PHYSIOLOGICAL POTENCY OF COMMERCIAL ERGOT PREPARATIONS.*

BY WM. T. McCLOSKY, MARVIN R. THOMPSON AND NICHOLAS G. BARBELLA.†

In this paper Commerical Ergot Preparations will be divided into two classes, Fluidextract of Ergot and Ergot Specialties. Fluidextract of Ergot is the official preparation of the U. S. Pharmacopœia, Tenth Revision. The term Ergot Specialties includes those preparations which are aqueous or hydro-alcoholic extracts, intended for either oral or hypodermatic administration, and which are prepared by methods usually differing from that described in the U. S. P. for Fluidextract of Ergot. For obvious reasons, the names of manufacturers have been omitted from the tables, and preparations are reported only under our laboratory number.

Results shown in Tables I and II of this paper represent a nationwide survey of products in interstate and import commerce, as well as many intra-state products. These tables contain data on all samples assayed during an eight-month period and include preparations distributed by practically every manufacturer and wholesale distributor in this country, as well as a number of foreign preparations offered for importation.

All of the preparations enumerated were assayed by the U. S. P. Cock's Comb Method, using cockerels which had been previously standardized by determining the dose of a standard preparation necessary to produce a satisfactory reaction. The intensity of reaction observed during assay or standardization of birds was recorded by the use of the "number code" previously described by one of us (M. R. T.) (2).

The U. S. P. method, when properly applied has been found to be reasonably accurate in estimating the alkaloidal activity of ergot preparations, if interfering amounts of histamine are not present. Histamine interference is rarely encountered in commercial ergot preparations, because it is so unstable as to be destroyed during the first several months after manufacture (2).

Whenever difficulty was encountered in arriving at definite and concordant results by the Cock's Comb Method, or the potency of the fluidextract was found to differ appreciably from that of the standard, the assay was checked by the Broom-Clark Isolated Rabbit Uterus Method (3), as modified by Pattee and Nelson (4). The latter method measures the alkaloidal activity irrespective of any amount of histamine or other amines which might be present.

The U. S. P. X Standard Fluidextract has been shown by Thompson (5) to be somewhat unstable, and consequently of variable potency, while at the same time, that of Ergotamine Tartrate was found to be constant. To avoid confusion, the potency of all preparations in Tables I and II is therefore expressed in terms of Ergotamine base,* 0.05 per cent, or 0.5 mg. per cc., being taken as 100 per cent U. S. P. potency. The present U. S. P. Standard Fluidextract Lot No. 2160, which has replaced Lot No. 636, because of deterioration of the latter, contains this amount of alkaloidal potency, *i. e.*, 0.05 per cent of alkaloidal activity in terms of Ergotamine base (5).

---

* Ergotamine Tartrate, containing 84.5% Ergotamine base.

† Pharmacological Laboratory, Food, Drug and Insecticide Administration, U. S. Department of Agriculture, Washington, D. C.

The results obtained are tabulated in Table I for Commercial Fluidextracts, and in Table II for Commercial Ergot Specialites.

TABLE I.—COMMERCIAL FLUIDEXTRACTS OF ERGOT.

P. C. No.	U. S. P. X., %	P. C. No.	U. S. P. X., %	P. C. No.	U. S. P. X, %
2294	240	2360	30	2478	66
2308	130	2361	200	2479	25
2311	20	2362	300	2480	133
2324	400	2365	66	2481	100
2325	200	2366	33	2482	100
2326	100	2367	25	2483	100
2328	100	2368	66	2490	133
2329	100	2378	200	2491	33
2331	133	2379	50	2502	50
2339	100	2380	120	2505	133
2340	133	2381	200	2511	150
2341	100	2382	133	2512	150
2342	200	2383	133	2513	150
2343	300	2384	200	2521	20
2344	50	2399	133	2522	25
2345	133	2405	100	2530	25
2346	200	2413	133	2531	25
2347	250	2415	100	2532	20
2348	250	2438	250	2533	20
2349	Inactive	2440	100	2534	20
2350	175	2469	133	2537	100
2354	130	2470	133	2539	100
2355	50	2471	133	2541	25
2356	100	2472	80	2542	75
2357	133	2473	250	2543	20
2358	133	2474	25	2602	50
				2635	50

TABLE II.—COMMERCIAL ERGOT SPECIALTIES.

P. C. No.	Potency, % U. S. P. X.	P. C. No.	Potency, % U. S. P. X.
2235	Inert	2372*	120% labeled potency
2246+	Approx. 33	2373	Inert
2252*	25 or 12.5 of labeled potency	2376*	50
2263*	Inert	2377*	Inert
2264	25	2401	Inert
2280*	25	2403*	20
2283*	25	2431	25% labeled potency
2297*	Inert	2506*	Inert
2303*	Inert	2598*	20
2323	Inert	2599*	20
2330	66		

* Ampul preparations recommended for hypodermic use.

DISCUSSION OF RESULTS.

Pattee and Nelson (4), Thompson (2) and Swanson (7) have shown that proper application of the methods involved in this paper provide for an estimation of the specific alkaloidal activity of ergot preparations within plus or minus twenty per cent. Sources of probable error, with methods of avoiding same, have been

explained by these investigators. In summarizing the results of Table I, therefore, it is reasonable to regard those fluidextracts containing a potency of 80 to 120 per cent as meeting the U. S. P. potency requirement. Those falling below 80 per cent are unquestionably substandard while those bearing a potency of more than 120 per cent exceed the potency requirement of the U. S. P. X.

