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The Pharmacology of the Natural and Dihydrogenated Alkaloids of Ergot

By **E. Rothlin, Basle**

In the last 40 years, the problem of the chemistry, pharmacology, and clinical use of ergot of rye has made great advances. It is not my purpose to give a chronological review of the whole subject, but to present some characteristic data obtained in the course of the quantitative and qualitative differentiation of the natural alkaloids of ergot and their dihydrogenated derivatives.

Table 1 shows that we have to deal with six natural alkaloids of different composition, each of them occurring in two isomeric forms ... ine and ... inine. The latter forms are rare, very little soluble and of lesser biological activity. They will not be discussed. According to *Stoll* and his coworkers (1) we distinguish three alkaloidal groups: that of *ergotamine*, characterised by the content of pyruvic acid; that of *ergotoxine*, containing dimethylpyruvic acid; and that of *ergobasine* (ergometrine or

Table 1

Composition of the natural Alkaloids of Ergot

	Cleavage Products of Alkaline and Acid Hydrolysis	
I. *Ergotamine-group* 1. *Ergotamine* Ergotaminine 2. *Ergosine* Ergosinine	Lysergic acid NH_3 *Pyruvic acid* d-Proline	+ *l-Phenylalanine* + *l-Leucine*
II. *Ergotoxine-group* 3. *Ergocristine* Ergocristinine 4. *Ergokryptine* Ergokryptinine 5. *Ergocornine* Ergocorninine	Lysergic acid NH_3 *Dimethyl-pyruvic acid* d-Proline	+ *l-Phenylalanine* + *l-Leucine* + *l-Valine*
III. *Ergobasine* (Ergometrine) Ergobasinine (Ergometrinine)	Lysergic acid	+ *d-2-Aminopropanol*

ergonovine). The latter has a smaller molecular weight and particular properties; it will not be included in this review. Furthermore, *Stoll* and his coworkers (2) have shown that ergotoxine is not a uniform chemical substance but a molecular complex of three alkaloids: ergocristine, ergocornine and ergokryptine. As will be shown later, this fact decides the former controversy concerning the chemistry and the biological properties of ergotamine and ergotoxine.

The composition of the five natural alkaloids with high molecular weight is quite similar, the only difference between ergotamine and ergosine being that the former contains l-phenylalanine while the latter contains l-leucine. The same distinguishing criterion is found in the three different amino acids of the three alkaloids of the ergotoxine group. *Lysergic acid* is characteristic for all these natural alkaloids. It is a non-saturated aromatic acid containing five double bonds (C=C). One of these can be saturated individually (*Stoll* and *Hofmann* [3]) resulting in the formation of the well-defined, stable and crystallised dihydrogenated alkaloids. In the following these will have our special attention.

The fundamental studies of ergot pharmacology go back to the skilful work of *H. H. Dale* (4). Further progress in the pharmacology and clinical application now allows a clear classification of the principal actions of these alkaloids. We may thus distinguish:

1. *Effects which have their point of attack in the central nervous system.* The respective functions comprise: respiration; circulation (pulse rate, blood pressure, baropressive reflexes of the carotid sinus and depressor-nerves); correlation between respiration and circulation; regulation of body temperature; emesis; sedation of emotional and motor excitation.

2. *Effects with peripheral points of attack.*

(a) Actions which are *actually visible*, e. g. direct stimulation of smooth-muscle organs, especially the uterus, the blood vessels, the iris, and the amnion (the latter free of nerves).

(b) Actions which are *latent* or *potential*, e. g. the inhibition of functions which are stimulated or depressed by either the excitation of sympathetic nerves or by adrenaline. These effects become visible only if the respective function is activated by either a sympathetic nerve or by adrenaline.

Toxicity

The criterion of toxicity is not characteristic for the specific action of these alkaloids since it is too general. However, it has theoretical and, above all, practical importance. From the figures in table 2 we see that toxicity depends on the degree of differentiation of the brain. Thus toxicity progressively increases from the mouse to the rabbit. In the

latter animal the relative toxicity of the natural alkaloids varies between 1 and 3, ergotamine being the least toxic. Since all three components of ergotoxine—ergocristine, ergokryptine and ergocornine—are more toxic than ergotamine, it seems logical that the molecular complex itself should also be more toxic. This supports our earlier concept (5) of the greater toxicity of ergotoxine in comparison with ergotamine. The most striking toxicological feature is the very much greater tolerance of the dihydrogenated alkaloids compared with the natural forms. It may be

