U. S. P. STANDARD FOR DIGITALIS.*

BY F. A. UPSHER SMITH.[1]

The Committee of Revision of the United States Pharmacopœia has under consideration the standard to be adopted for digitalis in the U. S. P. XI, and the best means of ascertaining its strength. The U. S. P. X standard is a minimum systolic dose, by the one-hour method, not exceeding 0.006 cc. of tincture, equivalent to 0.0000005 Gm. of ouabain, for each Gm. of body weight of frog. In Europe there is a strong movement in favor of the adoption of the International Standard Digitalis Powder as the standard for digitalis.

At the Frankfurt Conference it was recommended: "That when the dosage of digitalis or its preparations is expressed in units of activity, the unit employed *for any preparation and in any country* should be an international unit, which should be defined as the specific activity contained in *0.1 Gm. of the international standard powder.*"

The International Standard Digitalis Powder has been adopted in the German Pharmacopœia, the French Codex and the British Pharmacopœia (1932). The standard as given for Digitalis Pulverata in the B. P. (1932) is as follows:

"This powder must be assayed by the *biological assay of powdered digitalis*, and its strength must be stated in terms of the *international standard digitalis powder* of which 0.1 Gm. is taken to have an amount of activity described as 1 Unit."

The B. P. gives alternative directions for the assay of digitalis and its preparations, using a frog method or a cat or guinea-pig method.

The International Standard Powder consists of a carefully dried mixture of ten samples of digitalis leaves collected from different sources. The Sub-Committee on Digitalis of the B. P. (*Pharm. J.*, 127, 23 (July 11, 1931)) stated that "it was intended, when the mixture was made, that the potency of the mixture should represent the average potency of digitalis leaves, and records published by the Pharmaceutical Society of Great Britain show this to be the case." (See *Quart. J. Pharm.*, 1, 19 (1928).)

Following the International Protocol, all official tinctures of potent drugs are of 10% strength. If a 10% tincture of digitalis is made from a digitalis of International standard then it will be stronger than one made from U. S. P. digitalis. A comparison was made by Edmunds, Lovell and Braden (JOUR. A. PH. A., 18, 778 (1929)). They concluded that the International Standard Powder was about 30 per cent stronger than the U. S. P. X standard, frogs being used for the assay.

L. W. Rowe (JOUR. A. PH. A., 22, 106 (1934)) finds, by the frog method, that the International Standard tincture is from 20 to 25 per cent more active than the U. S. P. X tincture of digitalis.

J. H. Burn, then head of the Pharmacological Laboratory, Pharmaceutical Society of Great Britain (in the *Quart. J. Pharm.*, 1, 19 (1928)), commented as follows on this question:

"Further, the substitution of the international standard for the present ouabain standard will make no appreciable difference in the United States. In the Pharmaceutical Society's laboratory the lethal dose of tincture prepared from the international standard by the cat method

* Scientific Section, A. PH. A., Washington meeting, 1935.

[1] From the Department of Therapeutic Trials of the Upsher Smith Company.

was found to be 0.76 cc. per Kg., and that of the official U. S. P. ouabain to be 0.06115 mg. per Kg. Hence 1 cc. of the tincture from the international powder was equivalent to 0.0804 mg. ouabain. But the present U. S. P. requirement is that 1 cc. of a tincture shall be equivalent to 0.083 mg. ouabain, so that the international tincture is for practical purposes the same as a tincture fulfilling the U. S. P. definition."

Dr. Burn suggests that the U. S. P. X tincture of digitalis is for practical purposes of the same strength as a tincture made from the International Standard Powder. It seems to me that his conclusion is based on the supposition that the lethal dose of ouabain is the same for the cat as for the frog.

It is apparent, therefore, that U. S. P. digitalis is weaker in strength than the International Standard Digitalis Powder, and consequently, weaker than digitalis official in the British and German Pharmacopœias and the French Codex.

