Contributed and Selected

THE PHYSIOLOGICAL ACTIVITY OF VARIOUS PHARMACEUTICAL PREPARATIONS OF ERGOT.

WILLIAM A. PEARSON, PHILADELPHIA.

Before any authoritative statement can be made in regard to the relative merits of the various pharmaceutical preparations of Ergot, some accepted method of testing them must be agreed upon and all tested by this method.

Possibly it is a little premature to assert that any one of the several methods proposed is a satisfactory one for testing preparations of this complex drug, however, the results of blood pressure tests on dogs have so generally been considered of value that this method has been used as a basis for comparing the activity of the samples tested, and several reasons will be given later for believing this method is a good index of physiologic and even therapeutic activity.

Outline of Blood Pressure Method Used in These Tests. All dogs were well fed for at least ten days before they were used, they were of various breeds, of both sexes, and most of them weighed about ten kilogrammes. Each dog was anesthetized by injecting intraperitoneally a sufficient quantity of 10 percent solution of trichlorbutyl alcohol dissolved in olive oil, to produce a deep narcosis (30 cc. is usualy sufficient for a dog weighing ten kilos).

The carotid artery was directly connected with a U shaped mercury manometer, using half saturated magnesium sulphate solution to fill cannula and rubber tubes. The preparations to be tested were injected into the femoral vein. Solid preparations were usually dissolved in sufficient physiological salt solution or dilute alcohol so that 1 cc. of the solution would represent 1 gm. of the crude drug. After filtering, 1 cc. of the filtrate was injected into the femoral vein.

Several reproductions of kymograph records of blood pressure tracings are presented. Unfortunately the reduction has obliterated the individual pulsations, time marks, and points of injection. Each plate represents a continuous tracing for about ten minutes. The blood pressure stated in each description has been obtained by measuring the original tracing, and is not multiplied by two as is sometimes done when using a U shaped mercury manometer.

Plate No. 1 shows the action on the blood pressure of a freshly prepared fluid-extract of Ergot, U. S. P. made from selected drug and under the best conditions of manufacture.

The dog weighed 8.2 kilos and the blood pressure promptly rose 65 millimeters after the injection of 1 cc. of the fluid extract. This greatly increased pressure was sustained throughout the tracing (and much longer).

This sample was found to test satisfactorily by the cock's comb test and by the uterine method.

Five hundred samples of this fluidextract were sent to as many physicians and the clinical reports returned were all favorable and several actually remarkable.

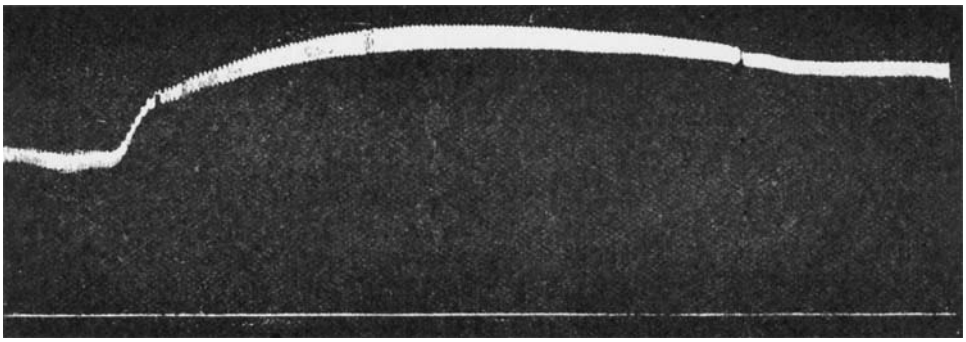

Plate No. 1

One physician reported that it stopped a very bad post partum hemorrhage in twelve minutes after it had been taken orally.

Activity After Heating—Experimental.

One cubic centimeter of a fluidextract of Ergot was heated on the steam bath (about 95° C.), for thirty minutes. At the end of this time the residue was taken up with about two cubic centimeters of dilute alcohol and the total quantity injected. The first half of Plate No. 2 shows the effect on the blood pressure, namely a temporary maximum rise of 13 mm. The last half of the tracing shows the effect of 1 cc. of the original fluidextract before heating. A sustained rise of 15 mm. It should be pointed out that the results of the first injection of Ergot must be considered most reliable. However, when the injection fails

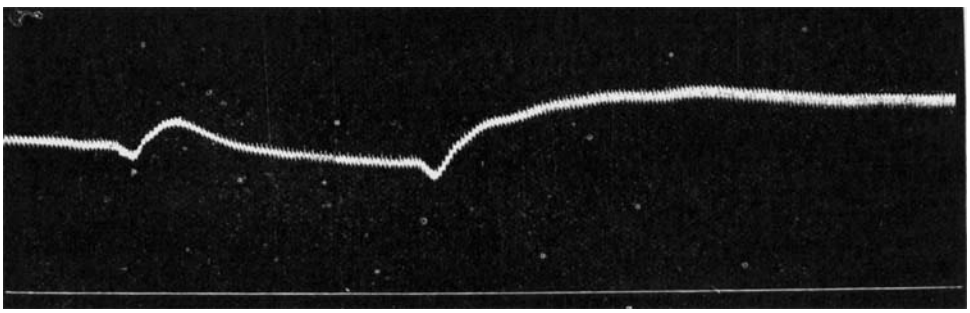

Plate No. 2

to produce much change in blood pressure the results of a second or even a third injection may be regarded of considerable value.