Table 2

Toxicity LD 50 of the Natural and Dihydrogenated Alkaloids of Ergot

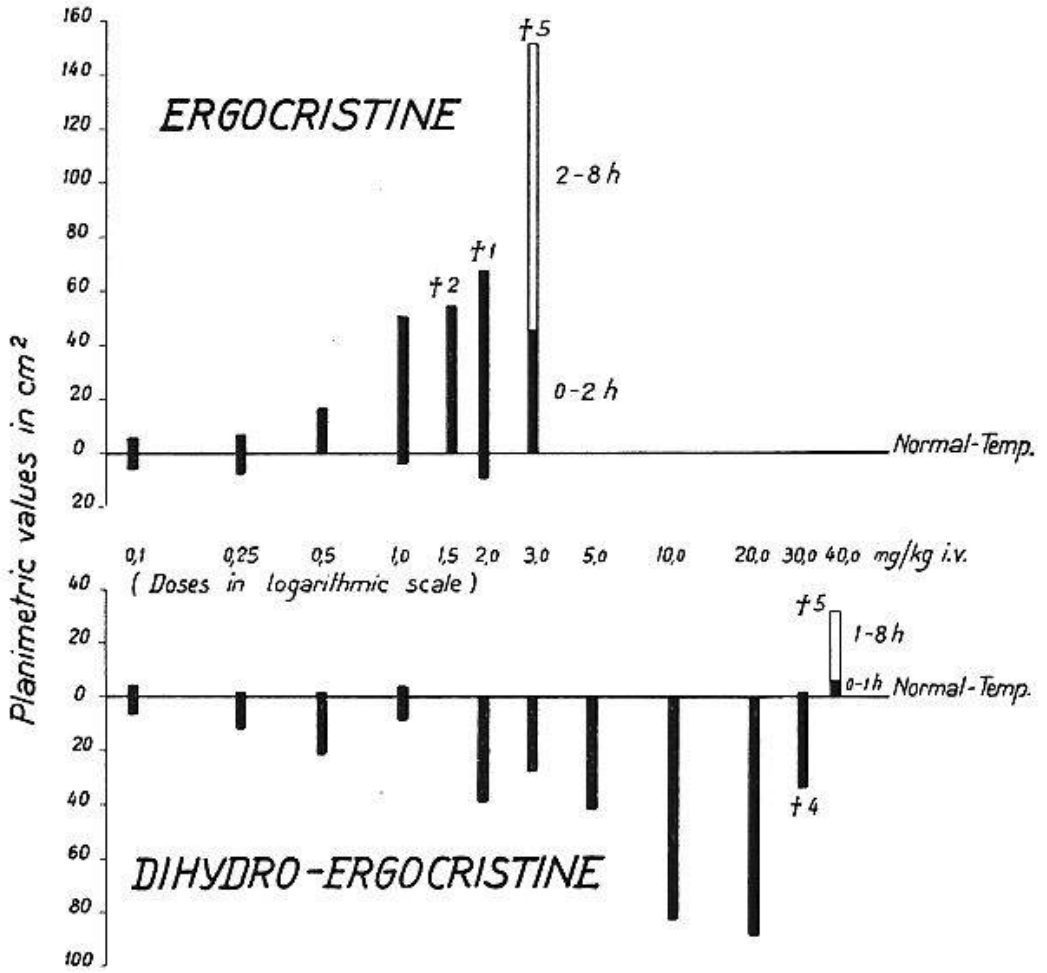
Animal	*Ergotamine* tartrate	*D·H-Ergotamine* tartrate
1. Mouse i.v.	62 mg/kg	118 mg/kg ca. 2× less toxic
2. Rat i.v.	80 mg/kg	110 mg/kg ca. 1,4× less toxic
3. Cat s.c.	11 mg/kg	68 mg/kg ca. 6× less toxic
4. Rabbit i.v.	3,55 mg/kg	25 mg/kg ca. 8× less toxic
Rabbit i.v.	*Ergosine tartrate* 1,24 mg/kg	*Dihydro-Ergosine tartrate* 37 mg/kg 28× less toxic
Rabbit i.v.	*Ergocristine tartrate* 2,17 mg/kg	*Dihydro-Ergocristine tartrate* 27 mg/kg 12× less toxic
Rabbit i.v.	*Ergokryptine tartrate* 1,05 mg/kg	*Dihydro-Ergokryptine tartrate* 19 mg/kg 18× less toxic
Rabbit i.v.	*Ergocornine tartrate* 1,17 mg/kg	*Dihydro-Ergocornine tartrate* 35 mg/kg 30× less toxic

said: *The more toxic the natural alkaloid, the less toxic the dihydrogenated form* (with the exception of ergokryptine). In the rabbit (i.v.) the ratio of toxicity for ergotamine and dihydroergotamine is 1:8, that for ergocornine and dihydroergocornine is as high as 1:30. Therefore, the same chemical change in the identical group of the molecule of the natural alkaloids elicits quantitative differences of a high order. This fact is evident also in the pharmacological behaviour.

Temperature Regulation

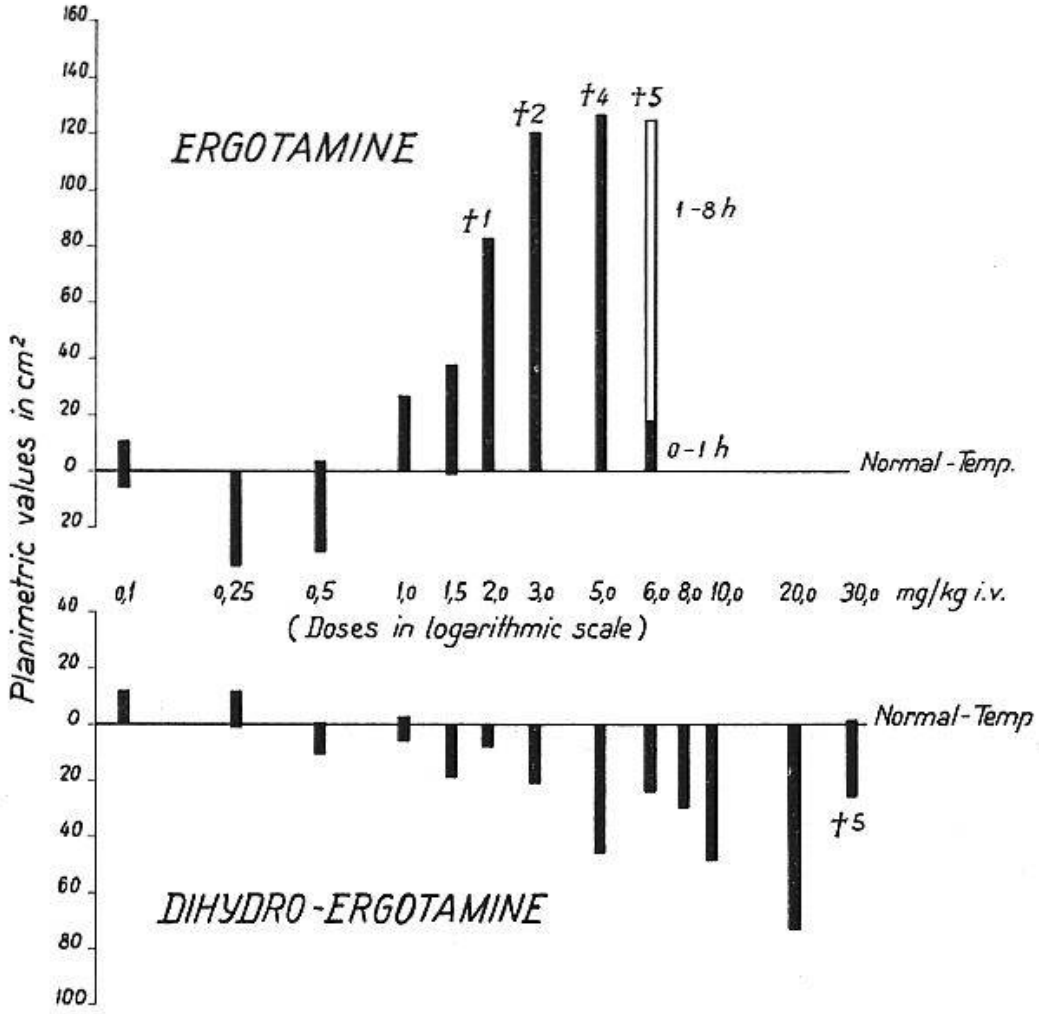
A good example of the action of these alkaloids on the central nervous system is their influence on the body temperature, an effect that lends itself easily to measurement. This action is of a central nature because it is suppressed by general anesthesia. The qualitative effect depends both on the type of alkaloid and on the size of the dose. Fig. 1 proves this for ergotamine and dihydroergotamine. Both alkaloids depress the temperature in small doses but in higher, and especially in toxic doses,

