A COMPARISON OF THE PHARMACOLOGICAL SYNDROMES OF ERGOSTETRINE (ERGONOVINE) AND THE ERGOTOXINE GROUP OF ERGOT ALKALOIDS.*,[1]

BY MARVIN R. THOMPSON.[2]

The confusion resulting from the almost simultaneous appearance of reports from four different laboratories, announcing the discovery of what has been called the "true oxytocic principle of Ergot," has been clarified to a considerable extent. Although the principle was at first rather widely believed to be non-alkaloidal, the writer's original identification of the principle as an alkaloid (1), and his original contention (2) that the principles obtained in the four different laboratories were one and the same alkaloid has been acknowledged by the different groups of workers (3) after an exchange of specimens. The matter of selecting a single name for the new alkaloid has been at least partially settled. Because of the obvious difficulty of choosing one from the four assigned by the discoverers (ergostetrine (Thompson), ergometrine (Dudley and Moir), ergotocin (Kharash and Legault), ergobasine (Stoll and Burckhardt)), the Council on Pharmacy and Chemistry of the American Medical Association voted to adopt the name "ergonovine" for the new alkaloid (4), thus creating uniformity of nomenclature in the United States but not in other countries.

The total alkaloids of ergot may conveniently be classified according to differences in oxytocic activity, with the least toxic but most clinically active ergostetrine on the one hand, and the most toxic but clinically least active ergotoxine group of alkaloids (ergotoxine, ergotamine, sensibamine and ergoclavine) on the other. The members of the latter group are qualitatively indistinguishable in important pharmacodynamic actions and indeed apparently differ only slightly in these actions from the quantitative standpoint (5, 6). Although all five of the alkaloids have been used in these studies, the similar nature of the action of the four alkaloids comprising the "ergotoxine group" makes it unnecessary to reproduce illustrations and devote space to detailed considerations of all of the individual alkaloids. Since ergotoxine itself is typically representative of the four alkaloids comprising the group, it suffices to confine the experimental data and discussion to ergotoxine and ergostetrine for the purposes of this paper.

The ergostetrine used in these studies was the crystalline free base prepared by the author as described elsewhere (5). The ergotoxine employed was in the form of the crystalline ethanesulfonate, kindly supplied by Burroughs Welcome and Co. The ergotamine used was in the form of the crystalline tartrate, generously supplied by the Sandoz Chemical works. The ergoclavine was obtained as an ampulled solution through the courtesy of Dr. Joseph Rosin of Merck and Co., while the sensibamine employed consisted of the ampul solution manufactured by Parke, Davis and Co. and distributed commercially under the proprietary name "Ergone."

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The ergotocin, ergometrine and ergobasine used in obtaining certain of the reproduced tracings consisted in all instances of authentic specimens of crystalline material obtained through exchanges with the three other groups responsible for the independent discovery of the variously named alkaloid.

BLOOD PRESSURE.

The effect of the ergotoxine group of alkaloids is well known. Single intraven-

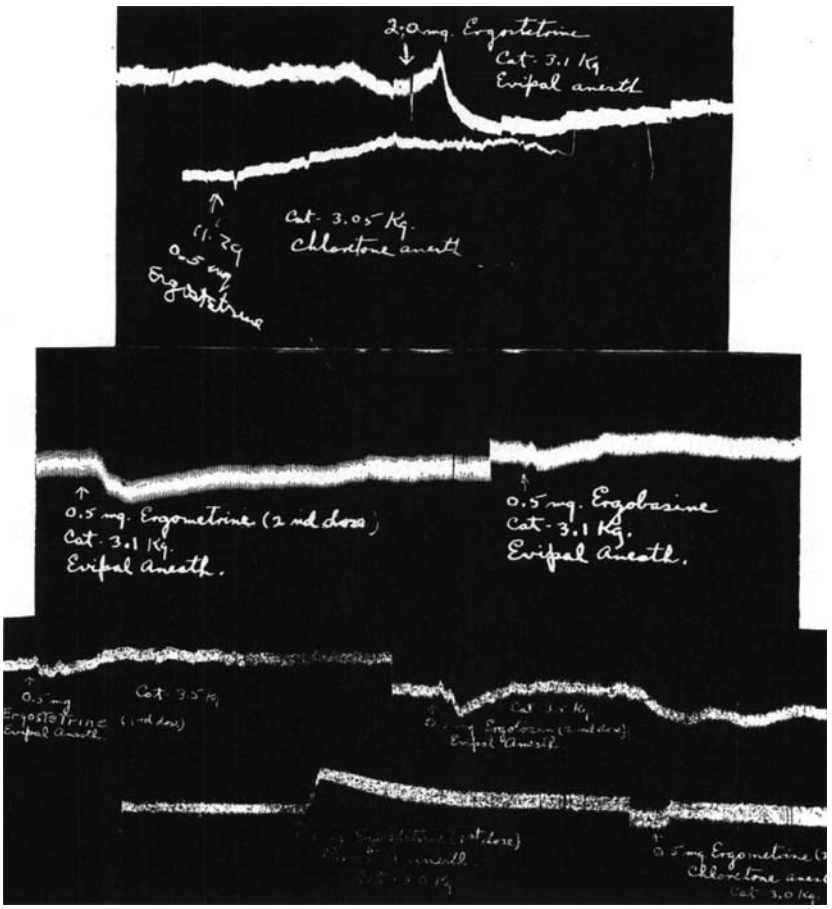

Fig. 1.—The carotid blood pressure effects of ergostetrine on cats anesthetized with chloretone and the barbiturate "evipal."