Of a total of 79 Commercial Fluidextracts examined, twenty-seven, or approximately 35 per cent of the total number, were substandard; sixteen, or approximately 20 per cent of the number, were of U. S. P. Standard potency; and thirty-six, or approximately 45 per cent of those examined, exceeded the U. S. P. X potency requirement.

By tracing the history of these fluidextracts it was found that the majority of the samples which equalled or exceeded the U. S. P. potency requirements had not attained an age of more than one year (after manufacture, assay and adjustment). At the same time, it was observed that many of those which showed a deficiency in activity had been purchased in bulk from the manufacturer and subsequently repackaged and distributed by a firm other than the manufacturer, thereby introducing conditions such as a prolonged period of storage and an excessive exposure to air, which give rise to serious deterioration.

For the non-uniformity observed in those fluidextracts which equalled or exceeded the U. S. P. potency requirements, it is believed that faulty standardization and attempts to allow for lack of stability are largely responsible. It is possible that those fluidextracts which exhibited a potency of very appreciably more than 100 per cent at the time of this survey had been standardized by the U. S. P. Method immediately after preparation, and that non-specific amine interference had instituted an error in standardization. As shown by Thompson (2), it is possible for freshly prepared fluidextracts to contain an alkaline-water-soluble fraction (consisting principally of histamine) in sufficient amounts to greatly interfere with the measurement of alkaloidal activity by the Cock's Comb Method. This interference is destructive rather than constructive, and results in the manifestation of an *apparent* potency which is lower than that *actually* present. The interfering activity rapidly decreases during storage, causing an *apparent* increase in alkaloidal potency instead of the slow decrease which actually takes place. Error caused by such interference can be avoided by aging the fluidextract for several months in completely filled containers in a cold-room prior to final assay and standardization. At the same time it was shown that the Broom-Clark Method, as applied in this work, yielded reliable results in all instances.

TABLE II. COMMERCIAL ERGOT SPECIALTIES.

Of a total of 21 Commercial Ergot Specialties examined, only one contained a satisfactory amount of alkaloidal activity, while the majority were practically inert. It is believed that this condition is due largely to faulty methods of preparation, since most of them proved to be essentially aqueous extracts, which are now known to be worthless because of the fact that extraction of ergot with aqueous menstrua does not extract significant amounts of the specific alkaloids (6), (8), (9).

A similar condition is encountered with solid or semisolid ergot extracts. Although none of these has been included in the tables of this paper, a number of such commercial extracts have been examined during the past two years and

have invariably been found to be devoid of significant alkaloidal activity. This is undoubtedly due to the fact that they had been prepared by a method involving extraction of the drug with an aqueous or hydroalcoholic menstruum containing no acid. Such procedure has been shown by Thompson (6) and others, to result in a preparation which is devoid of significant amounts of the desirable specific alkaloids.

CONCLUSIONS.

1. Of the Ergot Preparations now available on the market, the U. S. P. X Fluidextract is the most satisfactory, aside from those which contain a specified amount of ergotamine or ergotoxine (hydroergotinine, amorphous ergotinine) in suitable solution.

2. Fluidextract of Ergot should be manufactured and packaged in well-filled, small-sized containers, preferably one-ounce and never larger than four-ounce capacity, to avoid excessive exposure of the contents to air due to frequent opening of the container for removing portions by the wholesaler, dispensing pharmacist or other distributor.

3. To prevent the possibility of the therapeutic use of Commercial Fluidextracts of Ergot which have lost the greater part of their activity due to age, the label should bear an expiration date.

REFERENCES.

(1) Thompson, JOUR. A. PH. A., Vol. XVIII, No. 11; Nov. 1929.
(2) Thompson, *Ibid.*, Vol. XIX, No. 2; Feb. 1930.
(3) Broom and Clark, *J. Pharm. & Exp. Ther.*, XXII, 1923–1924.
(4) Pattee and Nelson, *Ibid.*, XXXVI, 1929.
(5) Thompson, JOUR. A. PH. A., Vol. XIX, No. 5; May 1930.
(6) Thompson, *Ibid.*, Vol. XIX, No. 1; Jan. 1930.
(7) Swanson, *Ibid.*, Vol. XVIII, No. 11; Nov. 1929.
(8) K. Schübel und J. Manger, *Arch. Exper. Pharm. u. Path.*, Bd. 148 d/4 Heft, pp. 246–256 (1930).
(9) Heinz Oettel, *Ibid.*, Bd. 149, 3/4 Heft, pp. 218–239 (1930).

ABSTRACT OF DISCUSSION.

Mortimer Bye asked regarding the length of time a fluidextract of ergot could be expected to retain the greater part of its potency. The author stated—six months to a year.

James C. Munch inquired whether any of the solid or powdered extracts were made in accordance with those of N. F. V. The author replied that some of them were.

F. W. Nitardy inquired relative to the relation of standard 636 to the present standard. The author replied that this would require going into the matter further than the paper. He said that No. 635 was the first standard fluidextract put out in accordance with the Pharmacopœia. At the time five manufacturers contributed the fluids used in the making of it. They were tested by the U. S. P. Cock's Comb Method. They were mixed and aged for six months: 0.4 cc. per Kg. instead of 0.5 cc. per Kg. was the U. S. P. standard. A means is afforded for checking and comparison of several standards. The 636 was somewhat weak, therefore was replaced.

E. E. Swanson asked whether ergotoxin had been used. The author replied that ergotinine had been used.

H. A. B. Dunning inquired whether studies had been made on the hydrogen-ion concentration and the effect of light. The author replied that E. E. Swanson had made some studies along that line.