Plate No. 3 shows the effect of heating the fluidextract of ergot on the steam bath for 15 minutes. It may be seen that but little diminution has taken place

of its power to raise and sustain blood pressure compared to the sample heated for 30 minutes (Plate No. 2).

One cubic centimeter of the same fluidextract of ergot as was used for Plate No. 2 and 3 was evaporated to dryness by placing near an electric fan for one

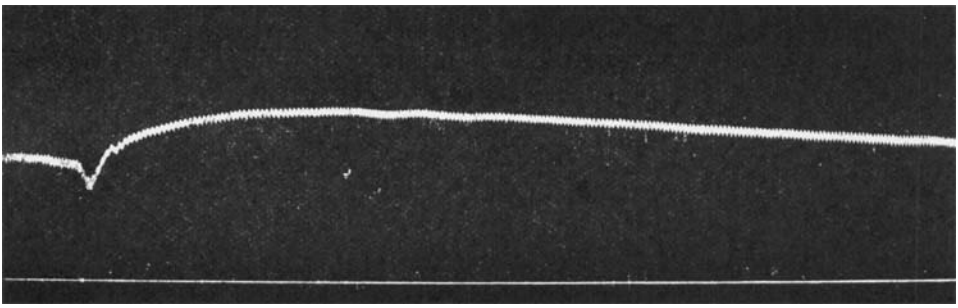

Plate No. 3

hour. The residue was set aside at room temperature in the light for three days, then dissolved in 1 cc. of dilute alcohol and injected into a dog. The blood pressure rose 20 mm. and was consistently sustained throughout the tracing. (See Plate No. 4.)

From an examination of tracings Nos. 1, 2, 3 and 4, it may be readily seen that (1) it is possible to obtain a fluidextract that will greatly increase the blood pressure and consistently sustain it, (2) 30 minutes on the steam bath greatly destroys the blood pressure raising power of a fluidextract of ergot, and (3) that 15 minutes on the steam bath or one hour over a fan does not greatly destroy the power of a fluidextract to raise and sustain blood pressure. Therefore solid preparations of Ergot which will materially raise and sustain the blood pressure are possible. Let us see the action of several of the more important solid preparations on the market. All of these samples were taken from the wholesale department of Smith, Kline & French Co., and represent products from several of the more prominent manufacturers.

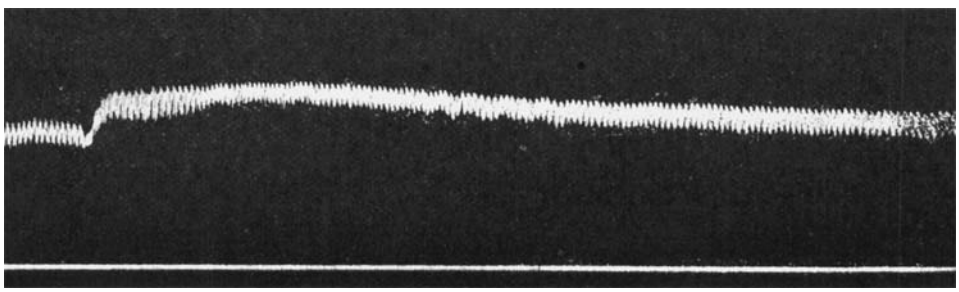

Plate No. 4

Plate No. 5 shows the result of injecting 1 cc. of 1-5 solution of extract of ergot, U. S. P. The only favorable indication produced by this sample is the slight widening of the tracing which is suggestive of some direct stimulation of the heart.

Plate No. 6 shows the result of injecting 1 cc. of a 1 to 5 solution of another sample of extract of ergot, U. S. P. This sample should be considered not only incapable of producing its intended therapeutic action, but actually dangerous to human life as it lowered the blood pressure 20 mm., greatly increased the pulse rate and depressed the contractions of the heart.

