THE PHYSIOLOGICAL ACTIVITY OF "ERGOTIN" AND POWDERED EXTRACT OF ERGOT.

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There now seems little question as to the therapeutic value of the official fluid extract of ergot. It is sometimes desirable, however, to have solid or semi-solid ergot preparations in a more concentrated form than the crude drug, and it is also often advantageous to secure the active principles in a water-soluble form. These considerations, however, should have no weight, if it is learned that the process of manufacture of such special preparations destroys or greatly lessens the therapeutic activity originally possessed by the crude drug.

Two such "special preparations" have recently been the subject of investigation in this laboratory, and it seems of interest to report the results secured.

The first of these preparations is so-called "Ergotin." It is made by treating powdered ergot with benzin to remove the oils; air drying in order to free from benzin; and percolation with water. The percolate is reduced to a syrupy consistence at 90° to 120° C. and alcohol added. The resulting precipitate is removed by filtration and the filtrate reduced to a semi-solid extract at 90° to 120° C.

The second preparation is a powdered extract made by percolation of ground benzin-extracted ergot with 50 percent alcohol; reduction of percolate to a solid in vacuum dryer and addition of approximately an equal quantity of benzin-treated powdered ergot.

From theoretical considerations, it would seem that little, if any, ergotoxin would be contained in the "ergotin" and what activity it possesses would be due to the amines described by Barger, Dale, Kraft, and others. The powdered extract, however, consists of about one-half powdered drug and the remainder of an alcoholic extract, so one would expect all the active constituents to be present, unless the benzin or the elevated temperature exercised a deleterious influence.

Ergot still finds its chief field of usefulness as an oxytoxic; consequently, any laboratory attempt to estimate the therapeutic efficiency of the drug should be based upon a determination of its oxytoxic power. It has been shown conclusively that a measurement of the pressor-activity of ergot gives no reliable information of the value of the drug as a stimulant to uterine contractions, and it is illogical and useless to make such tests if the drug is to be used in obstetrical practice. It is not improbable, however, that blood-pressure tests upon dogs may give reliable data as to the efficacy of the drug as a circulatory stimulant for man.

The excellent work of Edmunds and Hale has demonstrated that the cock's comb test gives results closely paralleling those secured when the drug is tested upon the uterus of an experimental animal. These authors point out that the cock's comb method is simple and allows of considerable accuracy.

During the past few months, we have had occasion to examine twenty-four samples of crude ergot; four samples of ergotin; and nine samples of powdered extract of ergot. In every instance, when a large enough dose was given intramuscularly to white leghorn cocks, bluing of the comb, diarrhoea and dyspnœa

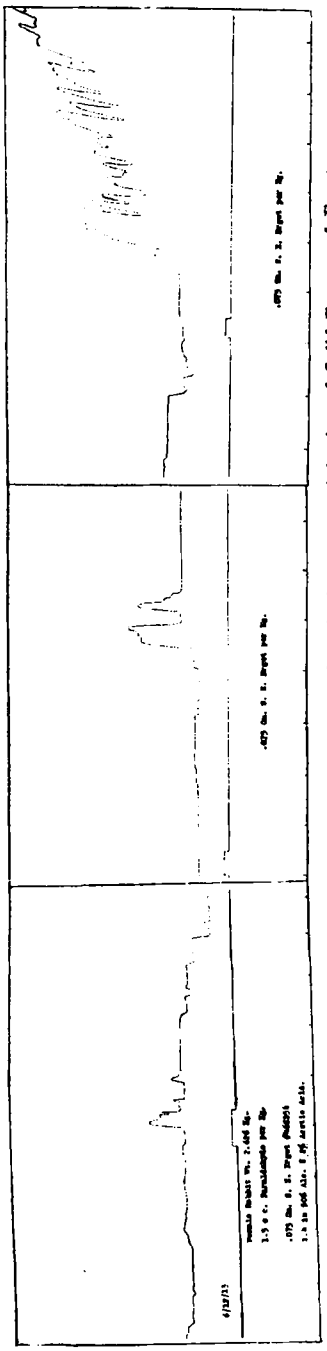

Figure I. Showing the contractions of a rabbit's uterus after the intravenous injection of Solid Extract of Ergot.