Fig. 1 *Effect upon the Temperature-Regulation of the Rabbit.*
Planimetric Representation Average 5 Animals for each Dose.



ergotamine raises the body temperature while dihydroergotamine lowers it even at the toxic level. Not identical is the behaviour of the other alkaloids, as will be seen in fig. 2 which represents the effect of ergocristine and dihydroergocristine. Ergocristine does not lower body temperature but raises it. The rise corresponds to the size of the dose, whereas dihydroergocristine like dihydroergotamine lower the temperature in all doses except the lethal one. The other alkaloids of the ergotoxine group—ergocornine and ergokryptine and their dihydrogenated forms—behave like ergocristine and dihydroergocristine respectively. As far as the regulation of body temperature is concerned, two essential facts should be retained: the difference between the ergotamine-like and ergotoxine-like alkaloids on one side, and the difference between the natural and the dihydrogenated forms on the other side. Hydrogenation appears to produce a *qualitative change* in the mode of action of tempera-

Fig. 2 *Effect upon the Temperature-Regulation of the Rabbit.*
Planimetric Representation Average 5 Animals for each Dose.



ture regulation which rests only on a minute alteration in the molecular structure.

A parallelism exists between the rise in temperature and other symptoms of the central nervous system, such as nausea, vomiting, general excitation, and convulsion; these central symptoms are much less pronounced in the case of the dihydrogenated alkaloids.

Blood Circulation

In considering the action of ergot alkaloids on blood circulation a complex situation is immediately evident. The direct actions are partly of a central, partly of a peripheral nature. The pharmacologic resultant, however, is dependent also on indirect actions. Moreover, it is a fact that even in normal animals large individual variations occur which complicate quantitative measurements.

Action on Blood Vessels. The natural alkaloids have a constrictor effect

on isolated arteries, blood vessels in the rabbit ear and extremities of the frog. The dihydrogenated alkaloids have a similar effect, though somewhat weaker. Besides this visible effect on smooth muscle, there is also present a latent sympathicolytic action. All alkaloids, with the exception of ergobasine (ergometrine, ergonovine), inhibit or reverse the action of adrenaline. The effect, therefore, on the blood vessels is a double or bivalent one.

Isolated Heart. In the cat and dog heart-lung preparation of *Starling* neither the natural nor the dihydrogenated alkaloids have, even in relatively very high doses, any visible or latent effect upon the main functions of the heart; neither frequency nor rhythm nor cardiac output are influenced. Moreover, there is no latent sympathicolytic effect in contrast to the action on the blood vessels, where sympathicolysis is characteristic (*Rothlin* [6]).

Blood Pressure. (a) *Pithed cat:* Both the natural and the dihydrogenated alkaloids raise the blood pressure but higher values are obtained with the