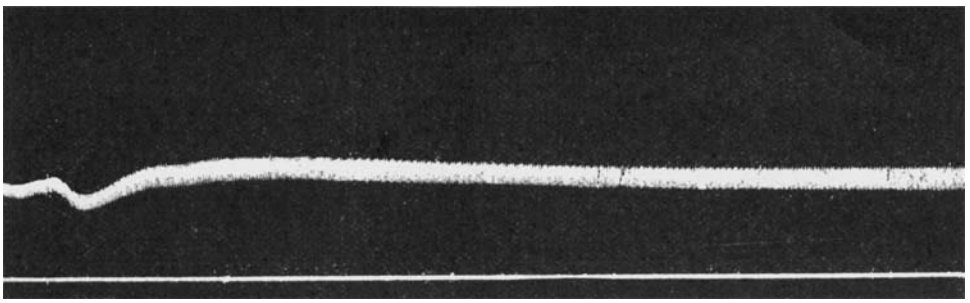

Plate No. 5

Plate No. 7 shows the result of injecting 1 cc. of a 1 to 5 solution of powdered extract of ergot. Note the marked preliminary fall and the temporary rise in blood pressure.

Just previous to each of the two depressions on the first half of tracing reproduced in Plate No. 8, powdered extract of ergot and solid extract of ergot were respectively injected in quantities corresponding to 2 gm. of the original crude drug. It is needless to say that neither preparation materially increased the blood pressure. About half way between the second depression and the marked rise, 2 cc. of 70 percent alcohol was injected. No appreciable change in blood pressure took place, showing that the alcoholic menstruum injected is not responsible for the change in pressure when an active fluidextract of ergot is injected.

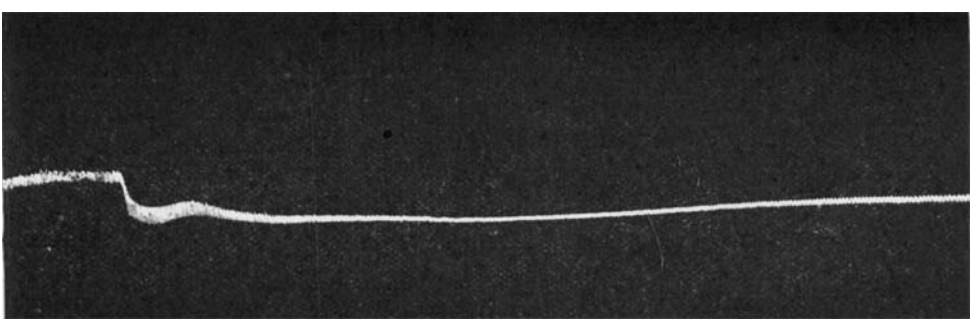

Plate No. 6

The first marked rise (20 mm.) in blood pressure was caused by the injection of 1 cc. of a good fluidextract of ergot and the second rise (35 mm.) by the injection of ½ cc. of tincture of strophanthus.

The first half of Plate No. 9 shows the effect on the blood pressure of an-

other brand of powdered extract of ergot, the second half, the effect of 1 cc. of a 1 to 5 solution of Ergotin Bonjean.

Plate No. 10 shows the effect of injecting 1 cc. of a 1 to 5 solution of another sample of Ergotin Bonjean.

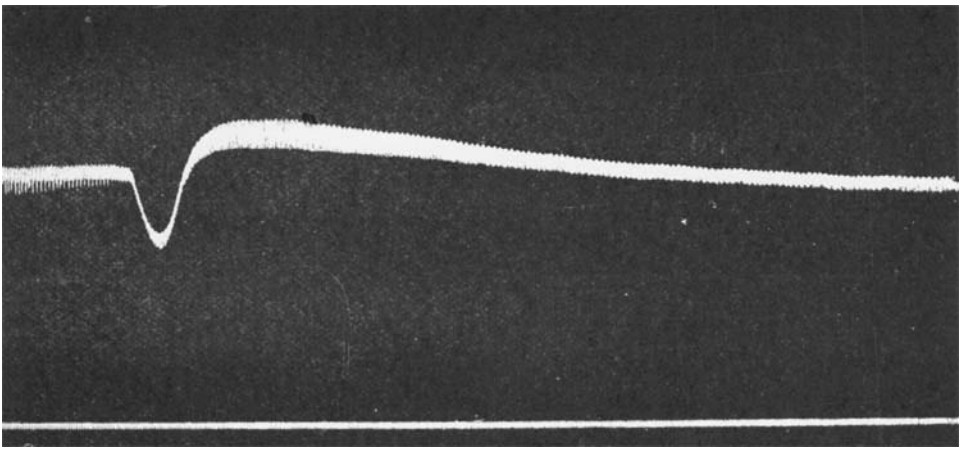

Plate No. 7

Plate No. 11 shows another kymograph record showing the bad effect of injecting 1 cc. of a 1 to 5 solution of Ergotin Bonjean. Although the heart of this dog was strong and vigorous this sample lowered the pressure, greatly increased the rapidity of the heart beat and actually killed the dog within five minutes. A dose of this product might stop a post partum hemorrhage by reducing the blood pressure, but it is very doubtful if any physician would use it if he knew its marked depressant action on the heart.

