THE SPECIFIC ACTION OF ERGOT ALKALOIDS ON THE SYMPATHETIC NERVOUS SYSTEM

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I

Sollmann and Brown (1) were the first to describe the inhibitory action of ergot extract on adrenalin; but they could not elucidate the cause of this interesting fact, because ergot chemically is very complex and at that time it was not known what its biologically active principles really were. To Dale (2) belongs the credit of having solved this question by taking it up in connection with the important chemical investigations of Barger and Carr (3) and Barger and Dale (4). Dale showed—first with impure chrysotoxine, later with pure ergotoxine—that between adrenalin and ergotoxine there exists a specific pharmacologic antagonism which gives rise to the phenomenon called vasomotor reversal. He furthermore showed that, between ergotoxine and the sympathetic nervous system, there exist closer affinities of a similar order to those described, for instance, by Langley for nicotine and by Dixon for apocodeine. He characterizes the action of ergotoxine in the following terms: "A specific paralysis of the motor elements in the structures, associated with sympathetic innervation, which adrenalin stimulates; the inhibitor elements retaining their normal functions, as do also both motor and inhibitor autonomic nerve-supplies of cranial and sacral root origin." These conclusions as to the influence of ergotoxine on the sympathetic augmentor functions were later confirmed and extended by a number of authors.

After this fundamental work of Dale's the problem of the pharmacologic action of ergot alkaloids was somewhat neglected, owing to several reasons. Tanret's ergotinine was found to be

almost or wholly inactive (Kobert (5), Barger and Dale (4), Hamet (6), Rothlin (7)). Ergotoxine, despite the remarkable experimental basis supplied by Dale, was clinically discarded (British Pharmaceutical Codex, 1923: "Ergotoxine has been used clinically for its action on the uterus, but it is disappointing and gynecologists are now generally agreed that it is not the active constituent of ergot they want"), and Kraft (8), who had discovered hydroergotinine (identical with ergotoxine), goes as far as to advise the removal of the alkaloids from ergot preparations intended for therapeutic use, on the ground that hydroergotinine (i.e., ergotoxine) has only toxic properties and no therapeutic action. The work on which these conclusions are based deals solely with toxicity determinations and is absolutely inadequate. The therapeutic significance of ergot alkaloids was correctly estimated only after ergotamine, which was discovered by Stoll, had been studied experimentally and tested clinically. These questions are summarized and discussed in the papers of Dale and Spiro (9), Rothlin (10), Stoll and Rothlin (11), Hamet (12), Bourne and Burn (13), Nelson and Pattee (14), from which the fact stands out clearly that the alkaloids, and not the proteinogenous amines, are the specific principles of ergot. This conclusion is accepted by the International Commission for the Standardization of Certain Remedies (Publications of the League of Nations, III, Health, 1928, III, 10, p. 38, C.H. 734). That Bourne and Burn (13) in their article put ergotamine and ergotoxine on a par is probably due to the fact that these two ergot alkaloids have the same pharmacologic action. As far as we know all clinical investigations—those of Bourne and Burn included—have been carried out exclusively with ergotamine.

Stoll (15) recently published on the chemical differentiation of these two alkaloids a few interesting data which show that the progress made in the ergot problem, particularly as regards practical therapeutics, is attributable directly to the finer chemical and physicochemical differences between ergotoxine and ergotamine: for instance, differences in crystallization and solubility. Ergotoxine is amorphous, ergotamine easily crystallizes, thus giving a guarantee of absolute purity. Ergotoxine salts (e.g., the phos-

phate) give only colloidal solutions with 0.9 per cent sodium chloride solution, whereas ergotamine salts (e.g., the tartrate) give clear solutions in concentrations up to 1:1000, which make practical use possible.

Ergotamine has not only received an extensive clinical trial in obstetrics and gynecology, in which its position is secure, but, owing to the fact that it stands in the same relation to the sympathetic nervous system as atropine to the parasympathetic, it has entered a new field, namely, the treatment of imbalance of the vegetative nervous system, especially of those conditions which for the sake of brevity, are termed sympathicotonies. However in regard to the specific action of ergotoxine and ergotamine on the sympathetic, there still persist some differences of opinion, to the study of which this work is more specially devoted.

II

Dale's view is that ergotoxine paralyzes exclusively the motor endings of the sympathetic and has no action on the inhibitory fibers that are stimulated by adrenalin. I have been able to show (16) that ergotamine can also annul in vitro the inhibitory action of adrenalin on various organs such as the small intestine of the guinea pig and of the rabbit and the uterus of the guinea pig. Planelles (17), working independently, has made the same observation on the small intestine of the guinea pig. At the same time I had also made experiments on the gut of the guinea pig and of the rabbit in situ and I had noted a distinct inhibition of the tonus-lowering action of adrenalin. These experimental findings were convincing, especially as regards the gut, less so as regards the uterus of the guinea pig and that of the cat which, in the nongravid state, are relaxed by adrenalin; for these the doses of ergotamine required to inhibit the action of adrenalin were comparatively high. This discrepancy in the necessary amounts was also mentioned at that time.

When, despite this, I put forward the theory that ergotamine paralyzes both the motor and inhibitory endings of the sympathetic and that, in their action on the sympathetic, adrenalin and ergotamine bear a relation similar to that of pilocarpine and atro-

pine in respect to the vagus, it was after due consideration of the fact that instances of atypical responses are noted not only with ergotamine, but also with many other substances acting on the vegetative nervous system, e.g., adrenalin, pilocarpine, atropine. To wit: Excitation of the sympathetic causes profuse perspiration: adrenalin does not. On the other hand, pilocarpine, a typical vagus stimulant, causes perspiration; it also contracts the retractor penis, while electrical excitation of the pelvic nerve, the branch of the vagus supplying this muscle, relaxes it. Again, atropine does not inhibit exclusively vagus endings, but also some secretory sympathetic endings, e.g., those of the prostate, submaxillary and sweat glands. Finally, it is known that adrenalin or excitation of sympathetic endings causes contraction of the splenic muscle fibers; pilocarpine does the same, but not excitation of the vagus. Comparable is the fact noted by us that both adrenalin and pilocarpine contract the isolated seminal vesicle of the guinea pig.

III

Issekutz and Leinzinger (18) have utilized the adrenalin-inhibiting effect of ergotamine on the small intestine for the quantitative estimation of ergot alkaloids and state that their results with this biological method tally accurately with those of chemical gravimetric procedures. Recently Mendez (19) has investigated anew the inhibition of the inhibitory function of the sympathetic by ergotamine in isolated organs (small gut, uterus). He summarizes his findings as follows:

> My results therefore support the original conclusion of Dale, in that ergotamine, in concentrations sufficient to abolish almost completely augmentor responses to fairly large concentrations of adrenalin, does not alter various inhibitor responses to adrenalin. At the same time I do not deny that high concentrations of ergotamine may diminish the inhibitor action of low concentrations of adrenalin. The effect of ergotamine in abolishing the augmentor actions of adrenalin, is, however, so much more powerful than its effects in abolishing inhibitor actions that the latter effect can be of little practical importance. . . . . My results agree with the conclusions that ergotamine paralyzes the aug-

mentor actions of the sympathetic but either does not affect the inhibitor actions; or at the most only affects these latter actions in a very feeble manner.