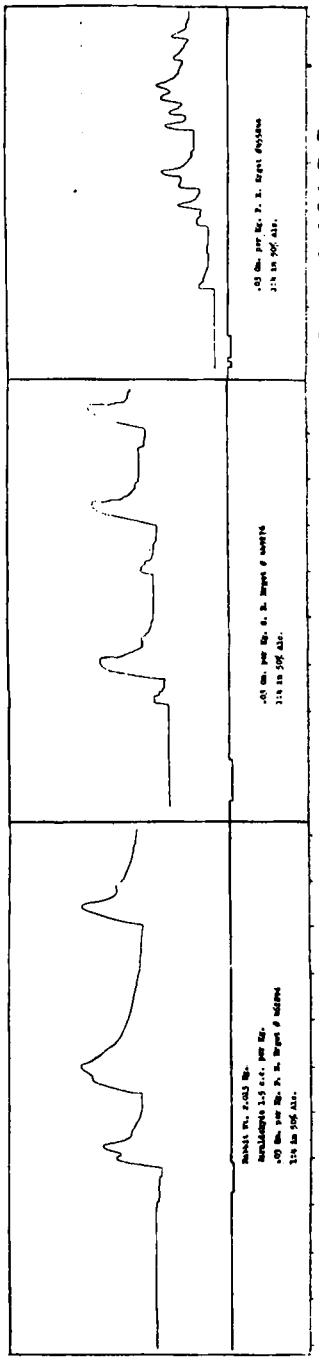

Figure II. Showing the contractions of a rabbit's uterus after the intravenous injection of Po. E. Ergot and of Sol. E. Ergot.

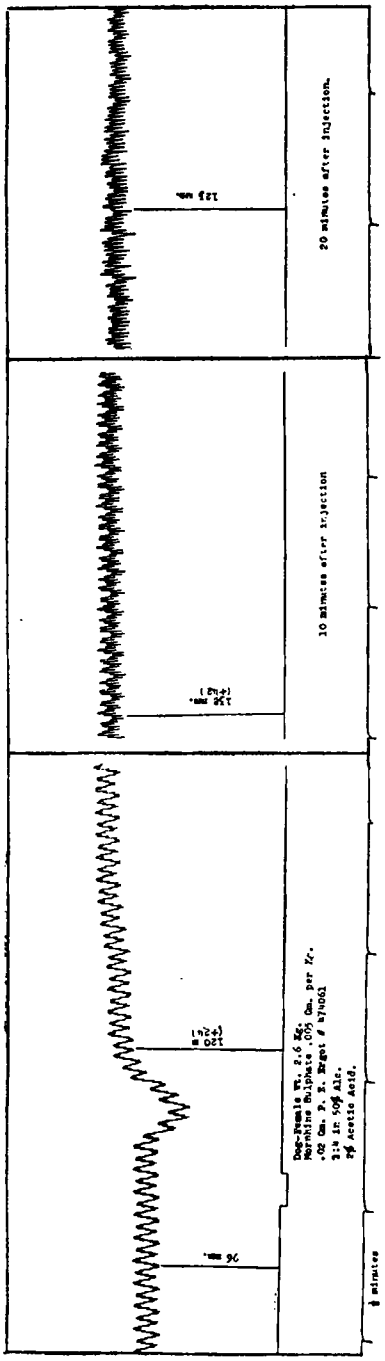

Figure III. Effect of Powdered Extract of Ergot on blood pressure of dog.

