THE EXTRACTION AND ASSAY OF CRUDE ERGOT.*

BY MARVIN R. THOMPSON (1) (*Continued from page 1141, November 1932*).

EXTRACTION BY PROCESS OF U. S. P. X.

The studies herein described were designed to shed light upon serious discrepancies in results obtained in the assay of crude ergot by experienced workers, which have from time to time come to the writer's attention. Also, to reveal, if possible, the cause of the all too frequent inability of pharmaceutical manufacturers to obtain an amount of standardized Fluidextract of Ergot in agreement with the previous assay of a small sample of the crude ergot involved. The fact that the yield of standardized product on different occasions has been observed to exceed as well as fall short of the amount predicted by previous assay of the particular crude drug involved, would at first cause one to suspect the accuracy of the assay method as the main cause of discrepancies. On a number of occasions, however, extremely critical check assays by all three of the most accurate of known methods (Rabbit Uterus, Colorimetric and Cock's Comb) left no doubt but that some discrepancies were of a magnitude greater than could possibly be accounted for by experimental error in the assays. Since the present U. S. P. requires the conversion of crude ergot into a Fluidextract of Ergot by a specified Type Process "B" for the assay, it appeared distinctly possible that the observed discrepancies might be accounted for by a difference in efficiency between "commercial scale" and "laboratory scale" preparation of the Fluidextract. A critical study of the official Type Process "B" was, therefore, undertaken.

The study yielding the results herein reported was conducted upon twelve different lots of crude ergot, although experience with ergot during five years has provided many more observations intimately related to this problem. Six of the lots selected were of poor to fair quality, while the other six were of good quality. These six lots were converted to fluidextracts by the official type process "B" of the U. S. P., and the "reserve" as well as the "exhaust" percolates were subjected to critical assay for alkaloidal activity by the Rabbit Uterus method according to the technique described in the preceding article of this series. After assay of the "reserve" and "exhaust" percolates, the "exhaust" percolates were concentrated as directed by the U. S. P. and incorporated in the "reserve" portion, adjusting the volume to 100 cc. (from 100 Gm. of drug) in all cases. These finished products were then likewise assayed. Ergotoxine Ethanesulphonate was used as the standard in these assays.

It is important to note that all six lots were subjected as closely as possible to the same type of treatment, *i. e.*, all lots were reduced to powders of equal fineness, percolators of the same size and shape were used, percolation was carried on very slowly and at identical rates for all, the same moderate temperature was applied to all during concentration of "exhaust" percolates, etc.

TESTS FOR EXHAUSTION OF THE DRUG.

These chemical tests have been developed in order to avoid the necessity of routinely testing for exhaustion by physiological methods. Their sensitivity and

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reliability have been carefully checked physiologically and approved for the intended practical purpose for which they were designed.

Percolation was in all cases carried to the same degree of exhaustion. Absence of color in the percolates was utilized merely as a rough criterion as to completeness of extraction. The following two chemical tests were used routinely in every case for proving exhaustion, as follows. (These tests were not ordinarily applied until percolate was nearly colorless.)

Test (*a*). Approximately 4 cc. of the issuing percolate is diluted threefold with a saturated aqueous solution of sodium bicarbonate. Failure to develop precipitate, turbidity or faint opalescence during one hour shows that extraction is sufficiently complete for practical purposes.

Test (*b*). This test is somewhat less sensitive than (*a*). Approximately 4 cc. of the issuing percolate is diluted twofold with water and made slightly but distinctly alkaline to litmus by the cautious addition of 1% ammonia water. Failure to develop precipitate, turbidity or faint opalescence during one hour shows that increasing the volume of the percolate by further extraction would not be justifiable.

These tests are also reliable and serviceable in the event tests are desired upon percolates containing some color, *i. e.*, before the color has disappeared from the percolate. If color is present, no other indicator is necessary in applying test (*b*), since this color changes upon being made faintly alkaline.