This statement of Mendez contradicts the above mentioned experimental results obtained by me and confirmed by other authors,[1] at least insofar as the small intestine is concerned. As this is a question of fundamental importance, not only as regards the action of ergotamine, but also for a proper conception of the sympathetic innervation and its function, Mendez' work led me to investigate anew the problem by experiments in vivo as well as in vitro. The isolated small intestine of the guinea pig and rabbit was selected by me as suitable material. I repeated these experiments after the methods of Trendelenburg and von Kehrer-Magnus.

The results of the experiments shown in figures 1 and 2 are in complete accord with my previous statements and those of Planelles, Issekutz-Leinzinger and Thienes.

Experiments on the small gut of the rabbit with the Magnus method are simple and, therefore, the causes of error are few. Moreover the demonstration of inhibition is remarkably even and regular. Accordingly, a series of experiments were made with this material with a view to analyzing more exactly on the small intestine the *inhibition* of adrenalin by ergotamine. The points investigated were:

1. The mode of action of adrenalin and ergotamine on the rabbit gut.
2. The promptness of response, that is, the length of the interval necessary for the adrenalin-inhibiting action of ergotamine to manifest itself.
3. The relative amounts of ergotamine and adrenalin.
4. The reversibility of the inhibition of adrenalin by ergotamine.

The related experiments shown in figures 3 to 6, which are confirmed by many others, enable us to answer our four questions as follows:

[1] Lately by C. H. Thienes, Proc. Soc. Exper. Biol. and Med., March, 1929, p. 501.

1. As a rule, ergotamine tartrate in concentrations which annul the adrenalin effect has no direct action on the isolated small intestine of the rabbit: in some cases there is noted a decrease in the tonus and in the amplitude of the rhythmic waves. But this phenomenon, provided too high doses have not been used, is not the expression of an inhibitory influence of ergotamine: it is rather ascribable to spontaneous changes in the tonus and rhythm of the test object during the course of an experiment. That such changes do occur we have directly observed.

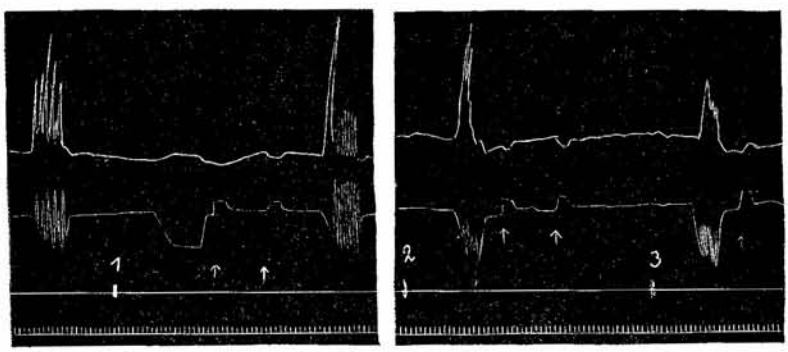


FIG. 1. (TRENDELENBURG'S METHOD.) ISOLATED GUINEA PIG GUT

Pressure 2.5 cm. water. Both the longitudinal and circular muscle fibers show normal activity.

At point *1*, adrenalin 1:10,000,000 is added. Under the same pressure conditions, a complete inhibition of intestinal contraction is noted. In this specimen, the activity of the longitudinal and circular fibers was already completely inhibited by adrenalin 1:20,000,000, and partially by a 1:30,000,000 dilution.

After a twice repeated washing both muscular layers resume normal function. Then ergotamine tartrate 1:1,000,000 is added and, after 10 minutes (point *2*), adrenalin 1:5,000,000: the gut activity remains almost normal, therefore the inhibitory influence of adrenalin has been counteracted. After a twice repeated washing the action of adrenalin 1:5,000,000 (point *3*) is still counteracted.

The same example proves also that this kind of test object for adrenalin retains its sensitiveness at least for the time required for the tests, i.e., about one hour. The experiments on the reversibility of ergotamine action charted in figures 3 and 5 also confirm this fact, which is an important prerequisite when it comes to drawing conclusions on the adrenalin-inhibiting influence of ergotamine.

2. The findings recorded in figure 3 indicate that the maximum of ergotamine action is reached in about ten minutes; between

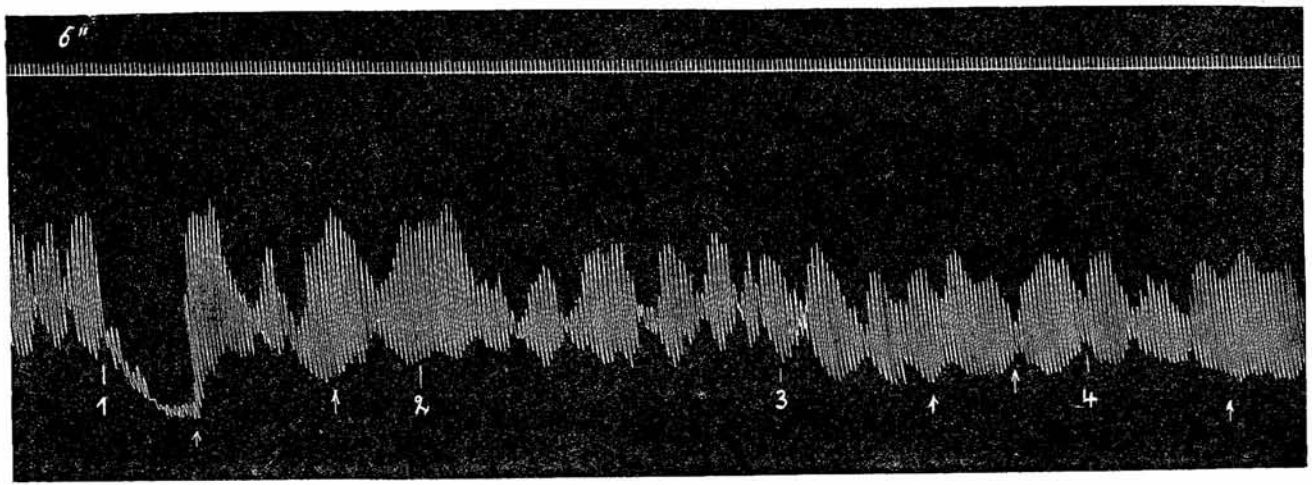
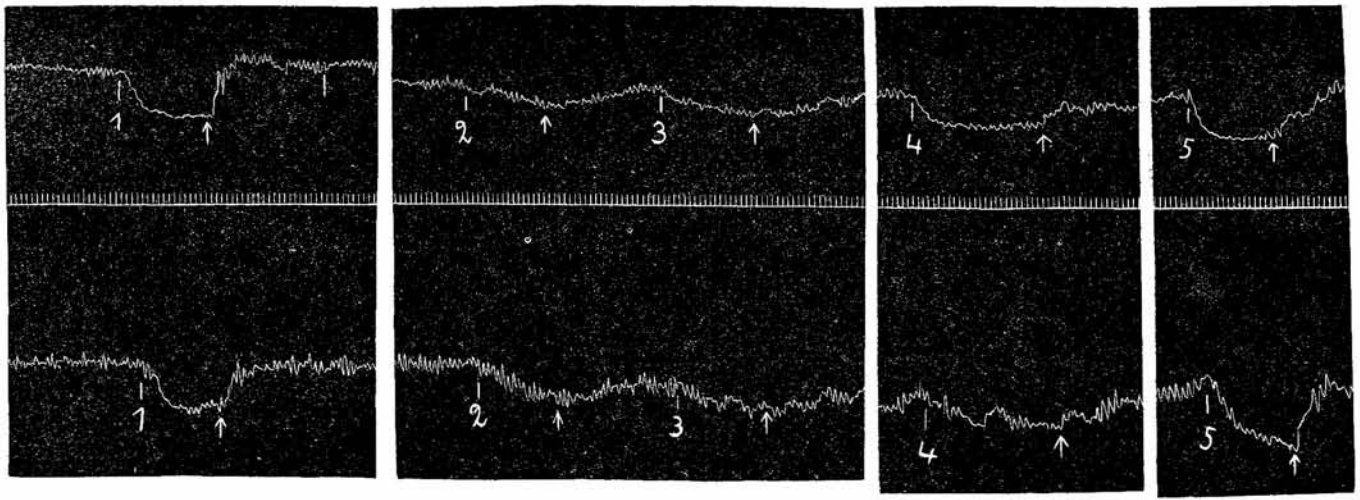


FIG. 2. (MAGNUS' TECHNIQUE.) ISOLATED RABBIT GUT

Time markings every 6 seconds.