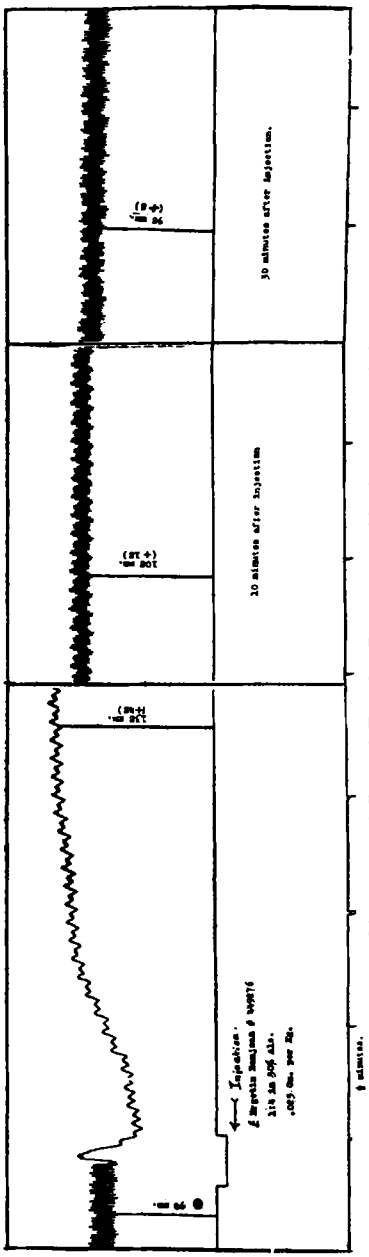

Figure IV. Effect of Ergotin, Bonjean, on blood pressure of dog.

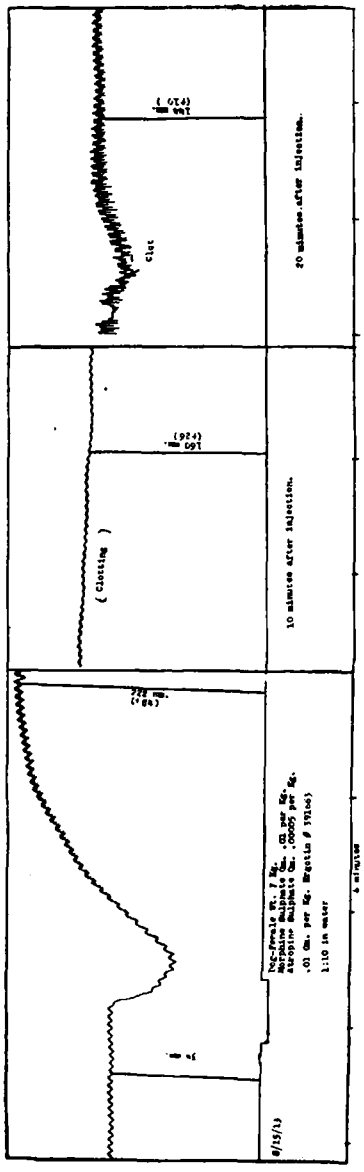

Figure V. Effect of Ergotin, Bonjean, in small amount on blood pressure of dog.

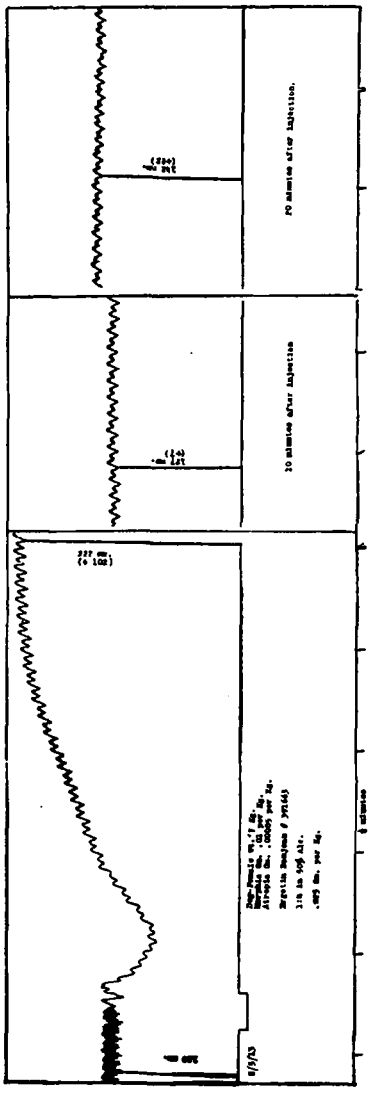

Figure VI. Effect of Ergotin, Bonjean, in medium amount on blood pressure of dog.

resulted; the symptoms produced by each preparation being practically identical. It seemed desirable, however, to test some of the samples of "ergotin" and powdered extracts upon the uterus of a lower animal. Consequently, rabbits were used in the way described by Cushny, and a marked effect was produced by these preparations in every instance in which they were employed. The tracings, represented in Figures 1 and 2, illustrate the results secured.