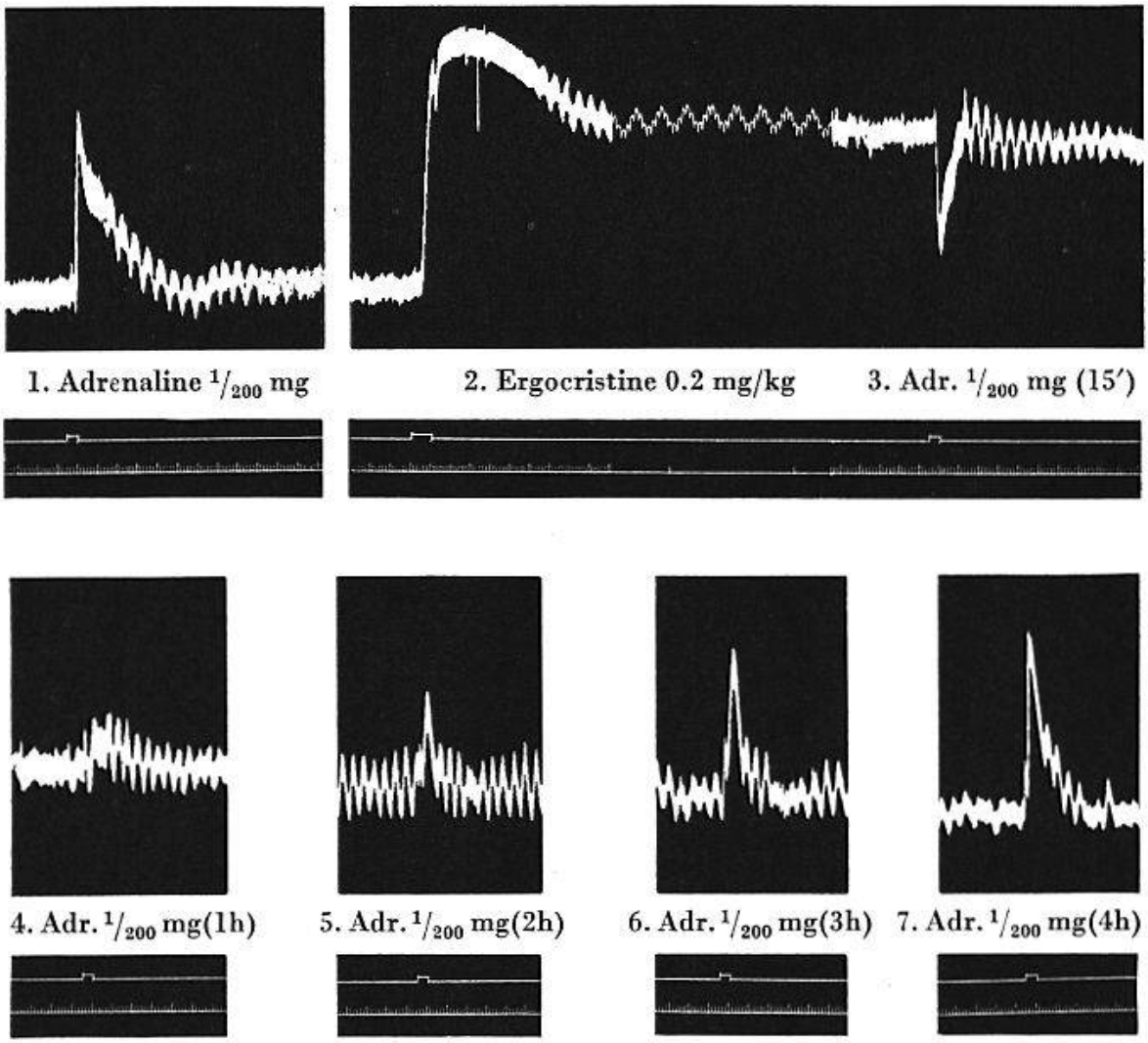


Fig. 3. Record of the carotid blood pressure of a spinal-cat. Adrenaline-reversal.

natural alkaloids. The blood pressure rise is the result of a direct action of the alkaloid on the blood vessels (fig. 3). In the pithed cat an identical dose of natural and dihydrogenated alkaloid decreases the pulse rate to a lesser degree than in the intact animal in urethane anæsthesia. This action, therefore, must be mainly of central origin. (b) *Anæsthetized intact animal:* Of all the natural and dihydrogenated alkaloids only ergotamine regularly produces an increase in blood pressure. Similar results are obtained in rabbits, cats, and dogs. In anæsthetized intact animals, without artificial respiration, we regularly obtain complete inhibition or reversal of the adrenaline pressor effect. This phenomenon is more pronounced in the case of the dihydrogenated alkaloids. This is evident in fig. 4, where the effect of 0,05 mg/kg dihydroergotamine is illustrated and where