At point *1*, adrenalin 1:5,000,000 is added. Rapid fall of tonus and inhibition of peristalsis: after washing, the activity becomes again normal. Addition of ergotamine tartrate 1:1,000,000 (point *2*) does not modify the muscular activity.

Without previous washing, adrenalin 1:5,000,000 is again added (point *3*); the action of adrenalin is inhibited; the same is noted at point *4*, after a twice repeated washing.



a b c d

FIG. 3. A TO D. TWO SPECIMENS OF ISOLATED SMALL INTESTINE OF RABBIT

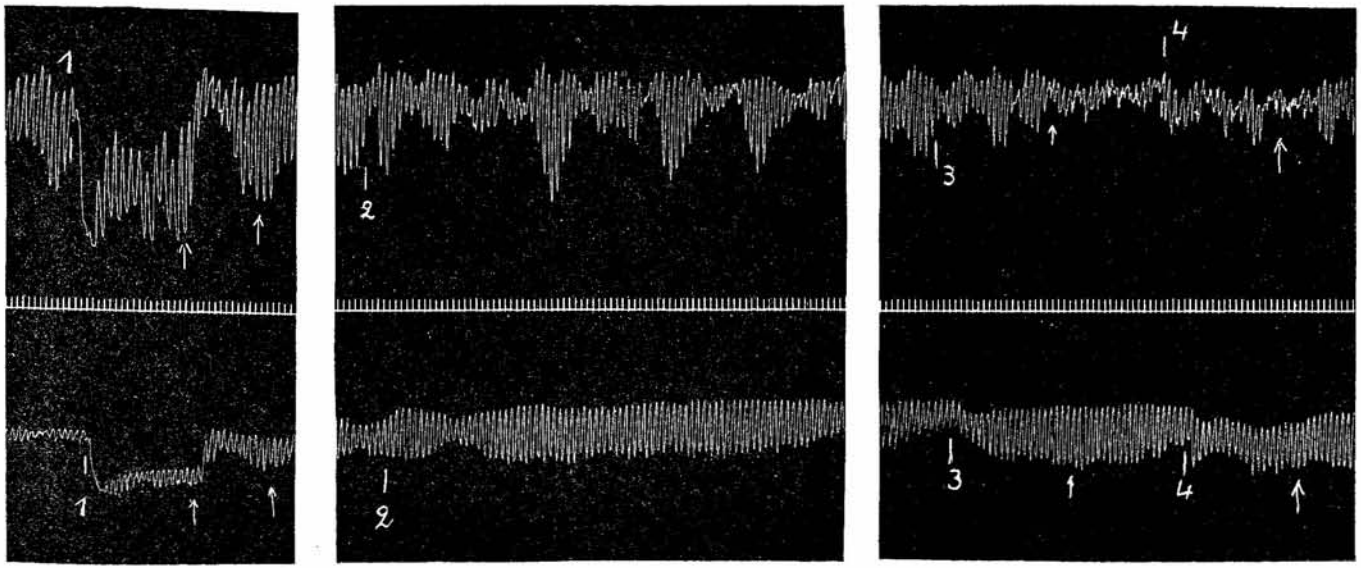
The experiments on both specimens were made 8 hours after the death of the animal.

Fig. 3 a. At point *1*, adrenalin 1:2,500,000 is added to both specimens. In both cases, marked fall in tonus and inhibition of peristalsis. Both go back to normal after washing. Ergotamine tartrate 1:2,000,000 is added to both specimens and allowed to act 10 minutes in the upper one and 5 minutes in the lower. No direct effect from ergotamine.

Fig. 3 b. The tonus and peristalsis in both specimens are unchanged. The ergotamine is not washed out from the upper one, but from the lower: At point *2*, adrenalin 1:2,500,00 is added to both specimens. In both, only very weak inhibition manifests itself. After washing out again, adrenalin 1:2,500,000 is once more added (point *3*): the inhibitory action has become slightly more marked in the upper specimen, but not in the lower one.

Fig. 3 c. Same, 15 minutes later. At point *4*, adrenalin 1:2,500,000. The inhibitory action is more marked above than below and stronger than in figure 3 b.

Fig. 3 d. Same, 30 minutes later. At point *5*, adrenalin 1:2,500,000. The inhibitory action of adrenalin has become normal in both specimens. Compare with figure 3 a.



a b c

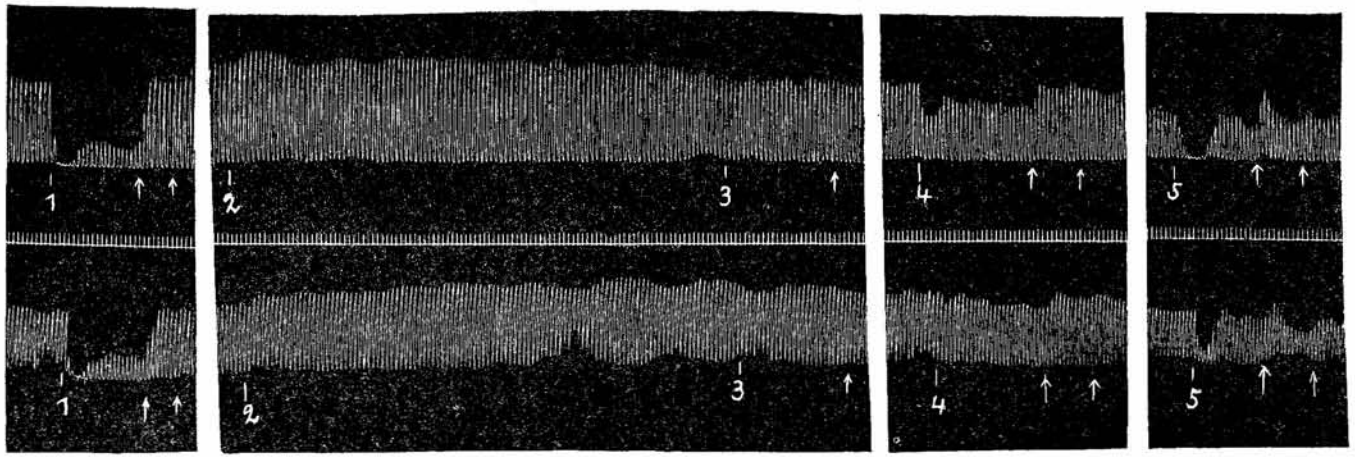
FIG. 4 A TO C. TWO SPECIMENS OF ISOLATED SMALL INTESTINE OF RABBIT

Time markings every 6 seconds.