The first injection in Plate No. 12 is 1 cc. of a 1 to 5 solution of Ergotin Bonjean. This sample actually raised the blood pressure 10 mm. The second

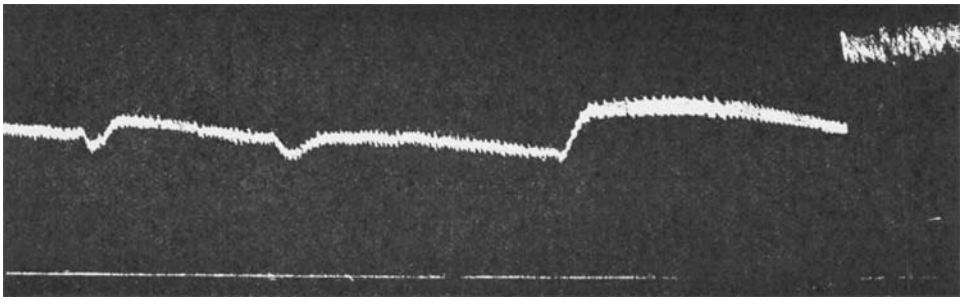

Plate No. 8

injection is 1 cc. of a fluidextract of ergot, which raised the blood pressure 20 mm. Still better samples of Ergotin Bonjean have been examined but most of those on the market will markedly lower the blood pressure as may be seen from the preceding plates.

The first half of Plate No. 13 shows the effect of a 1 cc. of 1 to 5 solution of one brand of Ergotin Bonjean, the second half of tracing shows the effect of injecting 1 cc. of a 1 to 5 solution of another brand of Ergotin Bonjean. The marked difference between the physiological action of the two samples is good

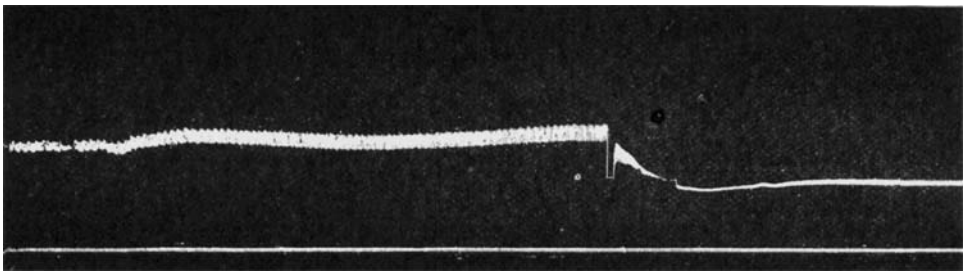

Plate No. 9

evidence that equal therapeutic results would not be expected. And the action of either would probably be different than the fluidextract shown in Plate No. 1.

The first injection in Plate No. 14 is 1 cc. of a 1 to 5 solution of Ergotin Bonjean. The second injection 1 cc. of a 1 to 5 solution of solid extract of Ergot; the third injection ½ cc. of tincture of Strophanthus, which raised the blood pressure 20 mm.

Plate No. 15 shows the action of another sample of Ergotin Bonjean. One cc. of a 1 to 5 solution was injected. Certainly the therapeutic action of this sample would be different from the fluidextract shown in Plate No. 1.

The first two injections of tracing reproduced in Plate No. 16 are respectively 1 cc. and 1.66 cc. of a 1 to 5 solution of the same solid extract of Ergot. It may be seen that the increased dose does not affect the blood pressure proportionally. The third injection is 1 cc. of fluidextract of ergot, which was one year and six

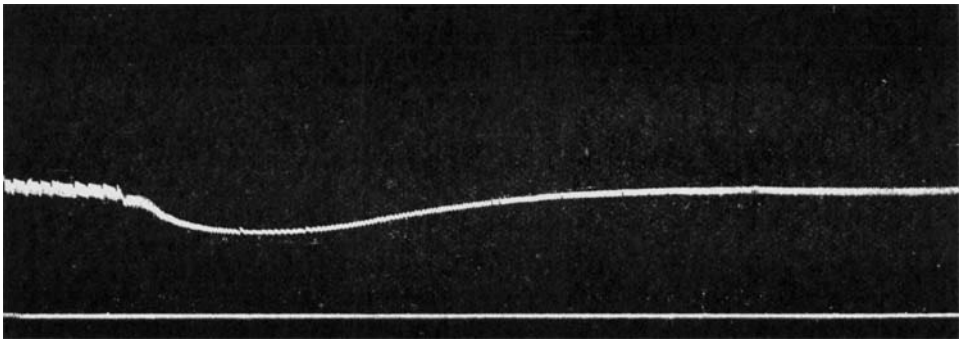

Plate No. 10

months old at time of injection. This fluid extract was a portion of the lot which was used for making Plates No. 2, 3 and 4, and when fresh it produced a rise in blood pressure of about 20 mm. and consistently sustained the blood pressure for at least thirty minutes. In this tracing may be seen one of the earliest signs of

deterioration, namely, a failure to consistently sustain the blood pressure. Therefore a complete blood pressure tracing is preferable to an "abbreviated" one where the drum of the kymograph is permitted to be stationary while making the tracing and recording only the maximum pressure reached.