These figures do not show the entire records, as the uterus was allowed to return to and remain in, a practically quiescent state for at least one-half hour before the drug was injected.

While feeling that blood-pressure experiments gave no positive information as to the value of the preparations as stimulants of the uterus, nevertheless a number of tests were made upon dogs, using the method of Wood and Hofer, except that 10 mgms. of morphine per kilogram were administered and the dogs also received a small dose of atropine, as suggested by Edmunds and Hale. The following tracings, Figures III and IV, show that these preparations have a marked pressor action.

From the evidence presented, it seems fair to assume that "ergotin" and powdered extract of ergot have the characteristic "ergot" action. It is of interest, however, to learn whether the full amount of drug activity is retained in these preparations.

In the manufacture of "ergotin," approximately six pounds of drug are used to finish one pound of extract. For the powdered extract eight pounds of drug usually furnishes one pound of extract. Consequently, "ergotin" should be six times as active and the powdered extract eight times as active as the crude drug.

Of the twenty-four samples of crude ergot examined by the cock's comb test, all were capable of causing bluing of the comb when given in a dose of 1 gram per kilogram. Of the nine samples of powdered extract examined, a dose of 0.25 gram per kilogram was efficient in all instances. Of the four samples of "ergotin" 0.25 gram per kilogram was efficient in two cases; while 0.3 gram was required in the other two. From this, it seems that the powdered extract is about four times as active as the crude drug; while "ergotin" is, roughly, about three and one-half times as active.

By blood-pressure experiments, however, a different relation is apparent. We have found that 0.1 cc. per kilogram is the optimum dose of fluid extract; that is, this dose usually causes the maximal rise of pressure. With "ergotin," however, the optimum dose seems 0.0125 gram per kilogram; or about one-eighth that of the fluidextract. Cronyn and Henderson have pointed out that large doses of ergot produce poor pressor response, and this is well illustrated by the following tracings, Figures V, VI and VII, where it is seen that with the same preparation of Ergotin (No. 391663) a small injection of 0.01 gm. per kilogram sustains an increased blood pressure much better than does an injection of 0.025 or of 0.05 gm. per kilogram. In fact the blood pressure twenty minutes after the injection of 0.05 gm. per kilogram is actually below its initial pressure. This may serve to explain the poor results that have been secured by others in testing the pressor action of these preparations.

In conclusion it may be said that:

1. "Ergotin" and powdered extract of ergot are capable of causing bluing of

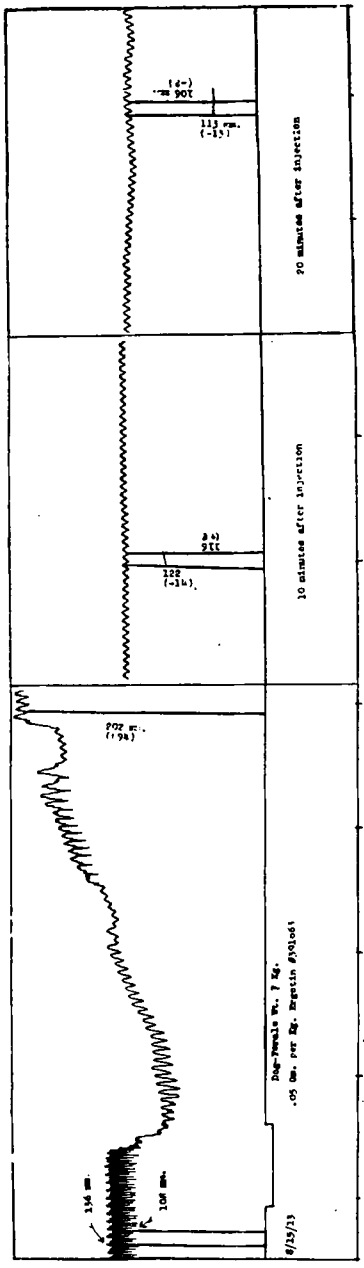

Figure VII. Effect of Ergotin, Bonjean, in large amount on blood pressure of dog.

the cock's comb; contraction of the rabbit's uterus; and rise of the dog's blood-pressure.

2. There is apparently a considerable loss in the manufacture of these preparations, of those substances influencing the uterine movements, while there is but slight loss in the pressor-activity originally possessed by the crude ergot.

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