Fig. 4 a. At point *1*, adrenalin 1:10,000,000. Typical inhibition with immediate return to normal after washing.

Fig. 4 b. At point *2*, ergotamine 1:10,000,000 in the upper specimen, 1:5,000,000 in the lower, is added and allowed to act for 10 minutes. No change in either one.

Fig. 4 c. Without washing, adrenalin 1:10,000,000 is added to both specimens (point *3*); then after washing, at point *4*, adrenalin 1:5,000,000. In neither specimen does any marked inhibition appear: there may be a slight and doubtful indication of it in the lower one.



a b c d

FIG. 5 A TO D. TWO SPECIMENS OF ISOLATED SMALL INTESTINE

Time markings every 6 seconds.

Fig. 5 a. Adrenalin 1:5,000,000 causes typical inhibition.

Fig. 5 b. At point *2*, ergotamine tartrate (1:5,000,000 in the upper specimen, 1:2,500,000 in the lower) is added and allowed to act for 10 minutes. The tonus and peristalsis are not modified by ergotamine. At point *3*, without washing, adrenalin 1:5,000,000 is added: no response: (*complete inhibition of adrenalin*).

Fig. 5 c. At point *4*, 20 minutes later, after a washing, repeated several times, adrenalin 1:5,000,000 is again added. A distinct adrenalin action is noted only in the upper specimen.

Fig. 5 d. Again after 20 minutes more (at point *5*) adrenalin 1:5,000,000 is added: the response to adrenalin, though weaker than normal, is visible in both specimens.

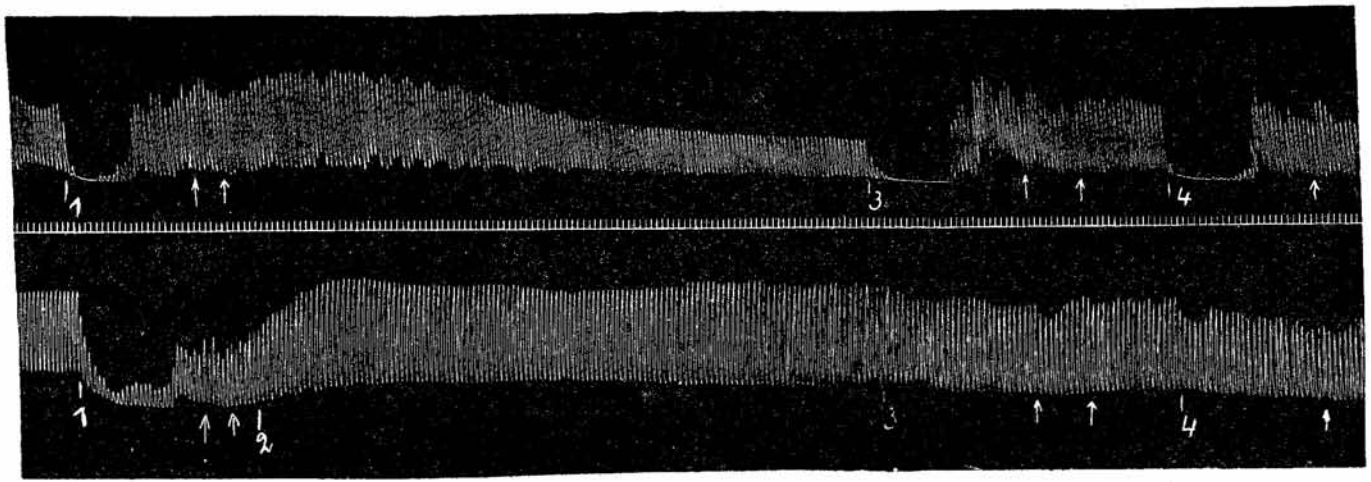


FIG. 6. TWO SPECIMENS OF ISOLATED SMALL INTESTINE OF RABBIT

Time markings every 6 seconds. At point *1*, adrenalin 1:2,500,000 is added to both. After washing, at point *2*, ergotamine tartrate 1:1,000,000 is added to the lower specimen and allowed to act for 10 minutes. No ergotamine tartrate is added to the upper specimen. The latter shows a distinct decrease in the tonus and particularly in the peristalsis: on the contrary the lower one under the influence of ergotamine remains normal. At point *3*, adrenalin 1:2,500,000: the action in the upper specimen is normal, while in the lower it is completely inhibited by ergotamine. After a twice repeated washing, adrenalin is again tested (point *4*): above, strong response: below, hardly any action (inhibition of adrenalin).

five and ten minutes marked differences are still noticeable. Therefore the latent period is brief; it is shorter than with the isolated rabbit uterus and about as long as with the isolated seminal vesicle of the guinea pig.

3. The most interesting question is that of the quantity of ergotamine necessary to inhibit the effect of a given amount of adrenalin. Figure 4 shows that experimental material of the kind selected by us manifests a very high sensitiveness to ergotamine. In the case related above a concentration of ergotamine equal to that of adrenalin sufficed, as practically the same adrenalin-inhibiting effect was obtained from the single as from the double dose of ergotamine. The average for all experiments is 1:1.5 to 2, that is, the typical adrenalin effect is neutralized, after five to ten minutes, with or without washing, by an amount of ergotamine one and a half or twice as large as that of adrenalin. The degree of susceptibility is exactly the same as that exhibited by the rabbit uterus after it has been submitted ten minutes to the action of ergotamine. So far as our own experience goes, this ergotamine-adrenalin proportion is exceeded only in one kind of test material, the isolated seminal vesicle of the guinea pig. Here the typical tonus-increasing influence of adrenalin 1:1,000,000 is, on an average, annulled by ergotamine 1:30,000,000. We do not want to dwell more at length here on this point, which is of special interest for the biological standardization of ergot alkaloids.

4. A general characteristic of the action of ergotamine is its long duration. This is particularly evident on the uterus and accounts for the great value of the drug in the treatment of uterine atony. Analysis of our findings shows that it is easier to obtain the reversal of adrenalin by ergotamine on the isolated gut than on the uterus. Comparison of reversal conditions in this and other kinds of test material shows them to be about the same in the isolated gut as in the isolated seminal vesicle. The ergotamine action disappears in about an hour, whereupon the sensitiveness to adrenalin becomes again normal.

In regard to the adrenalin-ergotamine proportion results obtained on the isolated gut are very similar to those given by the isolated uterus. On an average ergotamine in the concentrations

1.5 times those of adrenalin abolishes the action of the latter on the uterus and we have found the same proportion for the isolated gut. Moreover, ergotamine in such doses does not modify intestinal peristalsis and, contrary to what has been claimed on experimental and clinical grounds, does not exert either a tonus-increasing or an inhibitory action. Kaufmann and Kalk ascribe to ergotamine an adrenalin-like (i.e., inhibitory) action on the gut; according to Stahnke, such an action is seen only with very high doses, and even then not constantly. Pharmacologic research, when undertaken with a view to finding a basis for therapeutic applications, must first of all consider the mode of action of physiological doses; the study of higher or toxic doses matters only for the recognition of possible by-effects. That high doses of ergotamine can relax or increase tonus in intestinal muscle is possible, but there is no unanimity on this point among authors: the phenomena that interest us are those which physiologic and therapeutic doses can produce.