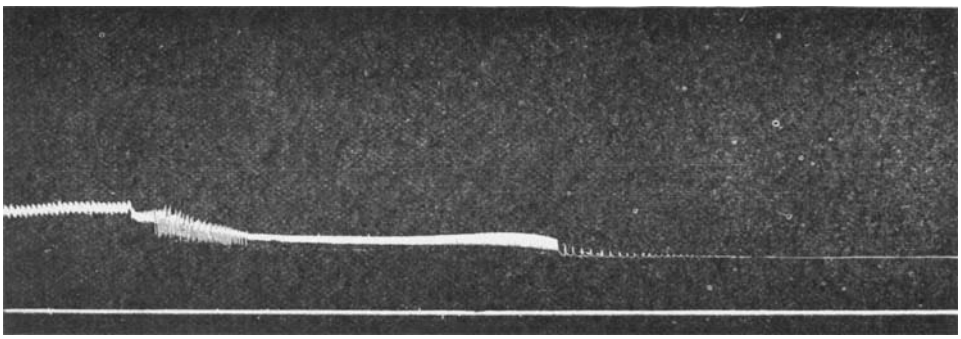

Plate No. 11

For the purpose of comparing one preparation of ergot with another it was formerly my custom to inject into the same dog 1 cc. of a standard preparation of ergot, but since the standard fluidextract of ergot changed so rapidly and the dog was not sensitive to two injections close together it has more recently been my custom to inject ½ cc. of the U. S. P. tincture of Strophanthus (see Plates 8, 14 and 17). This procedure has a two-fold advantage; first, it gives an idea of the sensitiveness of the dog to drugs which increase the blood pressure and, second, the action of Strophanthus is not interfered with by previous injections of ergot.

Plate No. 17 shows how the increase in blood pressure due to ergot may be compared with the increase in blood pressure produced by Strophanthus. In this case 1 cc. of fluidextract was injected which produced a rise in blood pres-

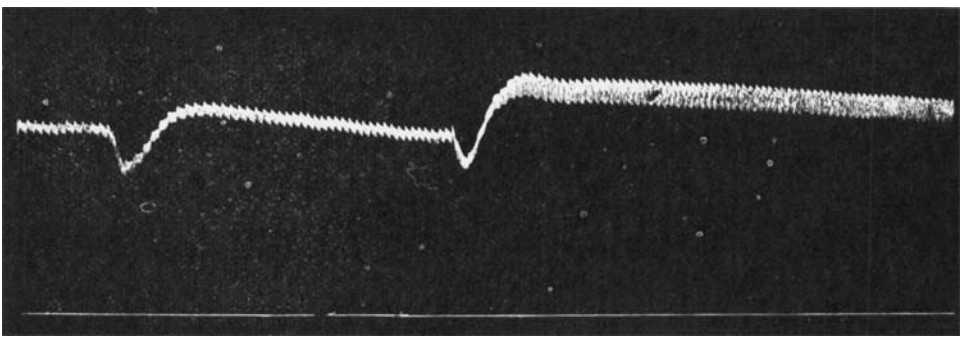

Plate No. 12

sure of 20 mm. and ½ cc. tincture of Strophanthus produced a rise of 25 mm. After the increase of blood pressure due to Strophanthus had taken place 1 cc. of ether was injected and this caused the blood pressure to return to nearly the same as before any injection had been made. It is seldom possible, however,

to make another tracing from the same dog after the injection of ½ cc. of tincture of Strophanthus. The tincture of Strophanthus used was found to have a minimum fatal dose per gm. weight of frogs of 0.000,16 cc. and the same lot of frogs to be killed by 0.000,001,1 gm. of crystalline strophanthin (Hough-

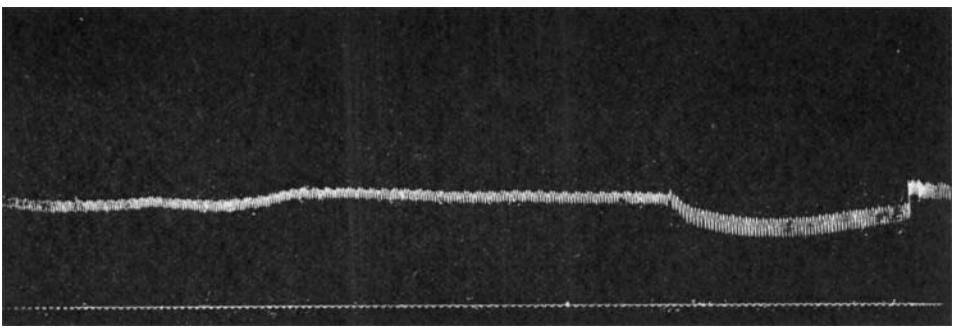

Plate No. 13

ton) per gm. body weight. There is no reason why crystalline strophanthin could not be used as a standard for comparison in blood pressure tests and this procedure would probably be an advantage.