The results obtained in the extraction experiments are recorded in the following Table I.

TABLE I.

The proportions of ergot alkaloidal activity appearing in the "Reserve Portion," the "Exhaust Percolate," and also comparing the alkaloidal activity of the Type Process "B" Fluidextract with that of a straight quantitative percolate. All assays by the Epinephrine-Inhibition method. Alkaloidal content expressed in terms of Ergotoxine Ethanesulphonate.* 100-Gm. samples of crude ergot used in each case.

Crude Drug.	Amt. of Alkaloid Present in the 85 Cc. Reserve Portion. Mg.	Per Cent of Total Alkaloid Present in Drug (Approx.).	Additional Vol. of Percolate Obtained to Exhaust the Drug, Cc.	Amt. of Alkaloid Present in the Total Exhaust Percolate. Mg.	Per Cent of Total Alkaloid Present in Drug.	Total Amt. of Alkaloid Present in Drug, Mg. (Calculated), Reserve plus Exhaust.	Total Alkaloid in 100 Cc. F. E. by Type Process "B," Mg.	Per Cent Total Alkaloid Lost by Concentration of Exhaust Percolate of Type Process "B" (Approx.).
1	33.2	55	415	27.2	45	60.4	46.5	23%
2	13.77	43	465	18.03	57	31.8	20.2	36%
3	50.97	58	515	37.23	42	88.2	62.7	28%
4	135.8	63	515	79.4	37	215.2	170.2	20%
5	92.02	52	565	85.98	48	178.0	108.5	39%
6	117.8	60	465	78.2	40	196.0	133.0	32%

* Generously supplied by Dr. C. S. Leonard, Burroughs, Wellcome & Co.

DISCUSSION OF TABLE I.

The results tabulated above are uniformly significant in showing that, in spite of most careful attention to details shown by experience to influence efficiency in extraction of drugs, the "reserve portion" cannot be expected to contain significantly more than one-half of the total activity of the drug, thus essentially confirming the experiments of Wokes and Elphick (2). It logically follows, therefore, that the remainder of the activity must be contained in the "exhaust percolate," which, the results show, attains a considerable volume before extraction is reasonably complete. From the standpoint of accurate bioassays of crude ergot, and also from the standpoint of commercial extraction of ergot, it is highly significant that concentrating the exhaust percolate for incorporation into the reserve portion results in a loss of activity that is great and

likewise considerably variable. Other experiments conducted in this laboratory have shown that the employment of partial vacuum in the concentration of the exhaust percolate does not avoid the loss of considerable activity. Similarly, the use of a hot air blast to affect the concentration was found to be attended by a loss of considerable activity. The writer has been unable to find any practical method of concentrating such hydro-alcoholic ergot percolates which could be carried out without the danger of losing an objectionable amount of the activity.

The above results make it readily apparent that the procedure at present specified by the U. S. P. for the assay of crude ergot cannot possibly reflect the true potency of the drug, even though the methods of testing the resulting fluidextract were 100 per cent accurate. Because of the loss of activity incurred in the procedure of concentrating the large volume of "exhaust" percolate, the most accurate assay possible must necessarily reveal a potency approximately 20 to 30% lower than was actually present or extractable from the drug. It is important to point out that the loss so incurred cannot be assumed to be even reasonably constant, for a number of reasons. Different samples of ergot vary greatly with respect to ease of extraction, some being well extracted by a 1 to 4 percolate, while others require percolation to the extent of 1 to 10. Aside from the natural variations in ergot, such factors as size and uniformity of particles of the ground drug, completeness of de-fatting, height of the column of drug in the percolator, amount of packing of drug, temperature during entire extraction procedure, time of maceration and rate of percolation are vitally concerned in extraction efficiency. Since certain of these factors cannot be precisely controlled, it is obvious that considerable variation in extraction efficiency as well as in concentration technique would occur from laboratory to laboratory, due in part to the personal equation of the operator. Consequently, the proportions of activity obtained, respectively, in the "reserve" and "exhaust" percolates are subject to considerable variation. Generally speaking, the greater the proportion of activity contained in the "exhaust" percolate to be concentrated for incorporation into the "reserve" portion, the greater is the loss of activity sustained. The converse is also true, *i. e.*, the greater the proportion of the total activity contained in the "reserve" portion, the less will be the loss sustained by concentration of the "exhaust" percolate.