The essential difference between the inhibition of adrenalin action on the gut and that on the uterus consists less in the readiness with which the inhibitory or augmentor mechanism is counteracted than in the duration of the action of ergotamine. Braun (22), Langecker (23), Mendez (19) have investigated this point for the uterus and the results of studies carried on by us for years are in accord with those of Langecker and Mendez. When a well-marked adrenalin effect has been completely inhibited by ergotamine, two to four hours, on an average, elapse before the susceptibility to a dose of adrenalin equal to that previously given again becomes normal. This interval is not uniform with all organs: with some it is shorter. In this respect one more point seems to me worthy of mention, namely, that in experiment II an equal adrenalin effect was inhibited by a concentration of ergotamine about 50 per cent lower than in experiment I on the same specimen, though the susceptibility to adrenalin had seemingly become normal again. There may, therefore, sometimes remain a certain hypersusceptibility to ergotamine. This question has only theoretical interest because after the isolated uterus has been submitted to ergotamine action it becomes useless for the practical titration of ergot.

On the gut the ergotamine action is of shorter duration and, as a rule, with the doses used by us, does not exceed an hour. The same is true of the seminal vesicle of the guinea pig which, in our experience extending over several years, has shown itself a very good test object for ergot alkaloids.

IV

For the determination of real physiological values experiments in vivo are undoubtedly more decisive than tests in vitro and are alone authoritative for practical purposes. We have carried out such experiments on the small intestine of the rabbit and the dog, with unfailing success. Suitable examples are given in figures 7, 8 and 9.

Technique. Experiments with a rubber bag placed in the lumen of the gut have not proved satisfactory because of the interference with regular peristalsis. As Trendelenburg (24) states: "With these methods increases or decreases in the intensity of the contraction waves cannot always be registered with certainty and accuracy, as what we see are not separate waves but a complex of waves in which the different movements may run in opposite directions and conflict with each other."

The following method seems to us the simplest and was constantly successful. Under general narcosis a glass cannula is introduced in the carotid and the jugular veins and a median abdominal section made. The animal is then dipped in a bath of Ringer's solution at 37°C. deep enough to keep the drawn-out loop of gut immersed. An intestinal loop is fixed with a clamp (fixed point) and at a point about 6 cm. colonward is provided opposite the mesenteric insertion with a small hook (movable point) from which a thread passing over rollers leads to the recording lever. Particular attention must be paid to the following precautions: The mesentery of the loop must be loose, otherwise reflex inhibition interferes with the development of regular activity. The loop must not be empty: the contents help to maintain peristalsis. As neither the fixed nor the movable point are blocked the normal intestinal content suffices for the filling of the loop. Generally it takes fifteen or thirty minutes after the gut has been placed in

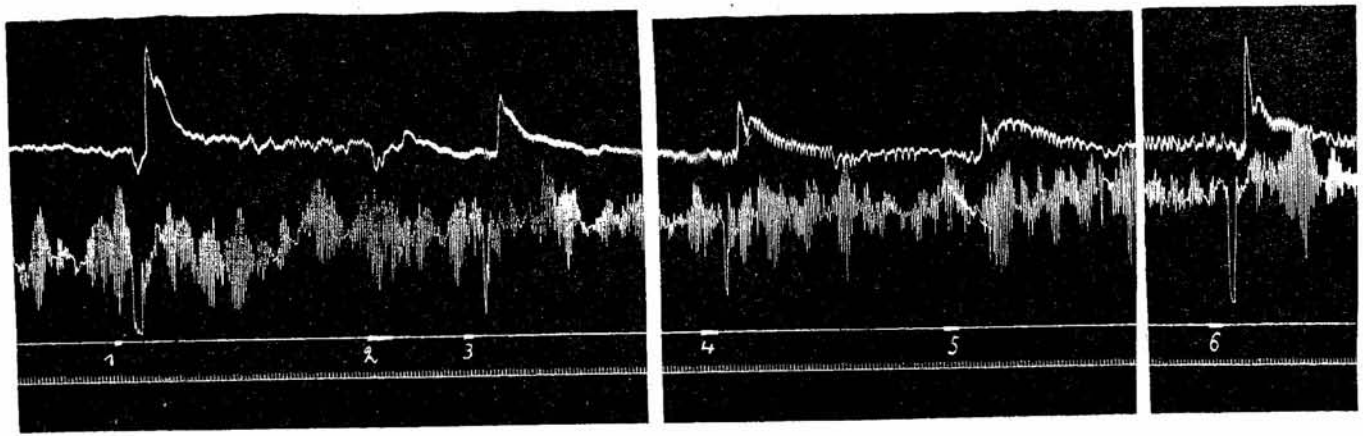


FIG. 7 A TO C. RABBIT WEIGHING 2.8 KGM.

Upper curve is that of the carotid pressure, lower, small intestine in situ. Signal for injection. Time markings every 6 seconds.

Fig. 7 a. At point 1, adrenalin 0.5 cc. 1:50,000. Rise in blood pressure, decrease in peristalsis, strong decrease in tonus. At point *2*, ergotamine tartrate 2 mgm.: slight fall in blood pressure, of short duration; no influence on the gut. At point *3*, adrenalin 0.5 cc. 1:50,000. Action distinctly weaker both on the blood pressure and on the gut.

Fig. 7 b. At point *4*, adrenalin 0.5 cc. 1:50,000, 6 minutes later: the inhibition of the adrenalin effect is still more marked. At point *5*, adrenalin 0.5 cc. 1:50,000, the inhibition of the adrenalin action on the gut is complete but not that on the blood pressure.

Fig. 7 c. At point *6*, adrenalin, 0.5 cc. 1:50,000. Thirty minutes later: the action of adrenalin is again normal both on blood pressure and gut.

the saline bath before it begins to work well and regularly. The activity lasts four to six hours. Should an intestinal loop remain inactive from the beginning or become exhausted after long testing, another one is selected. So far we have had hardly any failures with rabbits or dogs. Cats are not suitable for this kind of work as the small intestine is very sluggish under fasting conditions.

We have used this method for the experiments of figures 7, 8 and 9.

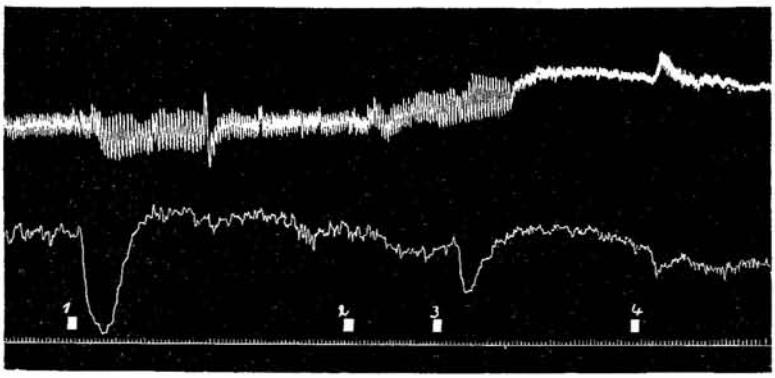


FIG. 8 A AND B. DOG

The upper curve is that of the carotid blood pressure, the lower that of the small intestine in situ. Signal line denotes injection. Time markings every 6 seconds.