Plate No. 18 shows the difference in pharmacologic action between a sample of fluidextract of ergot that has been tightly corked and the same one when frequently exposed to the air. The first injection consisted of 1 cc. of a fluidextract of ergot that had been kept for one year and six months in a brown pint bottle protected from the light but at room temperature and uncorked about every two weeks and a little poured out, much in the same condition as a retail druggist would keep his stock bottle. The rise in blood pressure was only temporary and amounted to a maximum of 20 mm. The second injection consisted of 1 cc. of the same identical fluidextract which had been kept tightly corked in a 4 oz. bottle

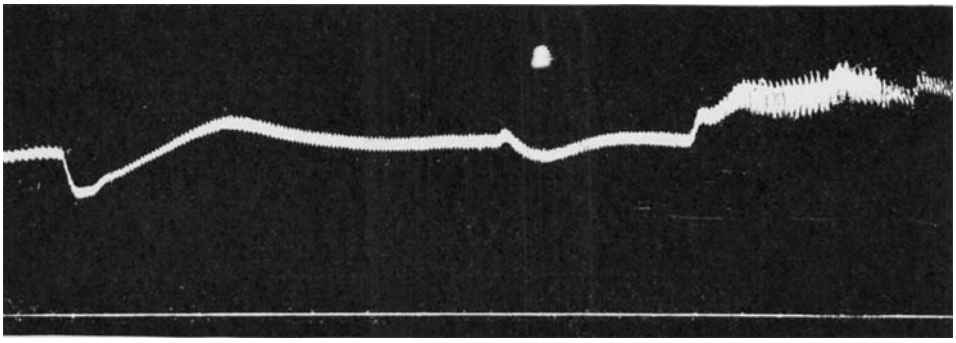

Plate No. 14

for the entire time, at the same temperature and protected in same way from the light. The maximum rise in blood pressure amounted to 25 mm. and this increased pressure was much more consistently sustained.

Discussion. The cause of the initial fall in blood pressure has not been set-

tled. In Plate No. 1 it is absent, in Plate No. 18 it is absent in the second injection, but present in the first. These examples and many others indicate that it is due to some deterioration. It may be due to amines formed in decomposition. Hydroxylamine produces a similar fall but para hydroxyphenyl-ethyl-amine

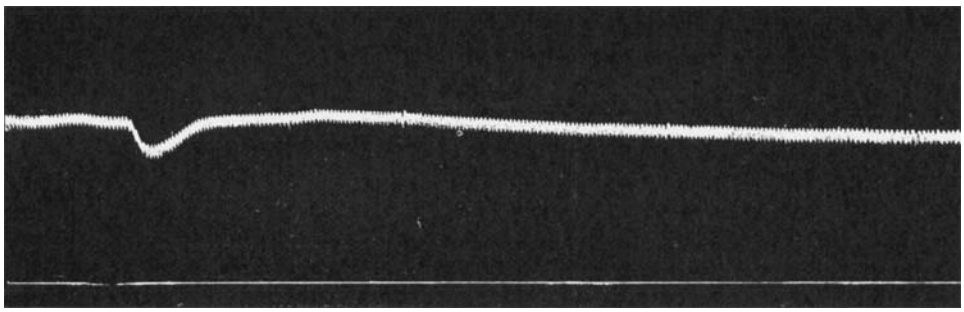

Plate No. 15

which is naturally present in ergot increases the blood pressure. Beta-imidazolyl-ethylamine which is also present, sometimes increases the blood pressure, sometimes lowers it. If the acetic acid in the U. S. P. fluidextract be exactly neutralized with sodium bicarbonate the temporary fall in blood pressure is diminished or eliminated.

No doubt there is a close relation between the cock's comb test and blood pressure test as there undoubtedly is between the blood pressure test and uterine test.

