THE NEED FOR AN IMPROVED FORMULA FOR INFUSION OF DIGITALIS, U. S. P.*

BY A. RICHARD BLISS, JR.

INTRODUCTION.

The United States Pharmacopoeia IX provides biologic assays for Digitalis,[1] Fluidextract of Digitalis[2] and Tincture of Digitalis,[3] but gives no method and states no biologic standard for Infusion of Digitalis.[4] One reason for the omission of a biologic assay in the case of the Infusion is indicated in the pharmacopoeial requirement:—

"*Infusion of Digitalis must be freshly prepared from the leaves,*"[5] it being doubtless taken for granted that an Infusion *freshly made according to pharmacopoeial instructions from standardized* leaves will represent the activity of the amount of standardized leaves employed. The results of the investigations reported hereafter show that the foregoing conclusion is incorrect. Because of the frequent complaints of clinicians concerning the variability and unreliability of Infusion of Digitalis, U. S. P., and the meager available data concerning the relative activity of this Digitalis preparation, particularly the preparation as it is found in the average retail drug store, the writer undertook the investigations the results of which are herewith presented.

Not very many years ago many, if not all, schools of medicine and pharmacy taught that the Infusion of Digitalis was a more active diuretic than the Tincture and the Fluidextract, explaining this supposed difference on the ground that the menstruum employed in the manufacture of the Infusion[6] (water) extracted the several active constituents of the crude drug in different relative proportions than the menstrua employed in the manufacture of the Tincture[7] (3 of alcohol to 1 of water—by volume) and the Fluidextract[8] (5 of alcohol to 1 of water—by volume). In spite of the fact that clinical experiences, animal experimentation and the physical properties of the active constituents of Digitalis long ago showed the errors of such belief, there are apparently many physicians and pharmacists who are seemingly firm believers in this "theory." Digitoxin, digitalin, and digitalein, the three glucosides that supposedly represent the activity of digitalis, are all soluble in alcohol. Digitoxin, which according to Bastedo[9] and others most nearly represents the Digitalis actions, is practically insoluble in water; digitalin is slightly soluble in water; and digitalein is soluble in water. Cushny[10] says Infusion of Digitalis contains only traces of digitoxin. Sollmann[11] says a 1:10 In-

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[1] U. S. P. IX, 1916, pp. 131, 606.

[2] *Ibid.*, pp. 182, 606.

[3] *Ibid.*, pp. 453, 606.

[4] *Ibid.*, p. 227.

[5] *Ibid.*, p. 227.

[6] *Ibid.*, p. 227.

[7] *Ibid.*, p. 453.

[8] *Ibid.*, p. 182.

[9] Bastedo, "Materia Medica, Pharm. & Thera.," 1919, p. 158.

[10] Cushny, "Pharmacology & Therapeutics," 1918, p. 399.

[11] Sollmann, "Manual of Pharmacology," 1917, p. 383.

fusion (not U. S. P.) contains two-thirds of the digitoxin of the leaves. A fourth principle, a saponin body called digitonin, is soluble in water, and is said by Bastedo[1] and others to possess the property of holding the otherwise water-insoluble or slightly soluble glucosides of digitalis in aqueous solution. It is also claimed that digitonin, by the intravenous method, is a physiological antagonist to digitoxin, but that it is unabsorbable by the alimentary tract. Kiliani[2] claims that the crude drug contains but traces of digitonin. Bastedo[3] says he has frequently seen the Infusion given in one-half ounce doses, the equivalent of 36 minims of the Tincture. The writer has seen one-ounce doses of the Infusion (U. S. P. VIII) administered without subsequent toxic symptoms.

Hatcher and Eggleston[4] showed that an Infusion made by pouring 1000 Cc. of boiling water onto 10 grammes of Digitalis, in No. 60 powder, allowing it to stand in a boiling water-bath for one hour with frequent stirring, and filtering while hot, retains its activity with little loss for several weeks. Weiss and Hatcher[5] showed that an Infusion of digitalis made by the foregoing method represents the activities of the crude drug completely. Pittinger and Mulford[6] showed an average loss of 47.8% in five samples, 8 months old, of a 50% alcohol, not defatted tincture; 22.8% loss in five samples, 8 months old, of a 50% alcohol, fat-free tincture; and 40.7% loss in five samples, 8 months old, of an 80% alcohol, fat-free tincture. They present no data concerning the infusion. Hale[7] found official fluidextracts to have lost only an average of 6.6% in two years.

Roth[8] found an average loss of activity in seven samples of fat-free tincture of 14% in six months; two of his samples showing no loss, while two others showed very high losses. Houghton and Hamilton[9] showed an average yearly loss of 8% in 11 samples of extract five years old; 4% average yearly loss in 8 samples of fluidextract, U. S. P. VII, six years old; 10% average yearly loss in 11 samples of fluidextract, U. S. P. VIII, 3½ years old; and 9% average yearly loss in 8 samples of tincture three years old. They concluded that a maximum average loss of 10% per year can be expected in the tincture and fluidextract. Goodall[10] states that probably tincture of digitalis retains its full activity for one year. Hamilton and Rowe,[11] following a series of experiments with the tincture which showed a loss of from 0% (with fat-free preparations) to 43%, the ages running from 5 months to 8 months, concluded that the degree of deterioration varies with different lots, that a fat-free tincture made with 70% alcohol is less subject to deterioration, and that the deterioration of the tincture is not as uniformly rapid as isolated experiments would indicate. Bastedo[12] states that under the influence of heat or acids,