ous doses of 0.05 to 0.15 mg. per Kg. to anesthetized or unanesthetized cats or dogs produce a strong pressor action lasting for 15 to 60 minutes or more. The blood pressure returns to normal long before the drug has spent itself, as evidenced by the fact that repeated dosage results in progressively decreasing pressor response, leading to a reversal of the pressor action of epinephrine (the latter especially in cats). The literature deals extensively with these effects.

On blood pressure, ergostetrine differs considerably from the four alkaloids

comprising the ergotoxine group, although the difference is not such as to enable one to detect or estimate ergostetrine in admixture with the other alkaloids. The author (5) ascribed a relatively weak pressor action to ergostetrine, with the occasional observation of a depressor effect on cats anesthetized with chloretone. Davis, *et al.* (7), concluded that the same alkaloid has sometimes a demonstrable pressor action in pithed cats, but a depressor action in anesthetized animals. It appears, therefore, that there is a disagreement regarding the blood pressure action of ergostetrine.

This discrepancy is apparent, however, rather than real. Whether one obtains a pressor or a depressor response depends upon the type and depth of anesthesia. Figure 1 shows the depressor action on cats anesthetized with a barbiturate, and the pressor action on cats anesthetized with chloretone. The same illustration shows the progressively decreasing response following repeated doses.

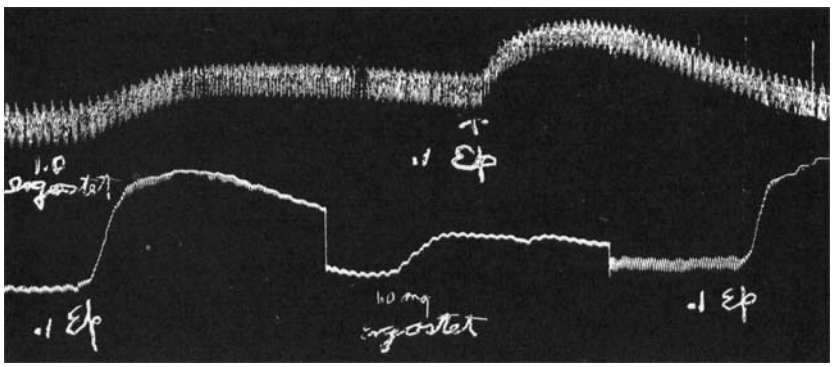

Fig. 2.—Showing the inability of ergostetrine to significantly influence the carotid blood pressure effect of epinephrine on a dog (upper tracing) and a cat (lower tacing), both anesthetized with chloretone.

Figure 2 shows the pressor action on a dog and cat, and the failure of ergostetrine to alter the pressor effect of epinephrine.

THE SITE AND CHARACTER OF THE ACTION OF ERGOSTETRINE AND THE ERGOTOXINE GROUP.

1. Isolated Rabbit Uterus.—That ergostetrine stimulates isolated segments of the mature rabbit uterus, in contrast to the depressing or paralyzing action of the ergotoxine group of alkaloids is already well established (5, 7, 8, 9, 10). Figure 3 is included merely to show the similarity of action of the four-named alkaloids now known to be one and the same alkaloid, and also to show how the presence of even relatively small amounts of the ergotoxine group in admixture with ergostetrine (as found in either aqueous or hydroalcoholic extracts) results in paralysis of the tissue so that the ergostetrine loses its effect in stimulating contractions. Preparations Nos. 42 and 43 in the last part of the tracing were solutions containing 0.15 mg. of ergostetrine and 0.15 mg. of ergotoxine activity (the latter by Broom-Clark assay) per cc. *For this reason, Ergot preparations containing ergostetrine, but free from the ergotoxine group, can be assayed on the isolated rabbit uterus, but the er-*

gostetrine activity of ergot preparations containing even small amounts of the ergotoxine group cannot be accurately estimated without prior chemical separation of the ergotoxine group. (Fig. 3.)