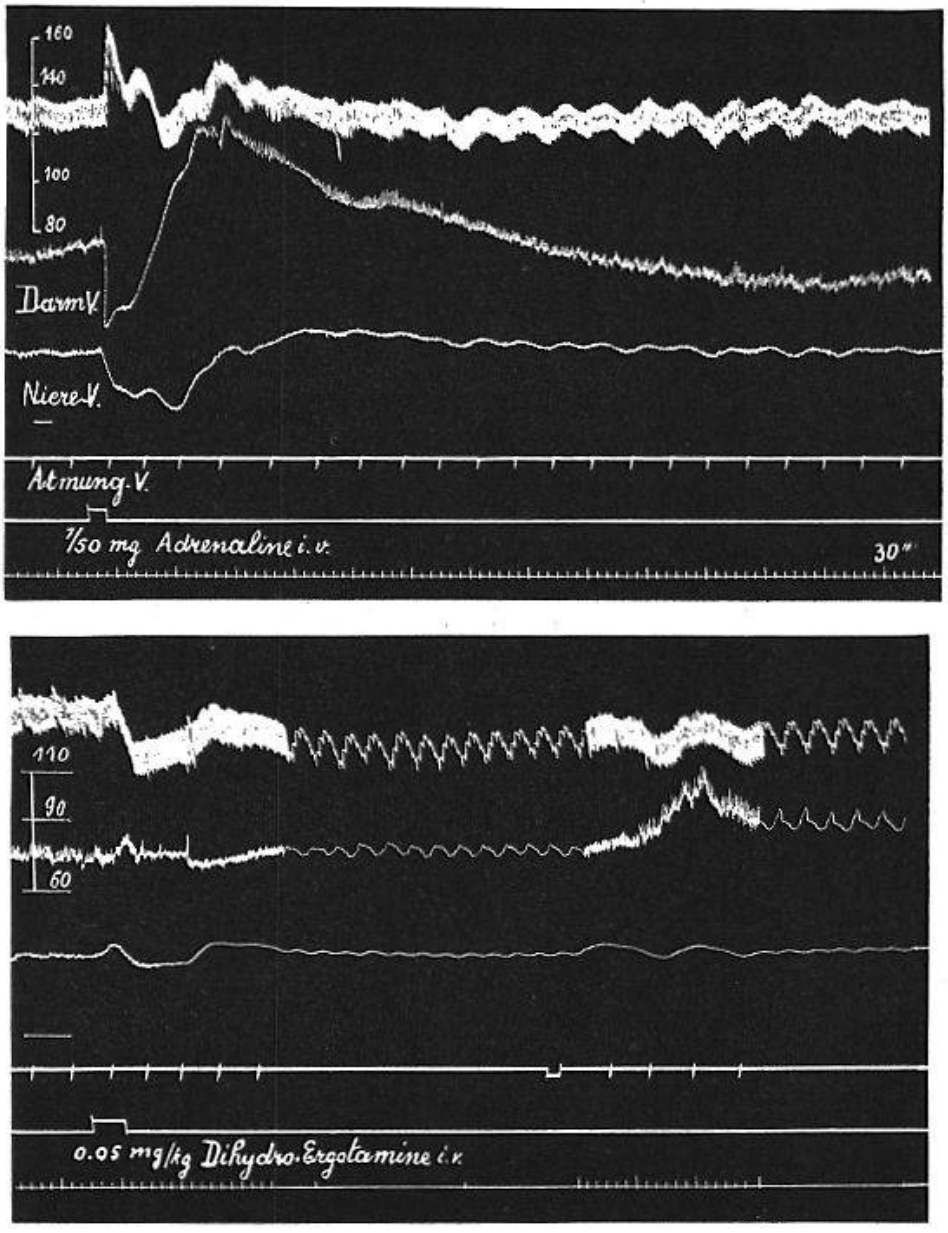


Fig. 4a. Record of adrenaline-reversal of a cat in urethane narcosis.

the blood pressure, the volume of one kidney, and a loop of the small intestine are plethysmographically registered. The vessels of these organs show no significant response to the alkaloid, but the action of adrenaline is reversed.

In 1925 we (7) demonstrated the inhibitory action of ergotamine on the effect of electrical stimulation of the depressor nerve in the rabbit and the cat. *Heymans* (8) confirmed this for the carotid sinus and found that the pressor effect obtained by temporary ligature of both carotids is depressed or inhibited. We have made a comparative study of these phenomena in the rabbit with all of the ergot alkaloids. At the same time, the effect of the alkaloids on blood pressure itself and on the adrenaline pressor effect was taken into consideration. All alkaloids are active on the four circulatory criteria which were studied. The *natural* alkaloids show quantitatively and qualitatively different actions as regards blood pressure and pressor effect of adrenaline. Ergotamine produces increase

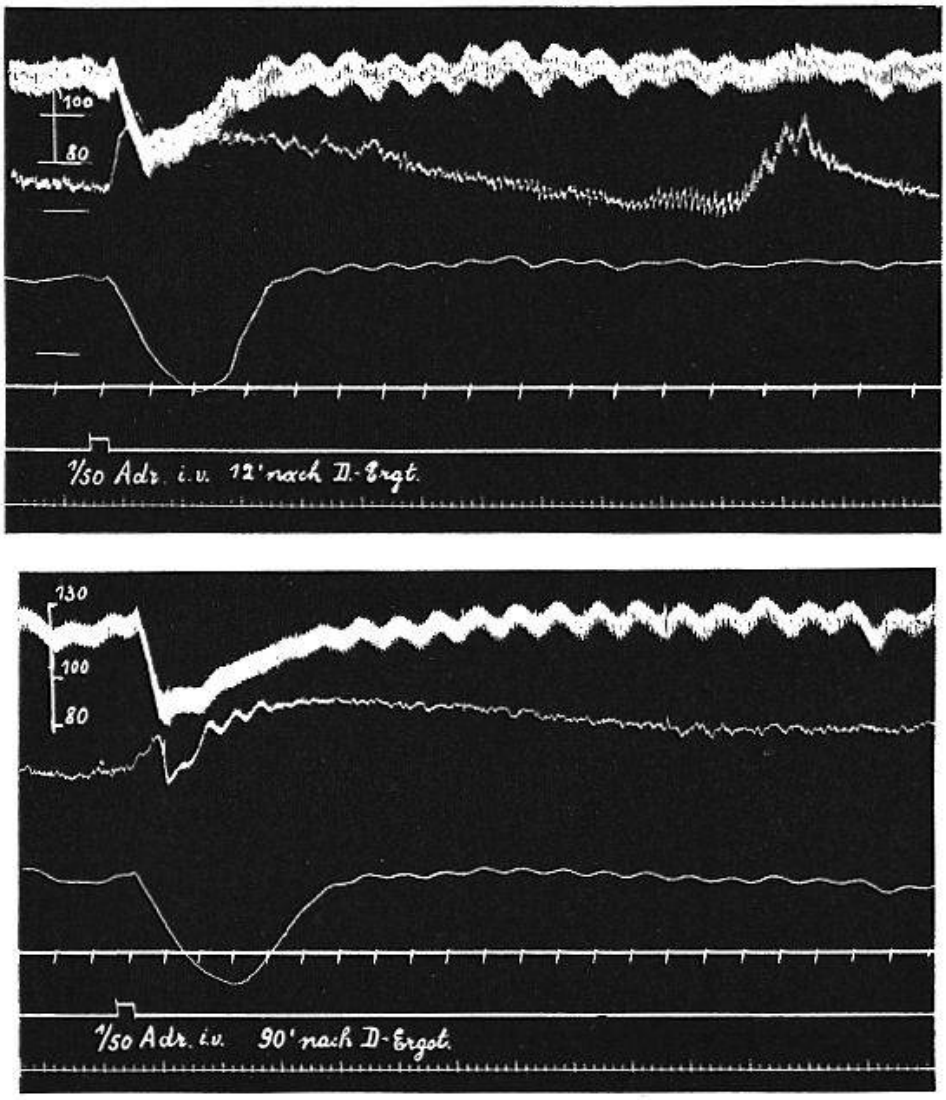


Fig. 4b. Record of adrenaline-reversal of a cat in urethane narcosis.

of blood pressure in doses of 0,1–0,2 mg/kg. Ergosine acts similarly in doses up to 0,125 mg/kg, higher doses decrease blood pressure. The other alkaloids exclusively lower blood pressure. The influence of the natural alkaloids on the pressor effect of adrenaline is biphasic, i.e. primarily always inhibitory and secondarily frequently sensitizing to adrenaline. The action on the depressor nerve and on the effect of temporary occlusion of both carotids is always inhibitory. There are quantitative differences but these are not identical for both criteria.