There seems to be no good reason for maintaining the present standard for U. S. P. digitalis, which may be considered as about four-fifths the International Standard. On the contrary, the continuance of the present standard is open to serious objection. It offers a market in the United States for grades of digitalis that do not meet the requirements of leading European markets. In the case of a delicate vegetable drug, like digitalis, depending for its action on glycosides that are sensitive to heat, moisture and air, it is desirable that the collection, desiccation and storage of the drug should be done under such conditions that the glycosides shall be changed in composition as little as possible. If the temperature is too low the drying process is prolonged and the enzymes have a greater opportunity of decomposing the glycosides. A digitalis of low glycosidal content may therefore be contaminated with an undue proportion of decomposition products and these may be obnoxious in their action when taken internally.

Digitalis is one drug in the production of which too great care cannot be taken. The better grades of commercial digitalis are obtainable in which decomposition has been held to a minimum and the biological strength is above that of the U. S. P. X.

In the world of finance it is generally accepted as a fact that "bad money drives out good money." If the standard for digitalis in the United States be continued below that of leading European countries it will result in attracting the lower grades of digitalis to this country.

Standards must, of course, be attainable. In recommending the adoption of the International Standard for digitalis in U. S. P. XI, I am confident that the standard will easily be met. As a grower of digitalis I have frequently produced a dried leaf of twice the activity of the U. S. P. standard. To adopt the International Standard means raising the present standard only about 25 to 30 per cent. One important result of taking this step would be that the tincture of digitalis of U. S. P. XI would be equal in strength to that official in many leading European countries.

A plea for uniformity in the strength of digitalis preparations was made recently in the *J. Am. Med. Assoc.*, 102, 862 (Mar. 17, 1934), in a letter signed by a number of leading cardiologists. If such a plea is valid within a country it is equally so in an international sense, in the interest of travelers. By raising the official standard about 25 to 30 per cent the need for stronger tinctures of digitalis will disappear and a big step will be made toward achieving the desired end—uniformity in strength of the preparations of digitalis. Once this change in strength

was made there would be no further changes to make in the standard for this important drug.

The value of a standard powder in bringing together the results of different workers has been described by this writer (JOUR. A. PH. A., 20, 471 (1931)). Figures are there given showing how reference to the International Standard brought the results of tests on five samples of digitalis leaf made in three different laboratories to a closer agreement.

THE CHOICE OF A BIOLOGICAL TEST.

The biological testing of digitalis has raised questions which bristle with difficult es, and about which there is no unanimity. The Revision Committee, according to Dr. Edmunds (*J. A. M. A.*, 102, 1246–1247 (April 14, 1934)) favors a frog method. It is not my intention to go into details in discussing the relative values of the frog and the cat method. I do want, however, to call attention to the well-known fact that a tincture of digitalis tested on frogs at intervals of three months or more will show a startling loss in strength, whereas the same tincture tested at similar intervals on cats, will only show a slight loss in strength. This was demonstrated by Wokes (*Quart. J. Pharm. & Pharmacology*, 2, 48 (1929), and 3, 205 (1930)). He found that tinctures from thirteen different samples of digitalis leaves, assayed by the frog method, showed a steady loss of activity in all cases. During the first nine months the deterioration proceeded at an average rate of about 3% per month. After that time the rate of deterioration gradually decreased, until about one-third of the activity had disappeared at the end of 16 or 17 months. Assays by the cat method failed to detect any deterioration.

Wokes cites the case of two tinctures A1 and A2, which were assayed when made, and found, in comparison with the International Standard leaves, to be 144 and 148 per cent by the cat method, and 189 and 206 per cent, respectively, by the frog method. They were assayed by the frog method again over a year later and both had lost 46% of their original activity, A1 being now 102 per cent and A2 112 per cent.