That ergostetrine is not wholly free from the depressant or paralyzing action characteristic of the ergotoxine group is shown in Fig. 4. This is important in connection with assaying ergostetrine on the rabbit uterus, emphasizing the necessity

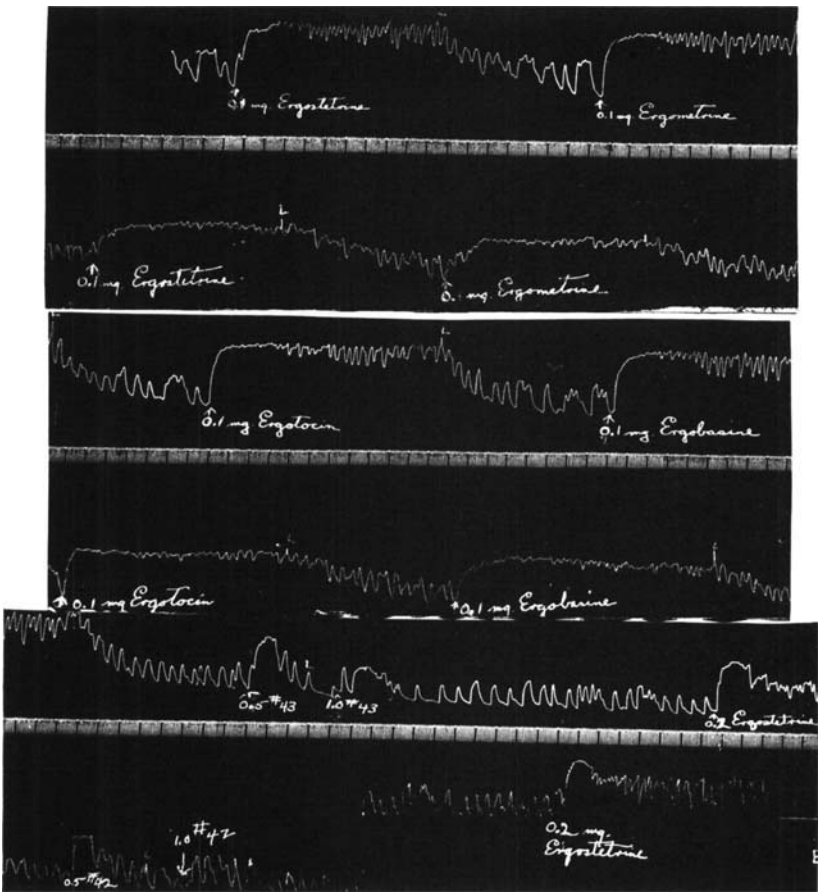

Fig. 3.—The stimulant effect of the new alkaloid on the isolated rabbit uterus, showing also the paralyzing effect of the ergotoxine-containing solutions Nos. 42 and 43.

of working with the smaller dose ranges to avoid a gradually developing paralysis from repeated doses which can significantly interfere with the quantitative accuracy of the method. (Fig. 4.)

From the foregoing, it would seem that ergostetrine produces its action by direct stimulation of sympathetic endings, since the sympathetic supply of the rabbit uterus is believed to be principally augmentor, and since the ergotoxine group can inhibit or abolish the stimulant action of either epinephrine or ergostetrine.

This explanation of the site and character of action is tenable if it is true, as widely believed, that the ergotoxine group acts exclusively upon the sympathetic endings. The latter has never been adequately proven, however, and it can be just as logically claimed, as far as the isolated rabbit uterus is concerned, that neither ergostetrine nor the ergotoxine group acts exclusively on the augmentor sympathetic endings

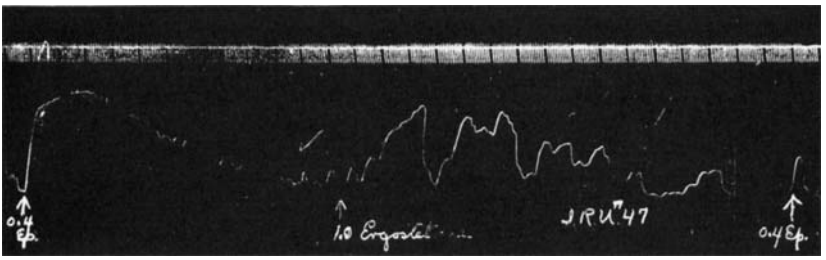

Fig. 4.—Showing how a large dose of ergostetrine produces first its characteristic stimulant effect on the isolated rabbit uterus, then distinct evidence of paralysis finally reaching such a degree as to almost abolish the action of 0.4 cc. epinephrine 1:10,000.

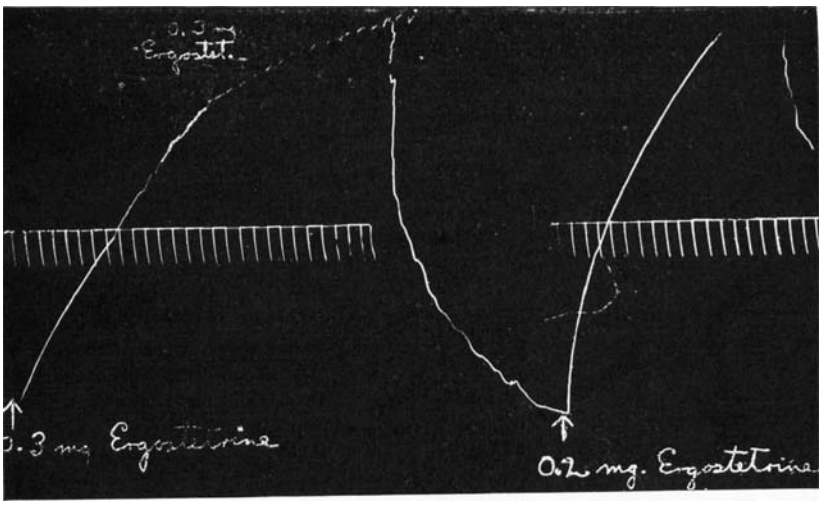

Fig. 5.—The strong contractions induced in the isolated uterus of an immature (250 Gm.) guinea pig. Note the complete absence of any epinephrine-like action.