In contrast to the variety of action of the natural alkaloids the dihydrogenated alkaloids act in the same manner on all criteria concerned. Dihydrogenation of the natural alkaloids, therefore, leads to a surprising uniformity in their mode of action. From the quantitative point of view, however, the dihydrogenated alkaloids differ in succession as regards their behaviour in the four circulatory tests.

These are some important facts demonstrating the complexity of the

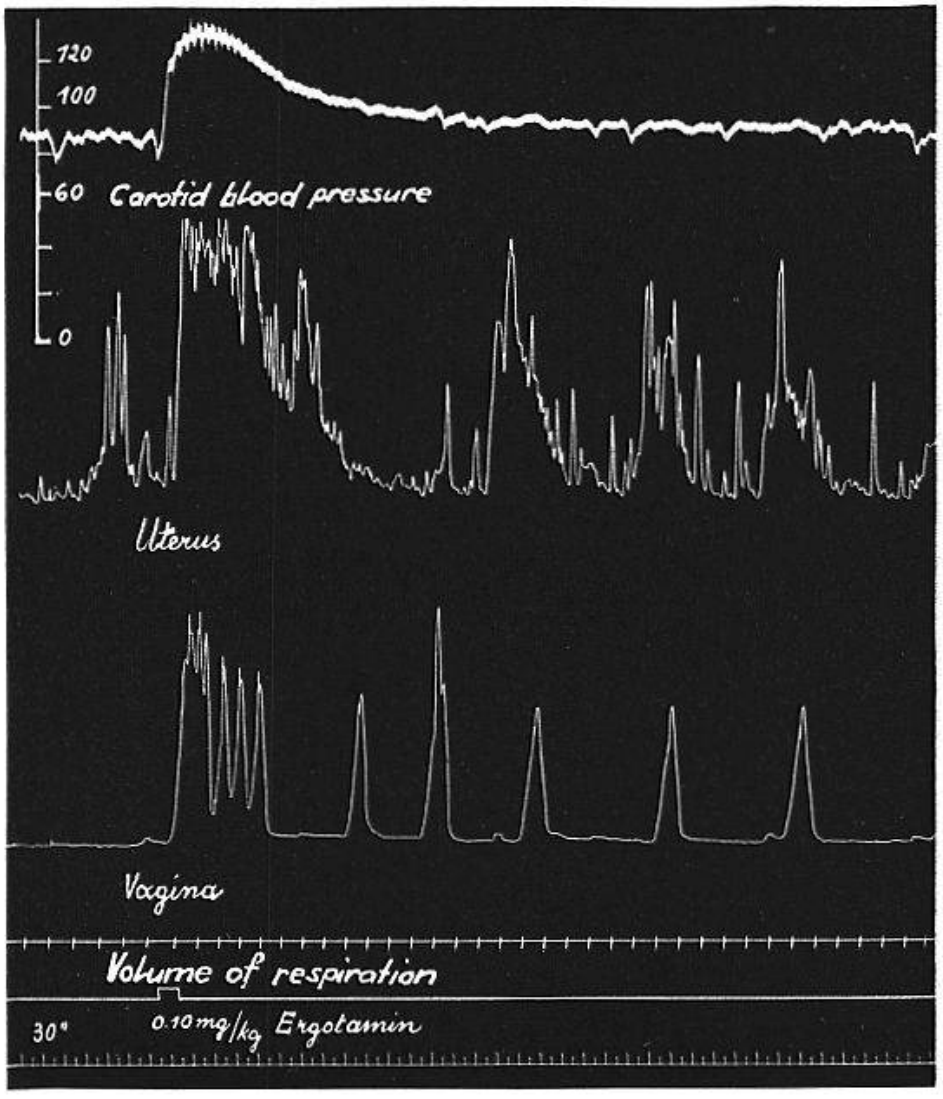


Fig. 5a. Record of a rabbit in urethane narcosis.

ergot action on the circulatory system. Both central and peripheral mechanisms are present and even act in competition with each other. We have a direct constrictor action in isolated vessels and in the pithed cat whereas, in the intact animal, with the exception of ergotamine, the blood pressure is lowered. Since the heart is not directly influenced by pharmaco-therapeutic doses, we conclude that the fall of blood pressure produced by ergot alkaloids is not of peripheral but of central origin: it is not caused by direct vasodilation but by inhibition of the vasomotor center or stimulation of an assumed vasodilator center. In other words the fall of blood pressure produced by the natural alkaloids is related to inhibition of the vasomotor center and the fall of blood pressure produced by the dihydrogenated alkaloids is attributed to stimulation of a vasodilator center. We also attribute the decrease in pulse rate in the intact animal to a central stimulation of the vagal center. Moreover, the influence of the baropressive reflex upon the depressor nerves and carotid