It will be apparent from the above, that it is virtually impossible, at least extremely improbable, for two or more different workers to obtain fluidextracts of identical potency from different portions of the same lot of ergot using the Type Process "B" specified by U. S. P. X. Even assuming that the several workers would attain absolute accuracy in assaying their respective fluidextracts, the results would necessarily be variable and in all cases show a potency considerably lower than that actually present in the drug under examination.

The failure of the procedure specified by the present U. S. P. to provide for the appearance of the total amount of activity of the drug in the liquid to be subjected to assay, was responsible for an investigation of other possible extraction procedures with the hope of developing one which would be more dependable in providing for the appearance, in the liquid extract, of the total amount of activity contained in the crude drug, thereby eliminating at least this serious source of error in assaying crude ergot.

The results of Table I suggested a fairly obvious course to follow for affecting such a dependable quantitative extraction of the sample to be assayed. Since the observed variable loss in activity was sustained only in the concentration of the "exhaust" percolate, it seemed certain that the direct assay of the total unconcentrated quantitative percolate would yield a true estimate of the activity contained in the crude drug. In carrying out such a simple quantitative percolation, it is obviously advantageous to obtain the total activity of the drug in as small a volume of percolate as possible, and at the same time, if possible, to have the nature of this quantitative percolate such that it would lend itself to direct assay without the necessity of subjecting it to chemical procedure prior to such assay.

Experience has shown that a menstruum consisting of approximately equal parts of alcohol and water is the most satisfactory for insuring an efficient extraction of ergot and at the same time providing for a percolate which could be assayed directly without further manipulation. It is now generally agreed that the extraction efficiency is enhanced somewhat by the addition of a small amount of acid to this menstruum. In an earlier series of communications (10), the writer emphasized the importance of the use of hydrochloric acid in the menstruum, partly because of a moderately favorable influence upon extraction efficiency, but mostly because of the

well-known work of Swanson which definitely showed that an appreciably acid p_H favored the stability of the finished fluidextract. Further reference to p_H and stability will be discussed later.

The fact that such straight quantitative percolates attain great volumes, causing the alkaloidal concentration of the usual run of samples to fall in the low range of 0.005 to 0.05 per cent in terms of ergotoxine, bars the accurate use of the official Cock's Comb method or any of its modifications. The Isolated Rabbit Uterus method, as described in the preceding communication, provides ample sensitivity for this purpose and was consequently the method of choice. Greatly excessive acidity in the test percolate is highly objectionable in the application of this method, as will be shown in a later report from this laboratory. Since added acidity exerts only a moderate influence on extraction efficiency, and since the stability of the percolate is not a disturbing factor in this assay procedure, there is no reason for employing excessive amounts of acid in the menstruum.

A considerable number of experiments has led to preference for the following procedure as a method for the assay of crude ergot, definitely more reliable than the method at present specified by U. S. P. X.

METHOD.

(*a*) *Assay Sample.*—It is extremely important to use all possible care in securing an assay sample that is representative of the lot in question. Crude ergot is invariably imported or shipped in bags. The potency shown by samples from different bags of the same shipment, or even samples taken from different parts of the same bag, has been found on a number of occasions to vary considerably. The writer is convinced that it is not advisable to conduct an assay upon a representative sample weighing less than 50 Gm., while the extraction of a 100-Gm. sample is preferable.