but that all of these alkaloids act directly upon the uterine muscle to a considerable extent in addition to the sympathetic endings, ergostetrine acting by stimulation and the ergotoxine group by depression following effective dosage. The material which follows also has direct bearing upon the question.

2. *The Guinea-Pig Uterus.*—It is well known that epinephrine causes relaxation of the isolated guinea-pig uterus. This action is believed to result from a purely stimulant action on sympathetic endings which are inhibitory to the guinea-pig uterus (in contrast to the reverse situation in the rabbit).

If ergostetrine acts by stimulation of sympathetic endings, sparing the muscle itself, one should obtain relaxation of the guinea-pig uterus as in the case of epinephrine. Such, however, is not the case, as shown in Fig. 5, in which the uterus of an immature guinea pig (as specified by the U. S. P. for assaying Liquor Pituitarii Posterii) was used. Ergostetrine produced strong contractions, whereas epinephrine relaxes the same type of uterine muscle. It could be argued that the innervation of the guinea-pig uterus is not well developed in the sexually immature animal, thus accounting for the unexpected (?) results, but even if this were true, the fact that contractions were produced definitely argues for a direct action on the uterine muscle, or upon parasympathetic augmentor endings. (Fig. 5.)

But can ergostetrine action on inhibitory sympathetic endings also be demonstrated on the guinea-pig uterus? Figure 6 shows that it can. In this experiment,

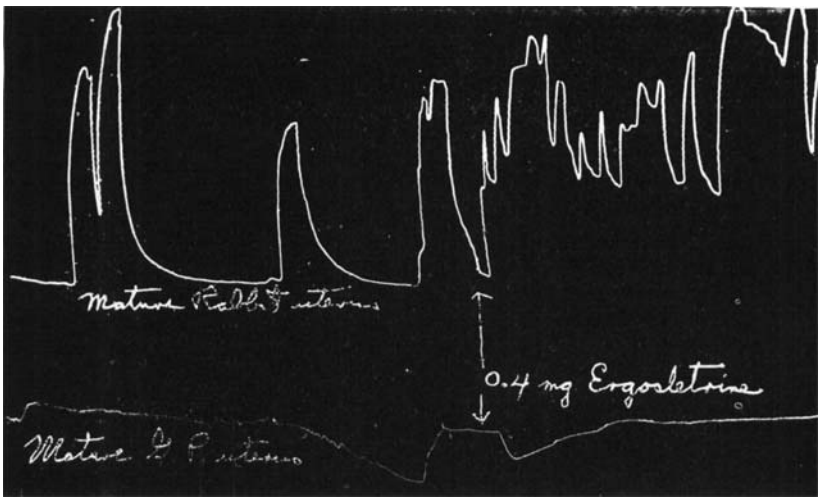

Fig. 6.—The effect of ergostetrine on the isolated rabbit uterus (upper tracing), and on the isolated mature guinea-pig uterus (lower tracing), the ergostetrine being administered to the guinea-pig uterus while in a state of contraction. Note the prompt relaxation followed by a return to the contracted state.

the uterus of a sexually mature guinea pig was used (lower tracing). It will be noted that as ergostetrine was administered, with the muscle in the contracted state, relaxation promptly followed, due presumably to stimulation of inhibitory sympathetic endings. It will also be noted, however, that the relaxation was soon followed by a return to the contracted condition, due, it is believed, either to a stimulant action directly on the muscle, or upon parasympathetic augmentor endings. (Fig. 6.)

It is again apparent, therefore, that a stimulant action on another site, as well as on the sympathetic endings, can be experimentally demonstrated on the guinea-pig uterus. (See also Fig. 8 under action on intestine.) On both the guinea-pig and rabbit uterus, the ergotoxine group of alkaloids shows an action somewhat related to that of ergostetrine. The action of ergostetrine is apparently predominantly stimulant, very gradually giving way to a feeble paralyzing action. In marked

contrast, the action of the ergotoxine group is characterized by an initial stimulation which rapidly gives way to a depressant or paralyzant action. The above is demonstrable especially in large doses, the action on the nerve endings probably predominating in concentrations comparable to therapeutic doses.

