filtrate concentrated to a syrupy consistence and precipitated with a large excess of alcohol, the alcohol is expelled, the residue taken up in water and the solution shaken several times with chloroform. The chloroformic solution is distilled and the residue taken up in diluted alcohol.

I have received a number of specimens of digitalis tincture from clinicians in well known hospitals, with the request that I test them because they failed to induce the usual effects of digitalis. In every case I found the tinctures fairly active.

The most striking case of this sort will be described briefly. Dr. Wedd, working in the service of Dr. Carter, in the Cleveland City Hospital, sent a speci-

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men of tincture of digitalis for examination because of the failure to secure any toxic effect with total amounts of as much as 149 Cc. administered to a patient, weighing 140 pounds, during a single course of treatment. This amount merely caused slowing. I found the tincture to be active by the biologic test.

The chloroform-soluble fraction varies in the percentage of the total active constituent, but the specimen just described showed an unusually low percentage, this fraction constituting only one-fourth of the total activity of the leaf. At the other extreme in the series thus far tested, is a specimen placed in alcohol by Professor Newcomb immediately after gathering a leaf of the first year. In this the chloroform-soluble constituent constituted about 65 percent of the active constituents.

It is my purpose to examine specimens of the leaf obtained from various sources, and variously treated, both from the first and second year, in order to determine whether one can be found of constant composition, or that which yields constantly the highest percentage content of the more absorbable constituent.

I have been fortunate in securing the coöperation of growers and dealers and hope to be able to report much progress during the coming year.

One specimen of fluidextract at least 38 years old was fractioned, and while the amount available was too small for satisfactory study (especially as it involved a probable accident) it seems that the content of the chloroform-soluble constituent in this specimen is very high.

The work raises numerous problems which cannot be discussed now, but it seems clear that the higher the digitoxin content (if digitoxin is present in the leaf) the lower should be the biologic activity measured by the official assay, but the more active by oral administration. It seems probable from previous work done in our laboratory that the water-soluble constituent is relatively more actively emetic than the chloroform-soluble. Not only is the chloroform-soluble fraction absorbed more readily than the water-soluble, but it is almost certainly more lasting in its effects, in other words, its action probably persists for as many weeks as that of the other in days.

I believe that we must assay digitalis with reference to the content of this more readily absorbable fraction, and that a specimen containing a high percentage of this fraction will be more active clinically than one showing a greater total activity but with a low percentage of this fraction.

Incidentally, I believe that this chloroform-soluble fraction may be made available for intravenous use, since it mixes perfectly with water. The permanence of such mixtures has not been sufficiently studied.

DETERIORATION OF HIGH TEST AMERICAN-GROWN DIGITALIS.*

BY J. F. O'BRIEN AND J. P. SNYDER.

In the Fall of 1916 we received a shipment of American-grown Digitalis from the state of Washington, which upon assay gave such a high test by the U. S. P.

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