By the cat method these tinctures now had a potency of 142 and 148 per cent, respectively, having lost no activity. Had they been diluted to the standard, when made, they would now be 46 per cent below standard, by the frog method, but satisfactory in potency by the cat method. If, however, they had been stored undiluted, the cat method would show them much too potent, but the frog method would show them both to be of correct potency. This illustrates a pitfall in assaying old digitalis tinctures.

Foster and van Dyke (JOUR. A. PH. A., 22, 381 (1933)) studied the effect of aging upon the potency of digitalis tinctures, assays being made on the cat and frog. Aged tinctures were found to be less potent by assay in both species; however, the greater reduction in potency was usually observed in the frog. The frog method makes it exceedingly difficult, if not impossible, for a manufacturer to guarantee the strength of tincture of digitalis, even for 3 months. If the frog method be used at the time of manufacture, and the tincture adjusted to the U. S. P. X standard, a check up 3 months later will show a greatly diminished strength. This renders the manufacturer vulnerable to attack by the Pure Food and Drugs authorities, who are obliged to take the U. S. P. for their guide.

Dr. Edmunds stated (in the letter referred to) that no manufacturer had advocated the cat method. By this I presume Dr. Edmunds means "no manufacturer on the Committee of Revision." Outside of that body there are manufacturers who have used the cat method, and are still using it, in the belief that they are on safer ground. The cat method has the further advantage that it affords a means of calculating the physiological dose for a patient, by dividing the patient's body weight by 10 and giving that number of cat units in divided doses.

The adoption of the International Standard for digitalis in U. S. P. XI, and the recognition of 100 mg. of this powder as an International Unit, using cats for determining the strength, would provide the physicians with products whose dose would be easily calculated by the method of Eggleston. Instead of taking one-tenth the body weight in pounds, as in using cat units, the physician would take *one-twelfth* the patient's body weight in pounds and give that number of International Units, in divided doses.

We have had practical experience of the use of a standard powder for over three years, and are well satisfied that by adopting it we were able to maintain uniformity of strength with greater certainty than without a standard powder.

A national Standard Digitalis Powder for the United States would preferably be prepared from a mixture of powdered leaves from different sources. It would not be necessary to adjust the strength of such a U. S. P. standard powder so as to make it equivalent, weight for weight, to the International Standard, but the ratio between the potencies of the two standard powders could be determined in a series of tests, one series with frogs, and another with cats.

The adoption by the U. S. P. of the International Unit as a standard for digitalis products would be a simple matter. The unit of digitalis would be defined as the amount of activity contained in 0.1 Gm. of the International Standard Digitalis Powder, so that 1 Gm. of the International Standard represents 10 units.

The British Standard Digitalis Powder tested by different workers showed an average potency, with frogs of 138% of the International Standard or 13.8 units per Gm., so that 1 unit is contained in 0.0725 Gm. of the British Standard Powder. When the comparison was made by means of cats the activity was found to be 116% of the International Standard, or 11.6 units per Gm., so that 1 unit is contained in 0.0862 Gm. of the British Standard Powder.

Whether a cat or frog method (or both) is adopted in the U. S. P. XI there will, therefore, be no difficulty in arriving at a satisfactory standard digitalis powder for use in the United States.

Paraphrasing the well-known axiom of homeopathy, there seems to be a unanimity of opinion among pharmacologists that, in the selection of standards, "similia similibus æstimantur" is a safe guide.

TWELFTH INTERNATIONAL CONGRESS OF PHARMACY.

The Twelfth International Congress of Pharmacy, as heretofore mentioned, will convene in Brussels, July 30th to August 6th, under the patronage of His Majesty Leopold III, organized under the auspices of the International Pharmaceutical Federation, the National Pharmacy of Belgium, the Pharmaceutical Society of Anders.

Members attending the Congress will have a free admission to the World's Fair being held at that time and reduction rates on railroads. The opening session will be held in the Hall of Fame of the University of Brussels. The banquet will take place on August 2nd.