(*b*) *Extraction Procedure.*—The drug is ground in the usual manner and sifted in a No. 30 sieve, returning portions remaining in the sieve to the mill, until all has passed through. The powder is then thoroughly mixed, and the accurately weighed assay portion of the powder is transferred without packing to a properly prepared glass percolator. The percolator should be of such a size and shape that the column of drug attains a height of at least five times the average diameter of the percolator while at the same time leaving space for menstruum above the drug. Within reasonable limits, the higher the column of drug, the greater is the extraction efficiency. The powder is then de-fatted as directed in U. S. P. X, and finally freed from the benzine. The de-fatted powder is then moistened with a sufficient quantity of a menstruum consisting of 2 per cent by volume of Hydrochloric Acid, U. S. P., in diluted alcohol (equal parts by volume of alcohol and water) to render it evenly and distinctly damp. It is then again transferred to the percolator, lightly shaken down but not packed. More of the same acidified menstruum is added, maintaining a layer of liquid above the drug, until the liquid reaches the lower orifice. The outlet is then closed and the whole allowed to stand for 12 hours or over night. After this maceration period, percolation is allowed to proceed at a very slow rate, using diluted alcohol as menstruum until the color is practically absent from the issuing percolate and the issuing percolate proves negative to the "Tests for Exhaustion" given above.

The volume of percolate obtained is then noted and the liquid is assayed by the Isolated Rabbit Uterus method, expressing the potency of the drug, after appropriate calculation, in terms of a suitable standard.

If it is preferred, the percolate likewise lends itself to assay by the Smith Colorimetric method or any of its several modifications.

As previously stated, the low concentration of alkaloidal activity in such quantitative percolates precludes the possibility of applying the official Cock's Comb method with any acceptable degree of accuracy.

The following Table II shows very clearly that a fluidextract prepared by Type Process "B" does not contain the full amount of activity actually contained in the drug sample, confirming the results of Table I. This table also shows the greater assay accuracy provided by the extraction method described above.

In explanation of Table II, it should be pointed out that the six samples of crude ergot involved were the same samples under examination in Table I. The identification numbers of the drug samples correspond in the two tables. The results shown in Table II are self-explana-

TABLE II.—THE POTENCY OF CRUDE ERGOT ASSAYED AS THE U. S. P. X FLUIDEXTRACT, AS COMPARED TO THE POTENCY REVEALED WHEN A "QUANTITATIVE PERCOLATE"** IS ASSAYED.

Crude Drug No.	Total Alkaloid* from 100-Gm. Drug after Conversion to U. S. P. X Fluidextract, Mg.	Total Alkaloid* in "Quantitative Percolate"** from 100-Gm. Drug, Mg.	Vol. of Quantitative Percolate from 100-Gm. Drug, Cc.
1	46.5	64.7	650
2	20.2	34.1	650
3	62.7	89.7	650
4	170.2	209.3	800
5	108.5	175.5	700
6	133.0	203.3	750

* In terms of Ergotoxine Ethanesulphonate.

** Prepared by the process just described.

tory. A source of serious error in the present U. S. P. X procedure for assaying crude ergot is clearly revealed. By adding the possible error caused by the present official extraction procedure to the possible error inherent with available assay methods, the discrepancies encountered in the assay of crude ergot by the same or different workers are readily accounted for. The first source of error can be eliminated in a very practical manner by employing the simple extraction technique just described. A further advantage over the U. S. P. X procedure lies in the fact that the concentration of "exhaust" percolate is eliminated, thereby saving time and expense.

The quantitative percolate obtained by the above procedure does not, of course, constitute an acceptable therapeutic ergot preparation. The potency represents that of a tincture rather than a fluidextract, and this would necessitate a prohibitively large therapeutic dose. A more efficient method of preparing a 1:1 fluidextract than is provided by the U. S. P. X requirements would obviously be desirable from the manufacturer's standpoint for economic reasons alone. A consideration of this problem follows.

AN IMPROVED METHOD FOR PREPARING FLUIDEXTRACT OF ERGOT, U. S. P.