[1] Bastedo, "Materia Medica, Pharm. & Thera.," 1919, p. 158.
[2] Kiliani, *Arch. de Pharm.*, 7, 243, 1905.
[3] Bastedo, "Materia Medica, Pharm. & Thera.," 1919, p. 159.
[4] *Journal A. M. A.*, 65, 1902, Nov. 27, 1915.
[5] *Ibid.*, 76, 508, February 19, 1921.
[6] JOURNAL A. PH. A., March 1918, p. 236.
[7] *Hygienic Laboratory Bulletin*, No. 74.
[8] *Ibid.*, No. 102.
[9] *American Journal of Pharmacy*, Oct. 1909.
[10] *British Medical Journal*, 1, 887, 1912.
[11] JOURNAL A. PH. A., May 1918.
[12] Bastedo, "Materia Medica, Pharm. & Thera.," 1919, p. 158.

or when kept for some time in aqueous solution, as in the case of the Infusion, the glucosides of Digitalis tend to decompose and may form toxiresins which have a central convulsant action. With the exception of Hatcher and Eggleston and Weiss and Hatcher, none of the foregoing investigators present data concerning the stability and the relative activity of the Infusion.

THE METHOD OF ASSAY.

The method of biological standardization used in this series of investigation is that known as the Hatcher and Brody Cat Method.[1]

THE SAMPLES.

The first 15 samples investigated were obtained from various retail drug stores. The last five samples were manufactured in the Laboratories of Pharmacology of the School of Medicine of Emery University according to the method of Hatcher and Eggleston referred to above.

THE RESULTS.

The results of this investigation are presented in tabulated form. The values of the last column of the table represent the activities of the samples expressed as percentage of the theoretical activity as calculated from the amounts of standardized drug supposedly used.

TABLE SHOWING THE RELATIVE ACTIVITY OF VARIOUS SAMPLES OF INFUSION OF DIGITALIS.

The values in the "Average activity" column express the percentages of the theoretical activity as calculated from the amounts of standardized crude drug employed or supposedly employed. Fractions are omitted.

Sample.	Method of preparation.	Number of estimation.	Average activity (percentage of theoretical activity) percent.	Sample.	Method of preparation.	Number of estimation.	Average activity (percentage of theoretical activity) percent.
1	U. S. P. IX	4	31	12	Dilution of fluidextract	3	65
2	U. S. P. IX	4	42				
3	Dilution of fluidextract	4	60	13	U. S. P. IX	3	42
				14	U. S. P. IX	4	41
4	Dilution of fluidextract	3	65	15	U. S. P. IX	4	35
				16	Hatcher & Eggleston	4	96
5	U. S. P. IX	4	33				
6	U. S. P. IX	4	51	17	Hatcher & Eggleston	4	94
7	U. S. P. IX	3	29				
8	Dilution of fluidextract	4	63	18	Hatcher & Eggleston	3	96
9	Dilution of fluidextract	4	60	19	Hatcher & Eggleston	4	95
10	U. S. P. IX	4	37	20	Hatcher & Eggleston	3	94
11	U. S. P. IX	4	40				

SUMMARY.

The fifteen samples of Infusion of Digitalis, selected at random from retail drug stores, showed an average activity of but 46.26% of the theoretical activity calculated from the amount of standardized leaves supposedly used in manufacturing the preparation.

Five of the fifteen drug store samples, prepared by a method that has received the hearty disapproval of the medical and the pharmaceutical professions (simple dilution of the Fluidextract), showed an average activity of 62.6% which

[1] *American Journal of Pharmacy*, 82, 360, 1910.

is 16.34% stronger than the average for the total fifteen drug store samples, and 24.5% stronger than the ten samples supposedly prepared by the U. S. P. IX method.

The ten samples manufactured according to the U. S. P. IX method showed an average activity of but 38.1%.

The five samples prepared according to the method of Hatcher and Eggleston, referred to above, showed an average activity of 95%, which is 48.74% stronger than the fifteen drug store samples' average, 32.4% stronger than the average of the five samples made by diluting the Fluidextract, and 56.9% stronger than the average of the ten samples made according to the U. S. P. IX method.

The results obtained are interpreted as indicating:

(*a*) A decided variability in the strength of the U. S. P. IX Infusion of Digitalis, all drug store samples examined falling well below the theoretical activity.

(*b*) A decidedly more active "Infusion" when prepared by dilution of the Fluidextract than when made by the U. S. P. IX method.

(*c*) A practically "100%" preparation when prepared according to the method of Hatcher and Eggleston.

(*d*) The need for an improved method for the preparation of Infusion of Digitalis, U. S. P. Several major faults in the case of the present official method are doubtless: (1) an insufficient amount of solvent actually employed for extraction, (2) too short a period of infusion, (3) the employment of an insufficiently fine powder. The adoption of the method of Hatcher and Eggleston would give the pharmacist a method that is simple and easily carried out in the retail drug store, and would provide the physician with an Infusion of Digitalis that would be reliable and of practically uniform strength.

(*e*) The possible need for standardizing Infusion of Digitalis. Many will doubtless look upon this as theoretically desirable, but at the same time impracticable.

(*f*) The fact that the present Infusion of Digitalis might be dropped from the Pharmacopoeia without handicapping modern medicine in any way. There is serious doubt in the mind of the writer as to whether a *standard* Infusion of Digitalis possesses any advantages over the more stable standard Tincture. Laboratory investigations and clinical experiences have certainly shown that the tincture is more uniform, reliable, and stable than the infusion.

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CANCER, CAUSE AND CURE.

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Everything has a definite cause and cancer is no exception. As to disease, physicians recognize two distinct cause factors. That factor which *must* be present before the disease can develop is known as the primary cause. Certain factors and influences may and often do encourage, stimulate or assist the primary cause and thus constitute the secondary cause or causes of the disease. For example, the primary cause of tuberculosis is the *Bacillus tuberculosis;* that is, this partic-