If a leghorn rooster be anesthetized with 5 cc. of 10 percent trichlorbutyl alcohol in olive oil, its carotid artery connected with a mercury manometer, and ½ cc. of fluidextract of ergot be injected either intravenously or intra muscularly the blood pressure rises, the comb becomes dark at the tips, and if a section be immediately made through the comb with a sharp knife the tips will be found

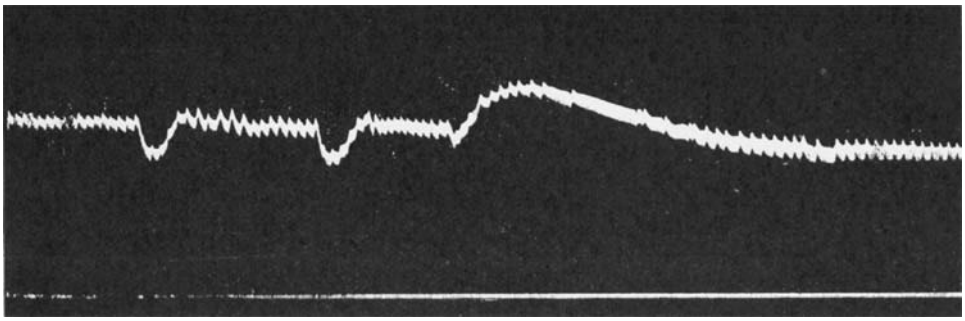

Plate No. 16

gorged with blood and scarcely any blood at the base of the comb. This experiment indicates a constrictor action of the arterioles which is directly the cause of the darkening of the cock's comb.

Ergot may be said to contract muscle tissue generally with a particular action

on the pregnant uterus. The greater portion of muscular tissue of the arteries and more particularly in the smaller arteries contract and this action is directly responsible for the rise in blood pressure. Even in the capillaries the single layer of endothelial cells may be contracted. The arteries in the gravid uterus are

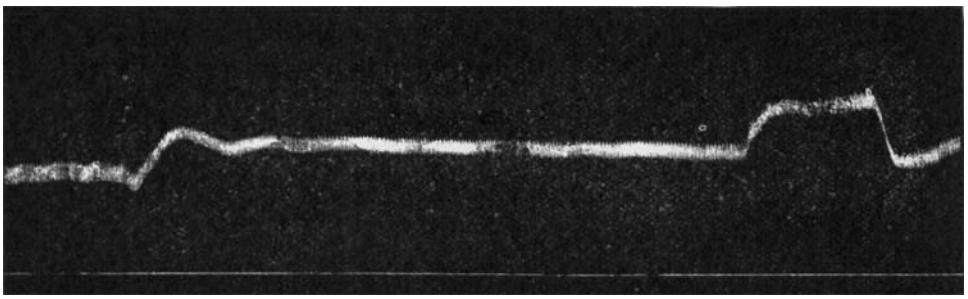

Plate No. 17

abnormally thickened and this fact may directly account for the selective action mentioned by authorities on materia medica.

It seems clear that the blood pressure method of testing ergot at least makes possible the rejection of inferior samples and preparations of ergot and that a preparation which will conform to the following standard could safely be recommended for therapeutic use.

Blood Pressure Standard for Ergot. One cc. of a fluidextract of ergot (or an amount corresponding to 1 gm. of crude drug of any preparation) when injected into the venous circulation of a dog weighing approximately 10 kilos, and which has been completely anesthetized with trichlorbutyl alcohol should promptly increase the blood pressure 30 mm. (60 mm. if reading is doubled) and

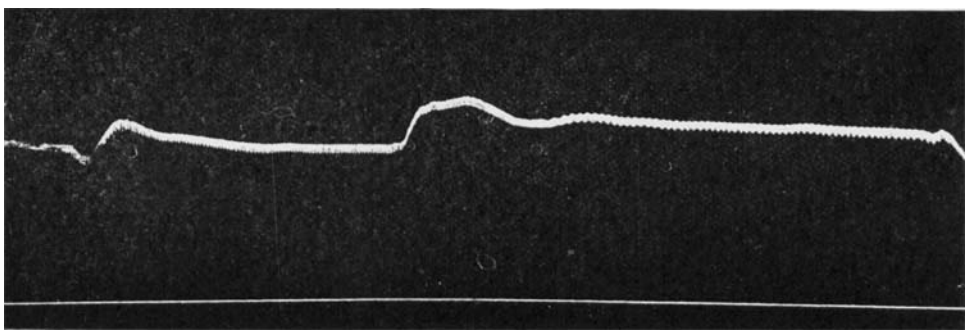

Plate No. 18

consistently sustain it for at least 10 minutes. Furthermore a preliminary fall in blood pressure should not be over 10 mm. (20 mm. if reading is doubled) and the width of the tracing should be increased at least one-fourth.

Summary. In the brief descriptions of the plates several ideas have been more or less clearly brought out. Other ideas may be suggested by a study of

the reproductions of the kymograph records. The more important points are as follows:

First—A therapeutically active preparation of ergot has a considerable vaso constrictor action, which increases the blood pressure of a dog. (Plate No. 1.)