3. *Islated Guinea-Pig and Rabbit Intestine.*—It is also possible to demonstrate the dual nature of ergostetrine action on both the guinea-pig and rabbit intestine. Figure 7 represents two sections of a continuous tracing in which isolated segments of the uterus and intestine of a sexually mature guinea pig were made to record their respective movements simultaneously. The uterine action has already been

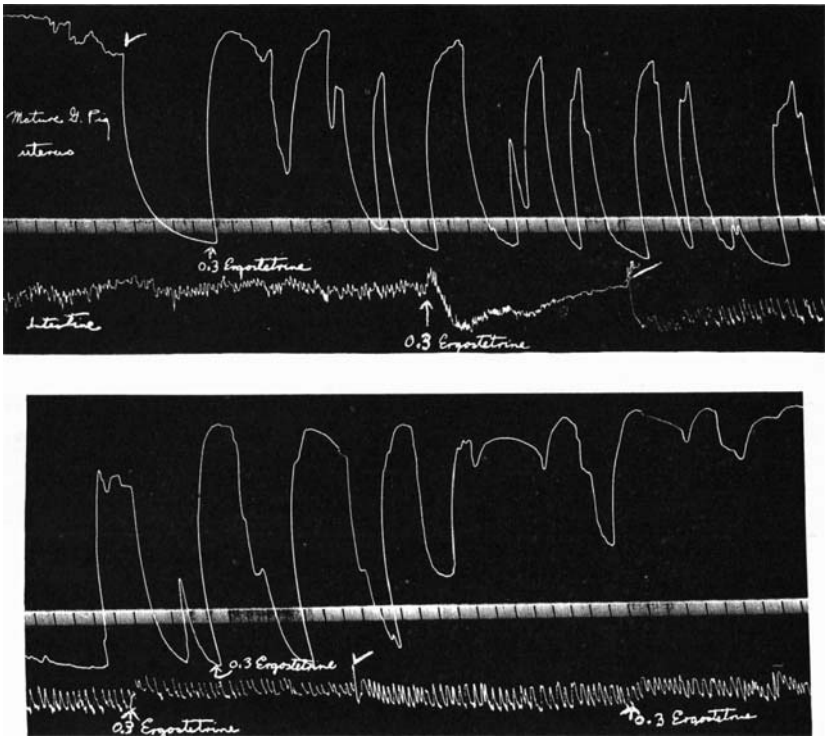

Fig. 7.—Two sections of a continuous tracing of an isolated segment of a mature guinea-pig uterus (upper tracing) and a segment of intestine from the same guinea pig (lower tracing). Fifty-cc. tissue chambers were used in all of the isolated tissue work.

dealt with, but it can again be noted in Fig. 7 that, with the ergostetrine administered to the uterus in the relaxed condition, the sympathetic inhibition is not in evidence (as would be expected), but the indication of the direct stimulant action on the smooth muscle (or parasympathetic augmentors) is strikingly present. Turning to the tracing of the intestinal movements in Fig. 7, one obtains still further evidence of the dual nature of the action. As one would expect, the first application of ergostetrine caused inhibition of the intestinal movements (presumably due to sympathetic stimulation), promptly followed by an increase in tonus before the drug was removed (presumably due to the direct muscle or parasympathetic

stimulation). After washing out the drug, relaxation followed (as one would expect from the removal of a drug having both types of action).

In working with guinea-pig intestine, it was observed that the sympathetic endings are rather easily paralyzed by all of the ergot alkaloids. It can be noted in Fig. 7 that although the first dose of ergostetrine (purposely rather large) produced inhibition, the second and third doses did not, but produced, instead, an increase in tonus. It is believed that this phenomenon is best explained by assuming that the first dose of ergostetrine produced the expected sympathetic inhibition, but that this dose was large enough to paralyze the endings to such an extent that the subsequent doses could exert only a direct stimulant action on the muscle, or upon parasympathetic endings, causing the tonus increase without the preliminary sympathetic inhibition. (Fig. 7.)

Figure 8 shows the rabbit intestine to be similarly affected by ergostetrine. Here, however, the sympathetic endings seem strikingly less subject to paralysis than in the case of the guinea-pig intestine. The prompt relaxation due to sym-

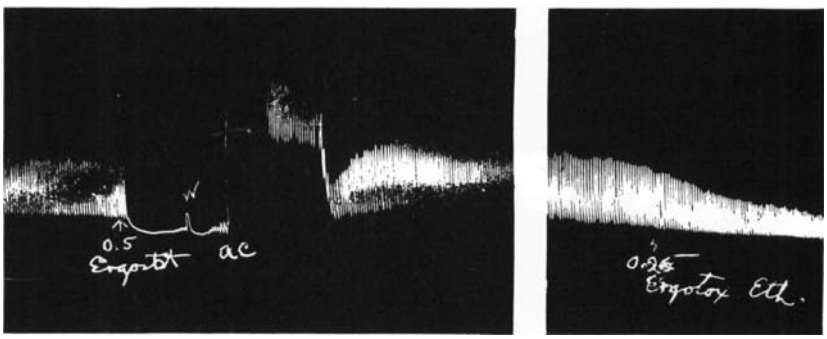

Fig. 8.—Isolated rabbit intestine. Showing the effect of ergostetrine and ergotoxine in inhibiting the rhythmical movements. Following ergostetrine, recovery was hastened with acetyl-choline.

pathetic stimulation is again characteristic. The ergotoxine group of alkaloids acts in a somewhat similar direction on the intestine, but the stimulant action is weaker and the paralyzing action much more powerful on the nerve endings in effective doses, than in the case of ergostetrine. The same is true for the action on the uterus. The direct muscle or parasympathetic stimulation (tonus increase after the sympathetic inhibition) can again be made to come into evidence on the rabbit intestine, especially from the larger dose levels. (Fig. 8.)