The preceding experiments clearly show that the active principles of ergot are partially destroyed by the moderate heat necessary for concentration of the "exhaust" percolate in the Type Process "B" at present specified by the U. S. P. It is obvious, therefore, that a method of preparation not involving the use of heat would avoid the loss of activity sustained in carrying out the present official method.

The "Fractional" or "Divided Percolation" method, designated as "Type Process C," of the U. S. P. X, page 160, is recommended for drugs containing constituents which are injured by heat. This entire procedure is carried out at room temperature, no concentration of weak percolates being necessary.

A series of experiments were undertaken to determine the relative applicability of Type Process "C" as compared to Type Process "B." The same single menstruum was used throughout for each process, and consisted of 1% of U. S. P. Hydrochloric Acid in diluted alcohol (equal vols. of water and alcohol). This amount of acid was chosen because of experiments showing that higher concentrations of acid did not significantly increase the efficiency of extraction. In ascertaining the relative efficiency and applicability of the two processes, the use of the same menstruum in each case was obviously imperative. For those who believe that higher acidity increases the stability of the finished product, the p_H may be adjusted to the desired level by the direct addition of the acid to the mixed percolates. This particular point requires much clarification, and will be dealt with later by a presentation of experimental evidence on the influence of p_H upon stability of the fluidextract. A brief discussion of the practical aspects of the adjustment of p_H is, however, necessitated by a recent publication by Wokes and Elphick (11) in which reference was made to an earlier communication by the present writer (12). This discussion follows Table III.

The results in Table III show conclusively that Fluidextracts of Ergot prepared by Type Process "C" are invariably superior from the standpoint of potency to those prepared by the present official process. A slight difference in p_H in the products yielded by the two processes is probably caused by a loss of hydrochloric acid during the concentration of the exhaust percolate involved in Type Process "B."

TABLE III.—TYPE PROCESS "B" COMPARED AS TO POTENCY AND p_H WITH TYPE PROCESS "C," FOR THE MANUFACTURE OF FLUIDEXTRACT OF ERGOT. 100-GM. PORTIONS OF DRUG USED IN ALL CASES. VOLUME OF EACH FINISHED FLUIDEXTRACT WAS 100 CC.

Drug.	Alkaloid Content of Finished F. E. Prepared by Type Process "B." Mg./Cc.	p_H.	Type Process "C." Mg./Cc.	p_H.	Potency Gained through Use of Type Process "C." Mg./Cc.
7	0.27	4.67	0.37	4.54	0.10
8	0.46	5.18	0.61	4.97	0.15
9	1.00	5.36	1.44	5.17	0.44
10	0.93	4.88	1.27	4.55	0.34
11	0.75	4.87	0.98	4.66	0.23
12	0.57	5.31	0.71	5.12	0.14

In terms of Ergotoxine Ethanesulphonate.

In addition to such results obtained on a laboratory scale, the writer has been privileged to introduce Type Process "C" and observe similar comparisons in the preparation of Fluidextract of Ergot on a commercial manufacturing scale. Assays were run on the crude ergot involved in each case; the "reserve" and "exhaust" percolates and finished product of Type Process "B" were tested, and in the case of Type Process "C," all three percolates as well as the finished product were assayed. In these observations, the greater efficiency of Type Process "C" was clearly evident in every case. Experience thus gained has brought out several points of particular interest to pharmaceutical manufacturers with reference to Type Process "C." In applying this process on either laboratory or commercial scale production, these studies have shown that the proportions of activity contained, respectively, in the three percolates are subject to considerable variation. Such variations appear to be due, *first*, to a natural difference in ease of extraction of different lots of ergot; *second*, to differences in construction details of extraction equipment; and *third*, to personal equation of the operator particularly with respect to the rate of percolation. Such variations are, however, of little importance in practice, since the final product consisting of the mixed percolates will necessarily contain the total activity extracted. All observations show Type Process "C" to be from 20 to 40% more efficient than Type Process "B" for the manufacture of Fluidextract of Ergot.

