THE INTERNATIONAL UNIT OF DIGITALIS.*

BY F. A. UPSHER SMITH.

The standardization of a potent drug like Digitalis presents numerous difficulties due to the fact that there is no one definite chemical constituent that can be taken to represent the full medicinal action of the drug. It is necessary, therefore, to resort to a biological method.

Needless to say biological methods lack the accuracy of chemical methods. They depend upon the reactions of the animal upon which the drug is to be tested, and in many cases these reactions are influenced by weather conditions, the state of health of the animal, the species of the animal, and many other causes.

The methods used in biological assay have not been unified, as is the case in chemical assays. Take the case of the assay of digitalis by means of cats, following the Hatcher and Brody Method. It will be found that in using this method more or less important modifications are used in different laboratories, and these are liable to produce differences in the results obtained by different workers.

When I was visiting the late Professor Cushny in Edinburgh University six years ago he told me that in the case of a sample of digitalis submitted to different laboratories by the League of Nations it had taken twice as much to kill the cats in Edinburgh as it did in London. For about eleven years we have been standardizing digitalis by the Cat Method of Hatcher and Brody, and at times we have noticed considerable difference between our results and those of other workers. The statement of the strength of Digitalis in terms of absolute Cat Units is open therefore to this grave objection that the results are liable to differ in the hands of different workers in different laboratories.

It is as though you asked a number of men to step out, heel and toe, to measure a bit of ground. Their results would vary with the actual length of their feet. If, however, we know the length of each man's foot in linear measure we are able to bring all their results to an agreement. This we have done in the case of digitalis by adopting as our standard the International Standard Digitalis Powder, prepared by the League of Nations. One hundred milligrams of this powder is regarded as an International Unit. We find out by the use of cats how much of a given sample of digitalis is equivalent in toxicity to 100 mg. of the International Standard Powder. This gives us the strength of the sample of digitalis relative to an International Unit. In this way the results of different workers in different laboratories are brought into closer agreement. However much their methods, technique, etc., may vary, by using the same methods and technique, on both the Standard Powder and the sample to be tested, they all obtain relative strengths of the same order of magnitude.

Among different workers a "Cat Unit" in terms of International Standard Powder ranges from 76.3 mg. to 104.2 mg. In other words, with the same Powder some workers find 76.3 mg. to constitute a "Cat Unit" while others consider 104.2 mg. to be a "Cat Unit." In testing another sample of digitalis in the same way these workers would obtain similarly varying results, but on reducing the results to the equivalent of 100 mg. of the International Powder these big variations would tend to disappear.

* Parts of a paper read before Minnesota Pharmaceutical Association.

TABLE I.—DIGITALIS PURPUREA, 1926 CROP, GROWN BY UPSHER SMITH.

Results in Cat Units.

	Observer.	Date.	Mg. = 1 Cat Unit.
1	A	2/1/27	65.0
2	A	2/1/30	68.9
3	B	2/1/30	85.5
4	B	2/1/30	79.85
5	C	2/13/30	62.50

From these results we find the Cat Unit of the 1926 crop ranges from 62.5 mg. to 85.5 mg., a range of 23 mg. But if we calculate the amount of drug each observer found equivalent to an International Unit (100 mg. of the International Standard Powder) it will be noted that the results of the different observers come close together.

TABLE II.—RESULTS IN INTERNATIONAL UNITS.

	Observer.	Mg. International Standard Powder = 1 Cat Unit.	Mg. of 1926 crop equivalent to 100 mg. International Standard Powder.
1	A	77.8	83.5
2	A	77.8	88.5
3	B	104.2	82.05
4	B	104.2	76.6
5	C	76.3	81.9

Here we find an International Unit of the 1926 crop ranges from 76.6 mg. to 88.5 mg., a range of 11.9 mg. In other words, the discrepancy in the results of different workers is here cut in two.

An International Unit of digitalis would appear to be equivalent to about two grains of U. S. P. Digitalis Powder, hence a tincture containing One International Unit in 1 cc. would contain the equivalent of about two grains of U. S. P. Digitalis Powder in 1 cc. Such a tincture would be about 25% stronger than the U. S. P. tincture.

The careful clinician in prescribing digitalis is influenced more by the reactions of the patient than by an arbitrary system of dosage. Following the method of Withering, he gives digitalis until certain symptoms are produced, and then stops the administration. Individual patients are liable to show wide variations in their tolerance of the drug, indeed these variations are probably greater than is generally supposed.

The biological methods that we use to-day in standardizing drugs will no doubt undergo considerable improvement as time goes on. The ideal method of biological standardization would depend upon the clinical effect on an animal rather than the toxic results. Up to the present it has not been found practicable to adopt other than toxic methods in standardizing drugs of the Digitalis group.

The author concluded his article by offering the following suggestions:

1. That the Pharmacopœia Revision Committee consider the desirability of accepting the International Standard Digitalis Powder, as adopted by the League of Nations, as a standard for the U. S. P.

2. That steps be taken to prepare such a standard powder for use in the United States in testing digitalis and its products.

3. That 100 mg. of this powder be recognized as a Unit of digitalis, the same as an International Unit.

4. That the strength of digitalis and its products be stated in terms of an "international unit."

SYRUP OF POTASSIUM GUAIACOLSULPHONATE.

BY CLYDE M. SNOW AND BERNARD FANTUS.

In view of the popularity of guaiacolsulphonate-containing syrups, and the desire felt by many physicians for a preparation of non-secret composition that may readily be prepared extemporaneously by pharmacists, experiments were undertaken to elaborate the most palatable and elegant administration form for this agent, especially with a view of having it considered for possible admission to the National Formulary.

Potassium guaiacolsulphonate is a colorless crystalline powder, odorless, of slightly bitter taste, soluble in water (7.5 parts), insoluble in alcohol and ether. It is alleged to be of value in the treatment of certain coughs in doses of 0.3 to 1.3 Gm. (gr. 5 to 20) three or four times daily.

The following vehicles were tried:

Aromatic syrup of eriodictyon
Syrup of orange
Syrup of tar
Syrup of wild cherry
Compound syrup of sarsaparilla
Compound syrup of asarum
Aqueous elixir of glycyrrhiza

While none of these preparations is disagreeable, it seems that the aromatic syrup of eriodictyon yields the most palatable preparation; the well-known bitter-disguising tendency of yerba santa being more efficient in overcoming the bitterish after-taste of the medicine than any of the other vehicles. We therefore offer the following formula for consideration by the National Formulary Revision Committee.

SYRUPUS POTASSII GUAIACOLSULPHONATIS.

Syrup of Potassium Guaiacolsulphonate.

Abbr.: Syr. Pot. Guaiacolsulph.

Potassium Guaiacolsulphonate	**75.0 Gm.**
Water	**100.0 cc.**
Aromatic Syrup of Eriodictyon, enough to make	**1000.0 cc.**

Mix the potassium guaiacolsulphonate with the water; add the syrup; and after solution is affected filter through cotton, if necessary, and pass enough water through the filter to make the product measure 1000 cc.

AVERAGE DOSE: METRIC, 4 cc. APOTHECARIES, 1 FLUIDRACHM.

One average dose represents about 0.3 Gm. or 5 grains of potassium guaiacolsulphonate.

While at normal temperature, the salt produces a clear solution with the syrup, there is a tendency for the potassium guaiacolsulphonate to crystallize out at lower temperature. This is obviously due to the alcohol contained in the syrup