The foregoing experiments have a definite significance in pharmacodynamic analysis of action. But it must be recognized that this significance is beset with certain limitations in predicting therapeutic parallels particularly in the matter of dosage or effective concentrations of the various alkaloids.

The results from isolated tissues and separate physiological functions quite naturally give rise to the question: What happens to the key functions of the intact animal body when therapeutically effective and sub-toxic or even toxic doses enter the circulation? It is extremely difficult to obtain a satisfactory answer to this question, since, in order to obtain a direct record of the behavior of the various

"key" organs and functions, simultaneously taken, the otherwise intact animal body must necessarily be subjected to anesthesia as a complicating factor. This, if nothing else, probably at least partially interferes with effects which might be otherwise reflexly induced, and probably interferes to some extent with the direct actions. However, most of the published evidence of the action of the ergotoxine group has been obtained from anesthetized or pithed animals, and the results similarly obtained with ergostetrine are of definite importance from the comparative pharmacological standpoint.

The Actions of Ergostetrine and the Ergotoxine Group on the Anesthetized Dog.— Because the innervation of the uterus in the dog apparently qualitatively approximates that of the human and because the use of a relatively large experimental animal would offer obvious advantages, the dog was selected for the experiments to be included in the present paper.

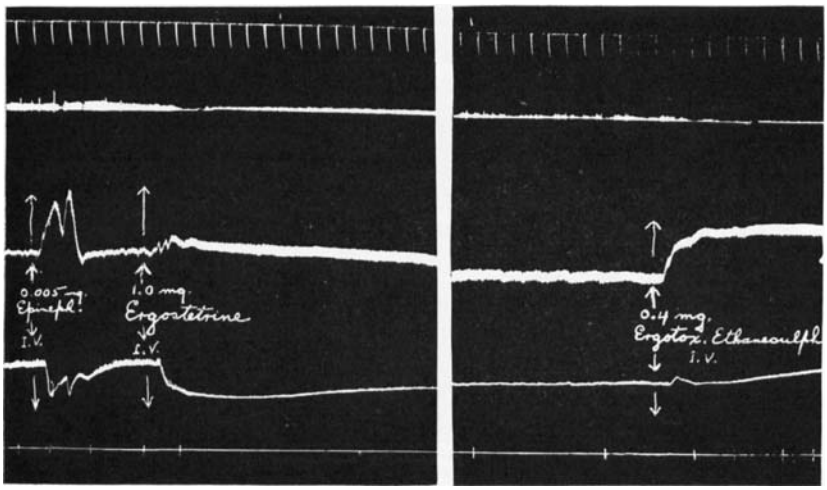

Fig. 9.—Dog, 10.5 Kg.; evipal anesthesia. Tracings top to bottom, time in minutes, respiration, carotid blood pressure, kidney volume and urine excretions from the ureters. Forty-five minutes of the tracing omitted between the two sections.

Anesthesia was induced and maintained at a rather light level (corneal reflex always present) with the barbiturate "Evipal," administered intravenously as required. Figure 9 represents a continuous tracing of time in minutes, respiration, carotid blood pressure, kidney volume and urine output (total uniform drops directly from both ureters), from a female dog weighing 10.5 Kg. The rather large dose of 1.0 mg. of ergostetrine, given intravenously, produced a depression or respiration, an almost negligible effect upon carotid blood pressure, an increased amplitude of the heart-beat, a great decrease in kidney volume, and a complete checking of urine excretion. At the end of approximately an hour, the various functions again approached the normal. The comparative effects of the ergotoxine group are then shown. Because of the much greater toxicity of the ergotoxine group, the smaller dose of 0.4 mg. of ergotoxine ethanesulfonate (U. S. P.) was given intravenously. The respiration, blood pressure and heart action are qualitatively similar to those of ergostetrine, but quantitatively the action of ergotoxine is much stronger even in less than half the dosage. The ergotoxine effects on kidney volume and urine output were strikingly different from the ergostetrine effects. The effect of ergotoxine on kidney volume was slight as compared with ergostetrine, and was increased instead of decreased. This difference is also reflected