In manufacturing Fluidextract of Ergot by this process, it is highly advantageous to know accurately the potency of the lot of drug involved. Only with such knowledge can one avoid the danger of obtaining a product sub-standard as to potency. Attempts at concentration result in a loss of activity which is unnecessary under proper control. In adjusting the potency of the finished product, reduction of potency should never be accomplished by the simple addition of menstruum. The potency should be reduced in such cases by continued percolation until the mixed percolates show the required potency, or until exhaustion is complete as indicated by the tests given above. In the event the potency becomes lowered to the required level before exhaustion is complete, the finished product may be set aside, and the additional weak percolate obtained from exhausting the drug may be stored in the cold room and used as the first menstruum for the next lot to be manufactured.

Type process "C" may also be used to advantage when assaying crude ergot by the official Cock's Comb method. In this case, percolation must be continued until exhaustion is complete as proven by the above tests even though the total volume becomes greater than 1:1. Rarely is it necessary to appreciably exceed this volume to ensure exhaustion, and never does the volume become so great as to interfere with the accuracy of the Cock's Comb method.

STABILITY OF FLUIDEXTRACTS PREPARED BY TYPE PROCESS "C."

Since proposing the change from Type Process "B" to Type Process "C," the question of comparative stability of the finished products has frequently been raised. Studies upon stability have been in progress for over two years, but are not yet ready for reporting in detail. It is possible to state at this time, however,

that, other conditions being identical, Type Process "C" Fluidextracts have proved to be fully as stable as Type Process "B" Fluidextracts.

ADJUSTMENT OF p_H OF FLUIDEXTRACT OF ERGOT.

Following the well-known work of Swanson (8) dealing with the influence of p_H upon the stability of Fluidextract of Ergot, considerable attention has been directed toward this factor by several workers. Swanson's results indicated that the optimum p_H for stability was in the region of p_H 3.0. The writer (12), in 1930, made recommendations relating to this factor, but even at the present time the subject needs clarification both as to the desirability of adjusting the p_H and also as to the method of accomplishment. In 1930, Wokes and Elphick (11) reported observations on extraction and p_H as related to the ergot problem, and stated that

> "Marvin R. Thompson (8)—has recently published a series of recommendations regarding ergot, which will probably exert an important influence on the ergot monographs in the next edition of the U. S. Pharmacopœia. On the basis of Swanson's results, he suggests that, in order to ensure efficient extraction of ergot, and maximum stability of the product, the amount of hydrochloric acid used should be very carefully controlled, both during the process of extraction and in the finished product. Apparently, he assumes that control of the amount of hydrochloric acid used will be sufficient to ensure a fixed p_H."

They then very adequately prove this "assumption" to be incorrect. It is important to point out that the writer in making the recommendation thus referred to by Wokes and Elphick, was very fully aware of the fact that the use of a controlled amount of acid in the manufacture of Fluidextract of Ergot would not ensure a fixed p_H in the finished product. A private communication prompted them to very kindly publish a withdrawal of their criticism (14). The recommendation in question was deliberately so worded after careful consideration of all available evidence relating to p_H and stability. The writer believed then as now, that while a fairly acid p_H possibly favors the stability of solutions or extracts containing ergot alkaloids under certain conditions of storage, there is even to the present time no sufficient evidence which would warrant the time and effort necessary to accurately adjust the p_H at a certain fixed level. Smith and Stollman (3) obtained results which indicated that decreasing the p_H of Fluidextracts of Ergot by varying it between 5.2 and 2.2 does not favor its stability. At approximately the same time, Swanson and co-workers (13) reported further studies on this problem, from which they concluded that ". . . no definite conclusions can be formulated that a certain hydrogen-ion concentration prevents the deterioration of the fluidextract or a solution of the pure ergot alkaloid," although their results caused them to state that their study would be pursued further. Thus it should be clearly apparent that the use of a carefully controlled amount of acid in the extraction menstruum can be made to ensure that the p_H of the finished product will fall, for example, between 3.0 and 5.0 in spite of the great and likewise variable buffer capacity of the usual run of ergot, provided that the extraction equipment is constructed of proper material. Existing evidence, including our own, does not at present indicate that there is any advantage in attempting to attain a level below p_H 4.0. Indeed a series of fluidextracts adjusted at p_H 4.5 to 5.5 have been observed during one year to retain their potency fully as well as those containing

more acid. The details of this study will appear later, since no conclusions of value can be drawn at present.