Fig. 8 a. At point *1*, intravenous injection of 1 cc. adrenalin 1:100,000: no rise in blood pressure, strong inhibiting action on the gut. At point *2*, ergotamine tartrate 0.12 mgm. per kilogram: weak action on the blood pressure, no definite effect on the gut. At point *3*, 1 cc. adrenalin 1:100,000: slight rise in blood pressure, inhibition on the gut weaker than before ergotamine. At point *4*, 1 cc. adrenalin 1:100,000: inhibition on the gut stronger than at point *3*.

The action of adrenalin on the gut in situ is inhibited by ergotamine just as readily as that on the blood vessels. The writer has been able to show previously that, in cats and dogs, the dose of ergotamine necessary for vasomotor reversal (as measured on the carotid blood pressure) is from 0.25 to 0.50 mgm. per kilogram. Figures 8 and 9 show that the same doses counteract the inhibitory action of adrenalin on the gut in situ. A remarkable fact is also to be noted in the experiment shown on figure 9, namely, that 0.25

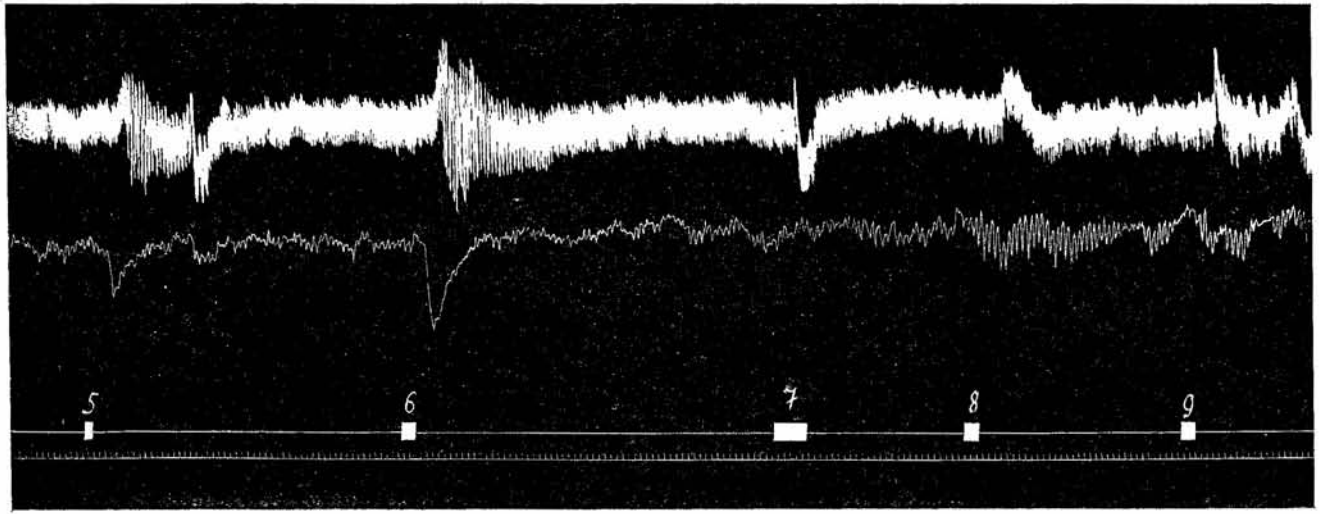


Fig. 8 b. At point *5*, 1 cc. adrenalin 1:100,000, action similar to that observed at point *4*. At point *6*, 1 cc. adrenalin 1:50,000, action on the blood pressure and the gut stronger, but still weaker than that observed at point *1*, with a dose only one-half as great. At point *7*, ergotamine tartrate, 0.24 mgm. per kilogram: slight fall in blood pressure, no influence on the gut. At point *8*, 1 cc. adrenalin 1:50,000, complete inhibition of the action of adrenalin. At point *9*, 1 cc. adrenalin 1:50,000, complete inhibition of the action of adrenalin.

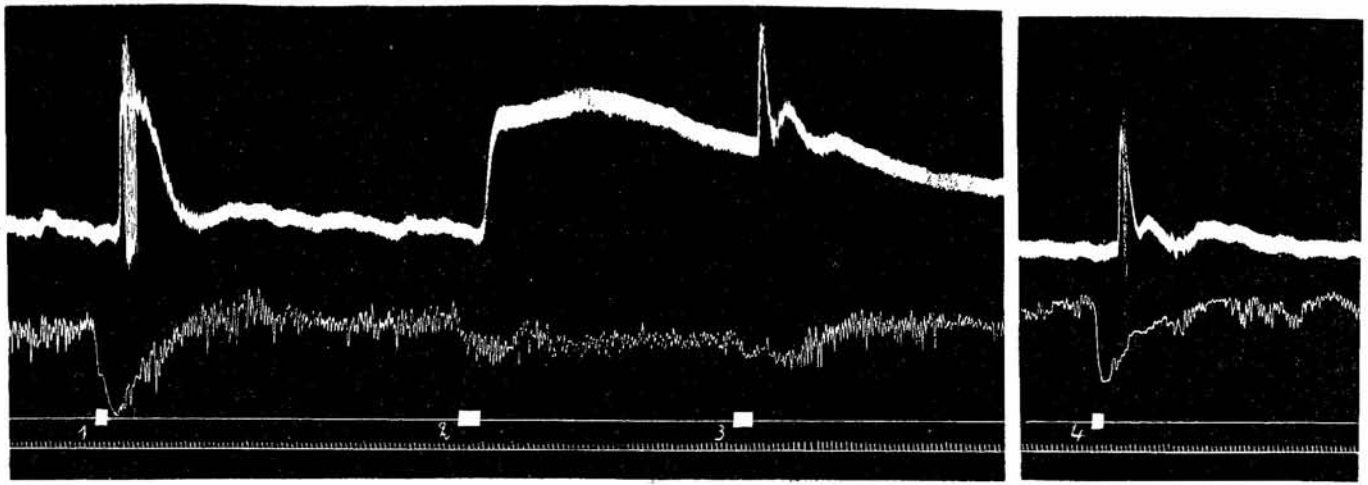


FIG. 9. DOG WEIGHING 8 KGM.

The upper curve is that of the blood pressure, the lower one that of the small intestine in situ. Signal line denotes injection. Time markings every 6 seconds. At point *1*, adrenalin 1 cc. 1:50,000, strong rise in blood pressure and marked relaxation of tonus and inhibition of intestinal peristalsis. At point *2*, ergotamine tartrate 0.25 mgm. per kilogram, strong increase in blood pressure, no marked influence on the gut. At point *3*, adrenalin 1 cc. 1:50,000, increase in blood pressure; practically complete inhibition of the action of adrenalin on the gut. At point *4*, 60 minutes later adrenalin 1 cc. 1:50,000, rise in blood pressure. The effect of adrenalin on the gut is again marked.

mgm. ergotamine per kilogram inhibits the action of ergotamine on the gut, while it does not produce vasomotor reversal. In figure 8 a and 8 b adrenalin exerts only a weak action on the blood pressure, but here also we note a stronger influence of ergotamine on the inhibitory action of adrenalin on the gut than on the blood pressure.