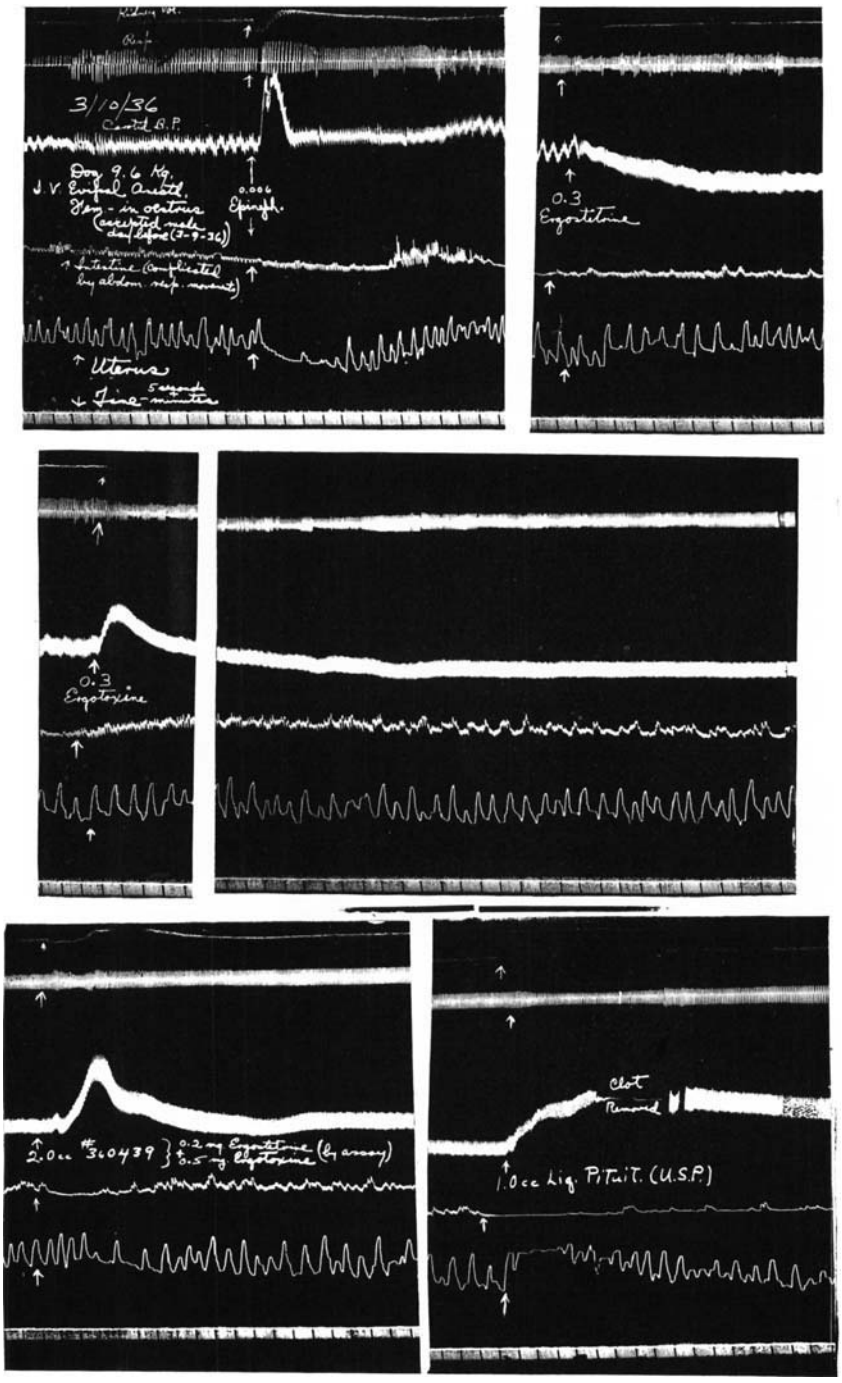

Fig. 10.—Continuous tracing in six sections. Five minutes of tracing cut out between Sections 1 and 2, forty minutes from between 2 and 3, five minutes from between 3 and 4, twenty minutes from between 4 and 5 and thirty minutes from between 5 and 6.

in urine excretion, which, instead of being decreased or checked, was definitely increased. The ergotoxine effects may have been complicated by the initial ergostetrine dose, even though there was a lapse of an hour between doses (Fig. 9).