Second—A therapeutically active proportion of ergot directly stimulates the heart muscle. The kymograph records show the slowing of the heart and an increase in the difference between the blood pressure during systole and during diastole. Of course the amount of increase in the blood pressure caused by the direct stimulation of the heart muscle is recorded along with the vaso constrictor action, yet a good idea of the direct action on the heart muscle can be obtained by observing the increase in the difference between the blood pressure during systole and during diastole, also by noting the decrease in the rate of the heart beat.

Third—It has been shown that a therapeutically active preparation of ergot increases the blood pressure of a rooster and that the vaso constrictor action of the arterioles in the comb may be directly responsible for the darkening.

Fourth—It is very doubtful if an active preparation of ergot contracts only the muscles of the uterus without affecting either the heart muscle or the muscular tissue of the blood vessels, both of which may be recorded in the blood pressure tracings.

Fifth—One of the first evidences of the deterioration of a preparation of ergot is the loss of power to sustain the blood pressure over a period of several minutes. A good preparation of ergot will sustain the blood pressure for about two hours.

Sixth—When the heat of a steam bath is applied to a sample of fluidextract of ergot it looses its power to materially increase and sustain the blood pressure. Evaporation of the fluidextract over a fan does not destroy its power to materially increase and sustain the blood pressure.

Seventh—Tincture of Strophanthus may be injected after the injection of Ergot for the purpose of determining the susceptibility of the test animal.

Eighth—Most of the solid preparations of ergot tested show a markedly different physiological action from a therapeutically active fluidextract of ergot. Some of the solid and powdered extracts of ergot tested showed practically no effect on the blood pressure, others markedly lowered the blood pressure. Various samples of Ergotin Bonjean were found to produce widely different changes on the blood pressure.

Ninth—The therapeutic activity of solid and powdered extract of Ergot and of Ergotin Bonjean should be regarded with suspicion and a recently tested fluidextract of ergot used.

Tenth—An important link of evidence to prove or disprove the therapeutic efficiency of Ergot preparations would be five hundred clinical reports upon a product which produced a marked fall in blood pressure such as was used for the kymograph record reproduced in Plate No. 11.

In this case the dog actually was killed by the preparation yet some might claim it was therapeutically efficient because a greatly lowered blood pressure

would stop a hemorrhage. The rank and file of physicians would, however, prefer to stop a hemorrhage by other means.

If any one cares to take the responsibility of making clinical tests with such a product let him who doubts the significance of blood pressure tests take the initiative.

PHARMACOLOGIC LABORATORY, SMITH, KLINE & FRENCH COMPANY.

DETERMINATION OF ALCOHOL IN TINCTURE OF IODINE.

J. W. MARDEN.

It is essential in the assay of tincture of iodine, to determine the percentage of alcohol used in preparing the tincture, as well as to determine the iodine and potassium iodide. The ordinary method of determining alcohol by making alkaline with potassium hydroxide and distilling cannot be used on this preparation because the ethyl iodide always existing in the tincture distills at even a lower temperature than alcohol and in experiments run for this purpose considerable amounts of the iodide were found in the alcoholic distillate. There have been various modifications of the distillation method suggested (1, 2, 3), but none of them combine the desired accuracy with the small amount of time necessary for a determination. The method proposed by Thurston and Thurston consists in the decolorizing of the iodine with sodium thiosulphate, making alkaline with sodium hydroxide, distilling and determining the alcohol in the ordinary way. The results by this method are "practically the percentage of absolute alcohol in the mixture." Experience has shown that with this method only approximate results can be attained, and often even after redistillation the alcoholic solution smells strongly of hydrogen sulphide and sulphur dioxide. It might be suggested, however, that arsenous oxide would be better than sodium thiosulphate for decolorizing the iodine.

A shorter method in which the percentage strength of the alcohol used in preparing the tincture can be calculated from the specific gravity of the tincture, based upon experimentally determined factors, is proposed in this paper. It was found in the laboratory that a correction factor could be obtained for varying amounts of either potassium iodide or iodine when dissolved in alcohol, so that the weight of a given volume of alcohol could be calculated by subtracting the increase in weight due to either. This factor for any given volume consists in the weight change due to one gram of the added substance dissolved in 100 cc. of alcohol. It is very obvious that each substance must have its own factor. If the factor be multiplied by the number of grams of iodide per 100 cc. as the case may be, the weight of alcohol used in the preparation is found by substracting both from the weight of the given volume of the tincture.

(1) Inversion of I with Hg as suggested by Alcock.—Proc. A. Ph. A., 1904, 583.
(2) Inversion of I with Fe as suggested by Roscoe & Schorlemer.—Treatise on Chemistry, Vol 1.
(3) Inversion of I with $Na_2S_2O_8$ suggested by Thurston & Thurston.—Proc. A. Ph. A., 1912, 1155.