The above quoted statement recommending control of acidity of the finished fluidextract as well as of the menstruum was made because of knowledge then at hand that certain manufacturers of this product were using extraction equipment constructed of materials which reacted with the acid with the result that all of the acid used in the menstruum did not appear in the finished product. Proper p_H determinations can be utilized to detect such a condition, this condition being objectionable not only because of the loss of acid, but also because of the appearance of foreign soluble matter in the finished product.

Since Wokes and Elphick (11) have published their work on extraction and p_H in detail, and since the observations in our laboratory on this subject completely confirm their results, it is felt that there would be little justification in taking the space necessary for presenting our detailed observations. The study on this phase of the ergot problem is now sufficiently complete to warrant certain statements of fact which should prove helpful, particularly with respect to the adjustment of p_H as follows:

1. Ergot is comparatively rich in substances capable of exerting a buffer effect, particularly phosphates, although the phosphates do not account for the total buffer capacity. Other inorganic as well as organic substances contribute to this effect. Obviously, therefore, any extract of ergot cannot show the same p_H value as the menstruum used.

2. The buffer capacity varies considerably from sample to sample. Therefore, even though menstrua of identical p_H are used, fluidextracts from different lots of ergot are subject to considerable variation as to p_H. There is no way to ensure a definite fixed p_H in a finished fluidextract by simply using a menstruum of a determined fixed p_H.

3. Having determined the p_H of a given fluidextract, the amount of acid necessary to raise the acidity to a certain desired p_H value cannot be calculated without first accurately determining the buffer capacity of the sample. It consumes much less time and effort to make the adjustment by simply adding the acid in small portions until the desired p_H level is attained.

4. Ergot is distinctly acid in reaction and highly buffered. Whether the diluted alcohol menstruum is acidified, alkalinized or neutral, the first extract issuing from the percolator is acid in reaction, showing a value in the vicinity of p_H 5.0 to p_H 6.0. As percolation proceeds and the buffer substances become extracted, the p_H of the issuing percolate gradually approaches that of the original menstruum employed, not attaining the value of the original menstruum, however, until extraction is complete.

For example, when a neutral menstruum is used, the first percolate shows an acidity in the region of p_H 5.3. As extraction progresses the p_H value gradually rises toward neutrality, ultimately reaching the p_H of the menstruum (in the region of p_H 7.0).

If an acidified menstruum is used, showing, for example, a value of p_H 2.0, the first percolate will show an acidity in the region of 5.3 as in the case of the neutral menstruum. Then as percolation proceeds, the p_H value of the issuing percolate gradually becomes lowered toward the p_H value of the original menstruum (2.0).

When an alkalinized menstruum is used, showing, for example, a value of p_H 9.0, the first percolate will again show an acidity in the region of p_H 5.0 to 6.0. Then as percolation proceeds, the p_H value of the issuing percolate gradually becomes raised toward the alkaline p_H value of the original menstruum.

From the above comments regarding p_H, it is obvious that the use of either a neutral or an acidified menstruum for the preparation of Fluidextracts of Ergot will result in products showing an acid p_H value. Owing to the buffer capacity of ergot, which varies considerably from lot to lot, the p_H of the finished fluid-

extract will necessarily show a lower acidity than that shown by the acidified menstruum employed, and the actual p_H of different lots of finished product is subject to considerable variation even though a menstruum of fixed p_H is employed.