There exist quantitative differences in the adrenalin-inhibiting action of ergotamine in the rabbit and in the dog. Dale (2) believed that ergotoxine produces no vasomotor reversal on the

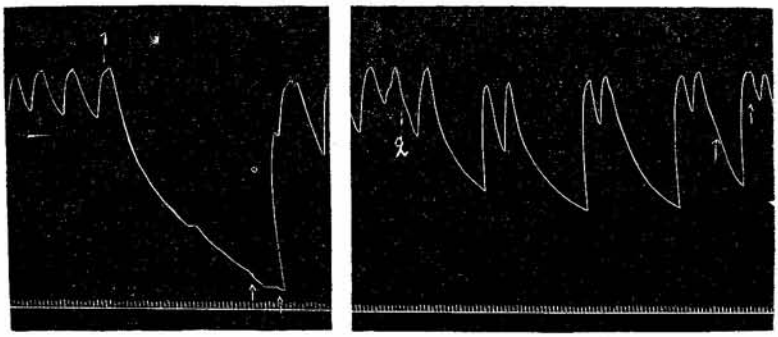


FIG. 10 A AND B. NON-GRAVID ISOLATED CAT UTERUS

Time markings every 6 seconds.

Fig. 10 a. At point *1*, adrenalin 1:20,000,000. Very marked relaxation and stoppage of the rhythmic contractions. After washing, tonus increases again.

Fig. 10 b. After ergotamine tartrate 1:500,000 has been allowed to act for 15 minutes, adrenalin 1:20,000,000 is added at point *2*. The distinct inhibition caused by adrenalin is stopped.

blood pressure in the rabbit, he even believes that inhibition of adrenalin can hardly be obtained regularly. Contrary to this opinion we were able to show that, between the rabbit on the one hand and the dog and cat on the other, there are only quantitative differences, and that is is also possible to produce vasomotor reversal in the rabbit. This, however, is not the rule, but the exception. On the other hand adrenalin inhibition is regularly observed. A similar condition exists apparently also as regards the adrenalin inhibition on the gut.

Our results afford a renewed opportunity to call attention to the variations in the adrenalin-inhibiting effect which are

noted, not only between different animal species, but even between individuals of the same species. Thus, in the experiment of figure 7 in the rabbit, the adrenalin action on the blood pressure is more strongly inhibited than in the experiment of figure 9 in the dog. Moreover, comparison of the experiments of figures 8 and 9 shows how variable is the influence of ergotamine on the blood pressure. In the first case figure 8 a, intravenous administration of 0.12 mgm. ergotamine per kilogram causes only an insignificant rise in blood pressure and subsequent injection of 0.24 mgm. per kilogram leads even to a slight fall in blood pressure. In the second case (fig. 9) the administration of 0.25 mgm. ergotamine per kilogram is followed by a strong and lasting elevation of the blood pressure. In this connection we wish to refer to the work of Heymans and Régniers (25), and that of Salant, Nadler and Brodman (26), in which attention is likewise called to the primary blood pressure-lowering effect of ergotamine.

From the foregoing experiments in vitro and in vivo it may be positively concluded that ergotamine in doses entirely within the range of those used for the exclusion of sympathetic motor mechanisms annuls the inhibiting action of adrenalin on the gut.

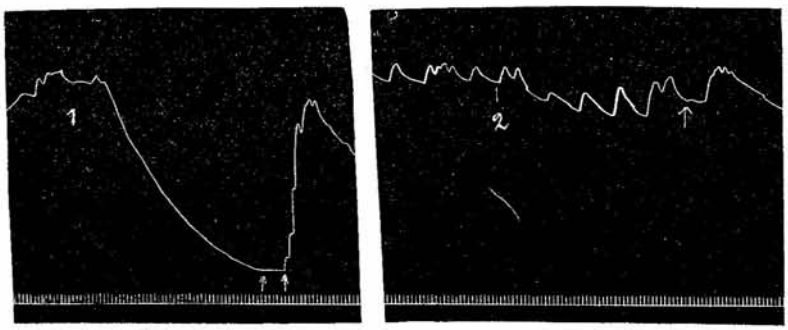
V

Adrenalin also exerts an inhibitory action on functions of the virgin and of the non-gravid uterus of several animal species, viz.: rat, guinea pig, cat and dog. It has already been stated that for these organs larger doses of ergotamine are required. Mendez (19) has experimented on the rat and the guinea pig and thus describes his results with the uterus of the rat: "In these cases therefore the action of ergotamine in paralyzing an inhibitor response, if it exists at all, must be at least three thousand times less powerful than its action in abolishing motor responses."

We have made new experiments on these organs. Figures 10 and 11 show the results with the uterus of the cat.

These experiments prove that inhibition of the adrenalin effect is produced in the uterus of the cat by doses of ergotamine 10 to 40 times higher than those of adrenalin. Let us emphasize again the fact that high doses of ergotamine are necessary to ob-

tain this effect and that even these doses 10 to 40 times higher cannot always, and do not always, inhibit completely the adrenalin action. Not only are higher doses of ergotamine necessary but inhibition is obtained less regularly. The above related experiments are too few in number to allow us to give exact quantitative proportions. With the uterus of the guinea pig and of the rat conditions are still more unfavorable and, particularly with the rat, we have not succeeded better than Mendez. What has been said above as regards blood pressure also applies here, namely, that ergotamine does not work as well in herbivora



a b

FIG. 11 A AND B. ISOLATED NON-GRAVID UTERUS OF CAT

Time markings every 6 seconds.

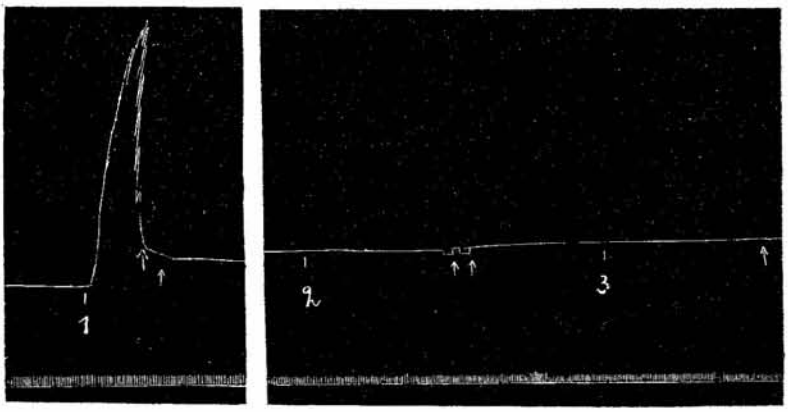
Fig. 11 a. At point *1*, adrenalin 1:10,000,000 produces the typical inhibiting effect. Washing and addition of ergotamine 1:1,000,000.

Fig. 11 b. At point *2*, adrenalin 1:10,000,000 which is followed only by weak action (almost complete inhibition of adrenalin).

as in carnivora; the uterus of the rabbit being an exception, but here we have to deal with the inhibition of an augmentor, not of an inhibitor adrenalin effect.

The fact that ergotamine practically does not counteract the inhibiting action of adrenalin in the isolated non-gravid uterus of the rat and of the guinea pig, and counteracts it in the cat only in high doses, cannot be invoked against the view that ergotamine also inhibits sympathetic inhibitory functions. For the non-gravid, inactive, uterus of the rat, guinea pig and cat reacts to adrenalin by relaxation and exhibits for the latter a sensitive-

ness so great that it may possibly be affected by normal concentrations of adrenal secretion in the blood. This is well in accord with the endocrine considerations advanced by Knaus (27) to explain why the uterus in situ behaves so sluggishly and exhibits such weak peristalsis. Moreover it is a well-known and interesting biological fact that the same organ during pregnancy reverses its mode of reaction towards adrenalin; as pregnancy progresses,



a b

FIG. 12 A AND B. ISOLATED UTERUS OF A CAT WHICH HAD KITTENS A DAY BEFORE
Time markings every 6 seconds.
Fig. 12 a. At point *1*, adrenalin 1:10,000,000 is added. Very strong contraction. Then ergotamine 1:5,000,000 is allowed to act during 10 minutes.
Fig. 12 b. At point *2*, adrenalin 1:10,000,000 is again added. The adrenalin is completely inhibited. At point *3*, after washing out of the test object adrenalin 1:5,000,000 is again added. This double dose of adrenalin is also completely inhibited.

adrenalin more and more exerts a tonus-raising action, so that finally, the uterus of those animal species responds exactly as that of the rabbit, the relaxing effect of adrenalin having disappeared. Such a progressive biological change under normal physiological conditions has been demonstrated with certainty only for the uterus. The inactive organ reacts by relaxation; on the contrary the organ in a state of physiological activity gives an augmentor response to adrenalin.