Figure 10 represents a similar experiment, but upon a female dog definitely in œstrus (accepted a male the day before the experiment). In this experiment, kidney volume, respiration, carotid blood pressure, intestinal movements, uterine movements and time in 5-second and minute intervals are recorded. The dog weighed 9.6 Kg. and intravenous evipal anesthesia was used as in Fig. 9. The effects of an intravenous dose of 0.3 mg. of both ergostetrine and ergotoxine ethanesulfonate are recorded for comparison. The tracing of the intestinal movements is complicated by respiratory movements, and must, therefore, be interpreted with caution. The effects of epinephrine and posterior pituitary are included to aid in the interpretation of the actions of the ergot alkaloids. (Fig. 10.) The effects produced are, in the main, in agreement with those in Fig. 9. It is interesting to note in this animal, however, that epinephrine produced a transitory relaxation of the uterus, while ergostetrine, ergotoxine and posterior pituitary produced a definite increase in tonus. It appears certain, therefore, that ergostetrine and ergotoxine exert their oxytocic action through a site other than the sympathetic endings stimulated by epinephrine, just as in the case of posterior pituitary. It does not necessarily follow that this other site would have to be the smooth muscle directly (the mechanism through which posterior pituitary is supposed to act). But from present understanding, one must necessarily conclude that this other site would have to be either (1) the smooth muscle directly, (2) parasympathetic endings (which could conceivably become augmentor in function during œstrus or pregnancy, with a corresponding reverse in the normal function of the sympathetics) or (3), a mechanism as yet unknown. After noting the positive evidence of significant sympathetic stimulation in normal, unanesthetized animals (mydriasis anger, etc.) one is inclined to believe that sympathetic stimulation must enter into the uterine action and yet, these other evidences of sympathetic stimulation (from rather large doses) may conceivably be due to an exaggerated liberation of epineprine from the adrenals as pointed out by Brown and Dale (8). Smaller doses of the alkaloids, as used in the anesthetized dog experiments, may not call forth enough epinephrine from the adrenals to complicate the action of the ergot alkaloids on the uterus. This hypothesis receives support from the effects produced by the larger dose of ergot alkaloids given in the form of solution No. 360439. Here some evidence of sympathetic stimulation (from elaborated epinephrine?) appears in both the intestinal and uterine effects. Nevertheless, results to date do not furnish a clear and indisputable answer to the question. It appears that the ergot alkaloids must certainly produce a part of their effects by an action on a site other than the sympathetic endings stimulated by epinephrine. The study is being continued.

SUMMARY.

The site and character of the pharmacological action of ergostetrine and the ergotoxine group of ergot alkaloids has been comparatively studied; *first*, on the various types of isolated smooth muscle normally innervated by the sympathetic and parasympathetic branches of the autonomic nervous system, and, *second*, upon autonomically controlled functions of anesthetized intact dogs.

CONCLUSIONS.

1. Evidence has been obtained which strongly indicates that the pharmacodynamic action of both ergostetrine and the ergotoxine group of ergot alkaloids is not confined to the sympathetic endings stimulated by epinephrine.

2. The character of the action of ergostetrine differs from that of the ergotoxine group of alkaloids in that the action of ergostetrine is predominantly stimulating, with only relatively feeble and delayed manifestations of a slowly developing paralyzing action, while the action of the ergotoxine group of alkaloids is characterized by a relatively weak initial stimulant action which rapidly gives way to a depressant paralyzing action, the stronger paralyzing action of the ergotoxine group undoubtedly accounting for the much greater toxicity characteristic of this group as compared with ergostetrine.

3. The clinically employed doses of 0.2 to 0.6 mg. of ergostetrine, or 0.5 to 1.5 mg. of members of the ergotoxine group, are not sufficiently large to call forth appreciable actions of the respective syndromes other than the oxytocic action, unless the larger dose ranges are administered too frequently over a period of time. It is believed that the spectacular effectiveness of ergostetrine as an oxytocic on either the ante-partum or post-partum uterus, or the uterus in the period of œstrus, of humans is due to a definitely increased irritability or responsiveness to the drug during those periods, thus making it possible for these small doses to produce a wholly satisfactory quantity and quality of oxytocic action without producing objectionable degrees of "side effects" or other actions of the syndrome.

REFERENCES.

(1) Thompson, Doctorate Dissertation, Johns Hopkins University (May 1934); JOUR. A. PH. A., 24, 24 (1935); 24, 185 (1935).
(2) Thompson, *Science*, 81, 636 (1935).
(3) Kharasch, King, Stoll and Thompson, *Ibid.*, 83, 206 (1936).
(4) Report of the Council of Pharmacy and Chemistry, *J. Am. Med. Assoc.*, 106, 1008 (1936).
(5) Thompson, JOUR. A. PH. A., 24, 748 (1935).
(6) Vartiainen, *J. Pharmacol.*, 54, 259 (1935).
(7) Davis, Adair, Chen and Swanson, *Ibid.*, 54, 398 (1935).
(8) Brown and Dale, *Proc. Roy Soc., B*, 118, 446 (1935).
(9) Rothlin, *Schweiz. med. Wochschr.*, 65, 947 (1935).
(10) Raymond-Hamet, *Compt. rend.*, 120, 1208 (1935).

POSTGRADUATE OF PUBLIC AND INDUSTRIAL OFFICIALS.

Sir Richard Livingstone, president of Corpus Christi College, Oxford, comes foreward with the suggestion that there be established a form of supervised re-education of public and industrial officials. He holds that these should keep abreast of the times by giving them an opportunity to attend school periodically on the supposition that the education of a generation ago is by no means automatically adaptable to the needs of a rapidly changing world.

The Littauer foundation, designed to improve public administrations, is working along these lines. It is contended that all the learned professions should endeavor to keep up with the latest discoveries through regular convocations in their respective fields. It is stated that the re-education of public officials would pay dividends far in excess of the costs.