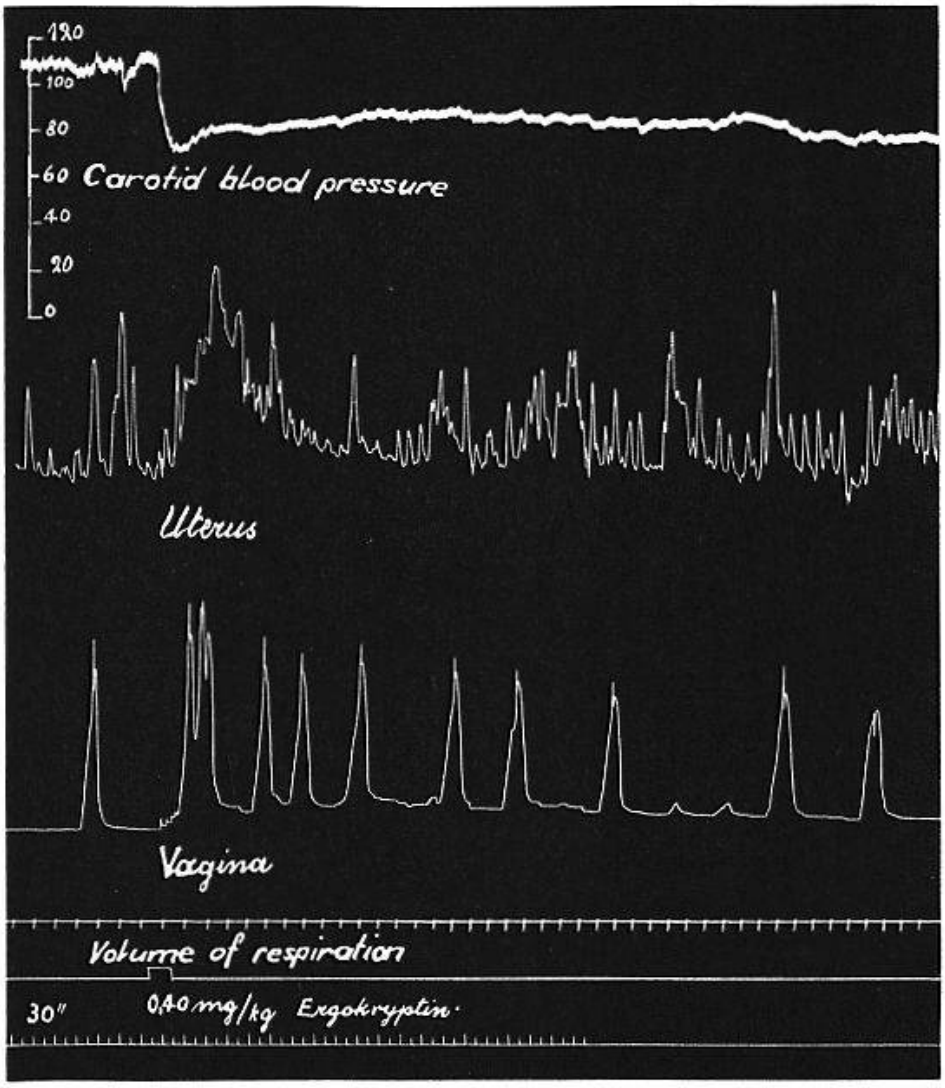


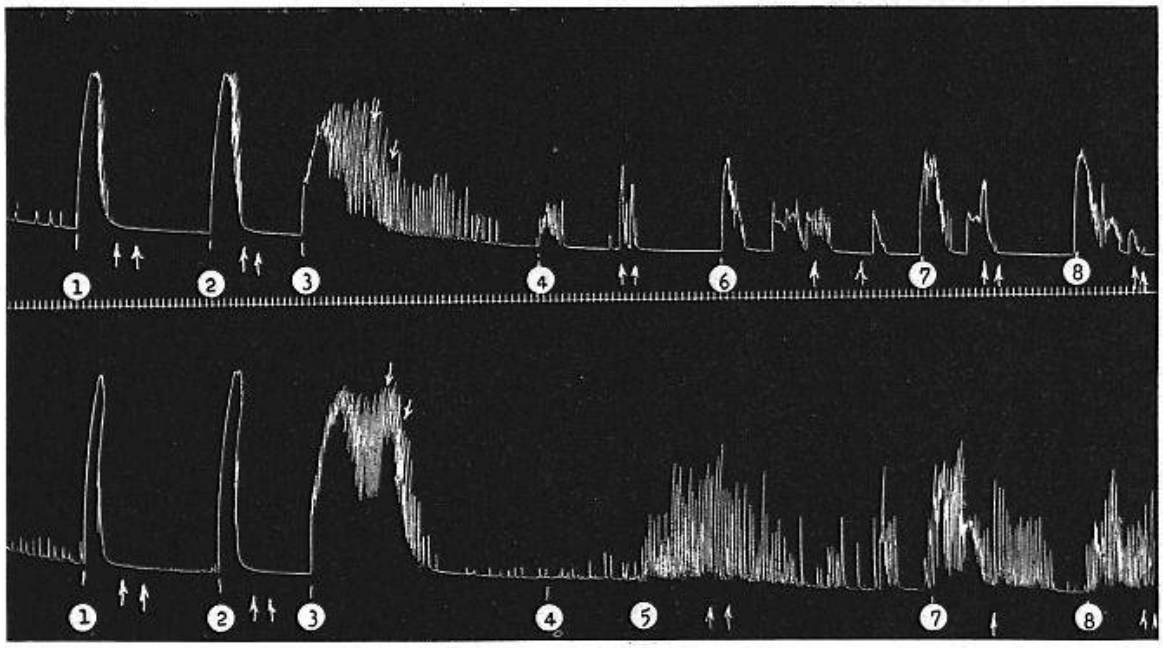
Fig. 5b. Record of a rabbit in urethane narcosis.

sinus are probably of central origin, as this has been suggested by *von Euler* and *Schmiterloew* (9).

Uterus

Among the directly visible actions of the alkaloids of ergot the long lasting effect on the uterus, especially in the puerperal phase, is experimentally and clinically characteristic. Convincing proof of the therapeutic usefulness of this action is given by the extensive clinical application of ergotamine (Femergine or Gynergen). With the exception of ergobasine (ergometrine, ergonovine) none of the other natural alkaloids has a comparable clinical background. We have already drawn attention to the greater toxicity of the natural alkaloids of the ergotoxine group. Their activity in the rabbit uterus in situ is from 3 to 5 times lower than that of ergotamine. Fig. 5a and 5b demonstrate a typical example for ergotamine and ergokryptine, the latter showing a weaker action although the dose is 4 times greater.