Mendez has described this for the uterus of the guinea pig and

figure 12 shows a demonstration on the uterus of a cat which had given birth to kittens the previous day. The augmentor adrenalin action is completely inhibited by a suitable dose of ergotamine.

From these variations in response to adrenalin the conclusion is drawn that the uterus possesses a double sympathetic innervation, an augmentor and an inhibitor, which quantitatively do not respond equally to adrenalin. When seeking an explanation of vasomotor reversal Dale (2) made a similar assumption for the vascular system, though proof of the existence of sympathetic vasodilators is yet lacking. He assumed that ergot alkaloids paralyze only the motor fibers, but not the inhibitory endings, of the sympathetic and that, therefore, the masked action of adrenalin on the sympathetic inhibitory fibers becomes more apparent. But what happens to the sympathetic motor endings in the nongravid uterus, and to the sympathetic inhibitory fibers in the gravid and parturient uterus? A similar question may be raised about vasomotor reversal. A plausible explanation is not available. Dale surmises that normally the sympathetic motor endings are more susceptible and react more quickly to adrenalin and are paralyzed by the ergot alkaloids, while the inhibitory sympathetic endings remain uninfluenced and still react to adrenalin. On the vascular system a uniform adrenalin reaction, or sympathetic inhibitory action, is not demonstrable. Of the depressor phenomenon we know that it causes vasodilatation and that this is completely inhibited by ergotamine, a fact which we were first to describe. The pharmacologic demonstration is complete, but we have no exact anatomic or physiologic proof that the efferent part of the reflex arc is really of sympathetic nature. On the other hand the sympathetic innervation of the virgin and nongravid uterus is not contested. We have consequently to deal here with conditions showing but little similarity, especially from the functional standpoint, as the two types of organ systems react differently to adrenalin.

The reaction to adrenalin of an actively functioning gravid uterus is the result of a functional change which runs parallel with the anatomical and physiological modifications occurring in the organ. It is likely that this altered reaction is not of nervous

origin but is exclusively due to modifications of the activity of the new formed tissue. Knaus (27) has shown that these local changes in the uterus are related to new influences of internal secretion organs, placenta, corpus luteum. The fact that these gravid uteri exhibit a different response to adrenalin and other excitants not only in vivo, but also in vitro, confirms our view.

These considerations lead to the conclusion that, physiologically and pharmacologically, there is a fundamental difference between the mode of reaction of the sympathetic-inhibitory function of the gut on one side and that of the non-gravid uterus on the other. With the gut we have to deal with an action antagonistic to the vagus, with the uterus on the contrary with a condition that occurs only in the inactive state and reverses itself when the organ assumes an active physiological function. When it comes to settling the question whether ergot alkaloids counteract the inhibitory functions of the sympathetic, the inhibition mechanism on the gut, which is physiologically well defined and constant, is certainly more important than that on the non-gravid inactive uterus. The first is a physiologically constant and regular adrenalin action; the second is an occurrence of considerable biological interest, which, however, varies.

In concluding let us insist again on the quantitative variations of the sympathetic-inhibiting effect of ergotamine in the different animal species and even in individuals of the same species. Even the different organs of the same individual do not respond equally quantitatively to ergotamine, as is proven not only by animal experiments, but also by clinical knowledge derived from the use of ergotamine in conditions associated with imbalance of the vegetative nervous system, exophthalmic goiter, migraine, etc. This is in accord with the known fact that the excitability of the various sympathetic nerves to electrical stimulation is subject to wide fluctuations. In this respect ergotamine behaves as do other substances influencing the vegetative nervous system, for instance, adrenalin, pilocarpine, atropine. The same, as already explained more in detail above, is also true of the qualitative variations.

The aim of research is not simply to state a number of isolated

facts. Much more important is the synthesizing of the essential points of separate facts in as few general deductions as possible. Only then does the isolated fact attain its real significance. This I have done for ergotamine with due consideration to the fact that the validity of such a synthesis can be no greater than that of the isolated tests. And my conclusion is: Ergotamine behaves fundamentally as regards the sympathetic nervous system as atropine does as regards the parasympathetic.

SUMMARY

1. In the introductory part of this article the theoretical and practical significance of ergotoxine and ergotamine is explained; it is shown that through the chemical and pharmacological study of ergotamine, not only the question of the practical use of ergot alkaloids is cleared up, but that the field of therapeutic indications has been extended through the application of the sympathetic-inhibiting action.

2. In the experimental part it is shown that ergotamine counteracts adrenalin, not only in organs stimulated by the sympathetic, but also in those inhibited by the latter.

3. Proof of this is obtained very easily in vitro on the small and large intestine of the guinea pig and of the rabbit with the same concentrations which influence the isolated uterus of the rabbit. The corresponding proportions of adrenalin and ergotamine are 1:2, that is, a dose of ergotamine twice as large as that of adrenalin inhibits the latter.

4. On the small intestine in situ in the dog and the rabbit the inhibiting action of adrenalin is partly or completely counteracted by the minimum amounts of ergotamine necessary to produce vasomotor inhibition or reversal. In many of our experiments a stronger action is noted on the gut than on the vascular system.

5. Other proportions obtain with the isolated virgin or nongravid uterus of the rat, guinea pig, and cat. In the cat it is possible to inhibit the effect of adrenalin with doses of ergotamine 10 to 40 times greater than those of adrenalin; but this does not happen constantly. In the guinea pig, and especially in the rat

the required amount of ergotamine is still higher; there is practically no inhibition.

6. It is known that the gravid or parturient uterus of those animal species is not relaxed, but contracted, by adrenalin. This augmentor effect of adrenalin is very distinctly inhibited by ergotamine.

7. To demonstrate whether ergotamine can paralyze the inhibitory sympathetic fibers the positive findings on the gut are much more important than the negative ones on the virgin and non-gravid uterus of certain animal species. The effect of adrenalin on the gut is physiologically constant, while that on the virgin or on the non-gravid uterus of certain animal species is only of biological interest and becomes reversed in the actively functioning organ during pregnancy and puerperium.

8. These experimental facts strengthen the view previously expressed by us that ergotamine paralyzes not only the augmentor functions of adrenalin on the sympathetic, but also the inhibitory functions. In our opinion, the exclusive action on the augmentor nerve fibers, as first proclaimed by Dale and recently restated by Mendez for ergotamine, is not borne out by facts.

9. The inhibitory influence of ergotamine affects both the augmentor and inhibitor endings, even if the different physiological mechanisms do not respond equally quantitatively, and if not inconsiderable individual variations exist. Similar conditions are known to exist also in regard to the action of atropine on the parasympathetic.

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