The author is greatly indebted to Mr. C. T. Ichniowski and Miss Dorothy Schmalzer for making a great many p_H determinations, and to Dr. E. G. Vanden Bosche for his very active interest in supervising this phase of the work.

NOTE: The studies dealing with isolation and pharmacologic action of the various constituents and preparations of ergot, particularly with respect to the recent clinical observations of Moir and Dale (15), will be reported shortly in a suitable publication.

SUMMARY AND CONCLUSIONS.

I. Certain factors influencing the extraction of ergot have been studied and discussed.

II. A detailed description of a satisfactory technique for applying the Isolated Rabbit Uterus method of Broom and Clark has been presented.

III. The official U. S. P. X process for the manufacture of Fluidextract of Ergot has been critically studied as to efficiency. Experimental results have been presented showing that this process does not provide for the appearance of the total activity of the drug in the finished fluidextract, thereby providing for gross inaccuracies in the official method of assay for crude ergot, and likewise providing for economic loss in the commercial manufacture of this product.

IV. A method of extraction, which avoids the error in assaying crude ergot resulting from the inefficiency of the official extraction process, has been described. The only objection to this method lies in the fact that the extracted activity is contained in a concentration too low to permit of the use of the official Cock's Comb method. The percolate must be tested by the more sensitive Isolated Rabbit Uterus method or the Colorimetric method.

V. Chemical tests for proving exhaustion of the drug of activity have been developed and described, and their limitations indicated.

VI. The U. S. P. General Type Process "C" for fluidextracts, has been studied upon ergot. This process was found to be very significantly superior, from the standpoint of efficiency, to the Type Process "B" now specified by the U. S. P. A change from Type Process "B" to Type Process "C" was recommended to the U. S. P. Committee of Revision in November 1931, on the basis of these results, *first*, because Type Process "C" afforded more accurate results in the assay of crude ergot, and *second*, because this process avoids a considerable loss of activity in actual manufacture of the product. This product, of course, is suitable for direct assay by either the official Cock's Comb, the Rabbit Uterus or the Colorimetric method. In utilizing this process for assaying crude or powdered ergot, the chemical tests for exhaustion should be employed.

VII. The p_H factor in extracting ergot has been discussed.

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(9) Thompson, *Ibid.*, 19 (1930), 113.
(10) Thompson, *Ibid.*, 19 (1930), 718.
(11) Wokes and Elphick, *Quart. J. Pharm. and Pharmacol.*, 3, No. 4 (1930), 599–625.
(12) Thompson, JOUR. A. PH. A., 19 (1930), 705.
(13) Swanson, Powell, Stevens and Stuart, *Ibid.*, 21 (1932), 320.
(14) Wokes and Elphick, *Quart. J. Pharm. and Pharmacol.*, 4, No. 1 (1931), 101.
(15) Moir and Dale, *Brit. Med. J.* (June 18, 1932), 1119.

PHARMACOPŒIAL EXHIBIT AT THE A. M. A. CONVENTION.

Herewith is shown the United States Pharmacopœial exhibit, installed at the convention of the American Medical Association, Milwaukee, during the week of June 12th. The exhibit was arranged by courtesy of the College of Pharmacy of the University of Wisconsin, and Edward J. Ireland and Al Rheineck were responsible for the display.

U. S. P. Exhibit at Milwaukee A. M. A. Meeting.

On the left of the picture may be seen an illustrated history of the Military Pharmacopœia of 1778, known as the Lititz Pharmacopœia. In the picture is shown Dr. William A. Brown, military surgeon with George Washington's army during their stay at Lititz, Pennsylvania; the Moravian Brethren's house in which the Pharmacopœia was written; to the left of Dr. Brown's photograph is a copy of the early pharmacopœia. The pharmaceutical preparations in the foreground were made by the pharmacy students according to the original formulas.

Continuing from the left may be seen pictures of modern pharmacopœias, then a reproduction of the Ebers Papyrus, an Epitome of Claudius Galen written in 1571, a copy of Dioscorides'