The action of the dihydrogenated alkaloids on the uterus is entirely different from that of the natural alkaloids. Not only have these lost the excitatory effect on the uterus but they are indeed able to inhibit in vitro and in situ the powerful stimulative action of the natural alkaloids such as ergotamine and ergotoxine. In fig. 6 we see that ergobasine produces



1 Adrenaline 40×10^6 — 2 — 3 Ergobasine 2.5×10^6 — 4 4a Ergobasine 2.5×10^6 + D·H-Ergokryptine 10×10^6; 4b D·H-Ergokryptine 10×10^6 — 5 6 7 Ergobasine 2.5×10^6 — 8

Fig. 6. *Record of the isolated uterus of the rabbit.* Inhibition of the action of Ergobasine (Ergometrine or Ergonovine) by Dihydroergokryptine.

a small or no increase of uterine tonus in vitro, either when given together, in combination or after dihydroergokryptine. It is usually easier to inhibit the action of ergobasine or ergotamine by the preliminary administration of the dihydrogenated alkaloid than by simultaneous administration.

An instructive example of the action in situ in the rabbit is given in fig. 7a and 7b. The effect on the blood pressure of 0,45 mg/kg ergobasine (ergometrine or ergonovine) is unchanged, the uterus and the vagina contract strongly and the rhythm increases. The effect of adrenaline after ergobasine is normal as far as blood pressure, uterus and vagina are concerned. 0,15 mg/kg of dihydroergocristine produces a fall of the blood pressure and inhibition of the tonus and rhythm of the uterus and vagina.

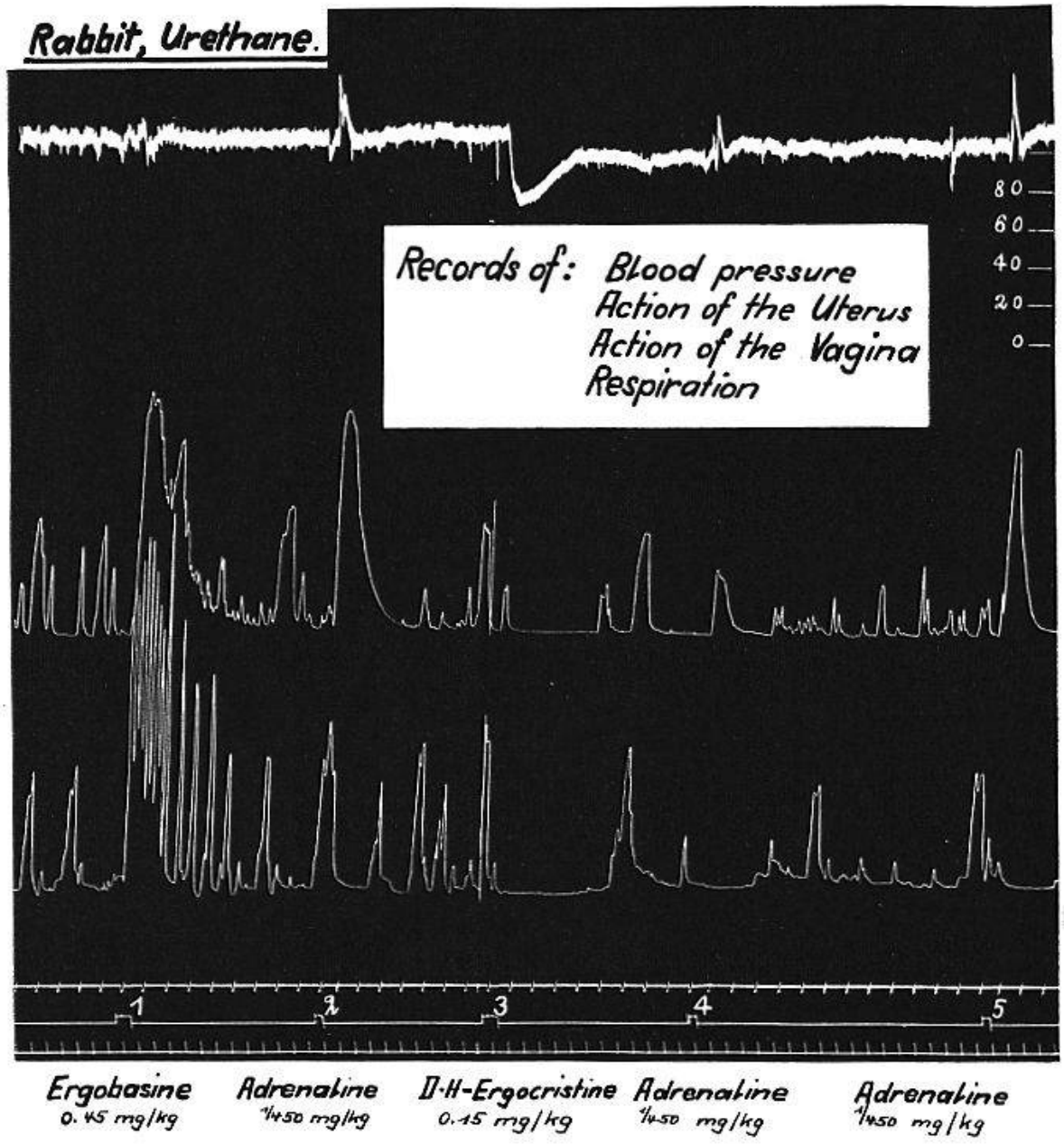


Fig. 7a.

The typical action of adrenaline now is impeded. After its full action has returned, the simultaneous injection of 0,15 mg/kg dihydroergocristine and 0,45 mg/kg ergobasine proves the inhibitory effect of dihydroergocristine on the normally excitatory action of ergobasine. This implies that even in vivo the dihydrogenated alkaloids are capable of inhibiting the uterotonic effect of the natural alkaloids, including that of ergobasine. It must therefore be concluded that the dihydrogenation of the natural alkaloids not only *abolishes their specific uterotonic effect but actually inverses this action.* This inversion of the uterine action is doubtless the most important qualitative change in activity brought about by dihydrogenation.

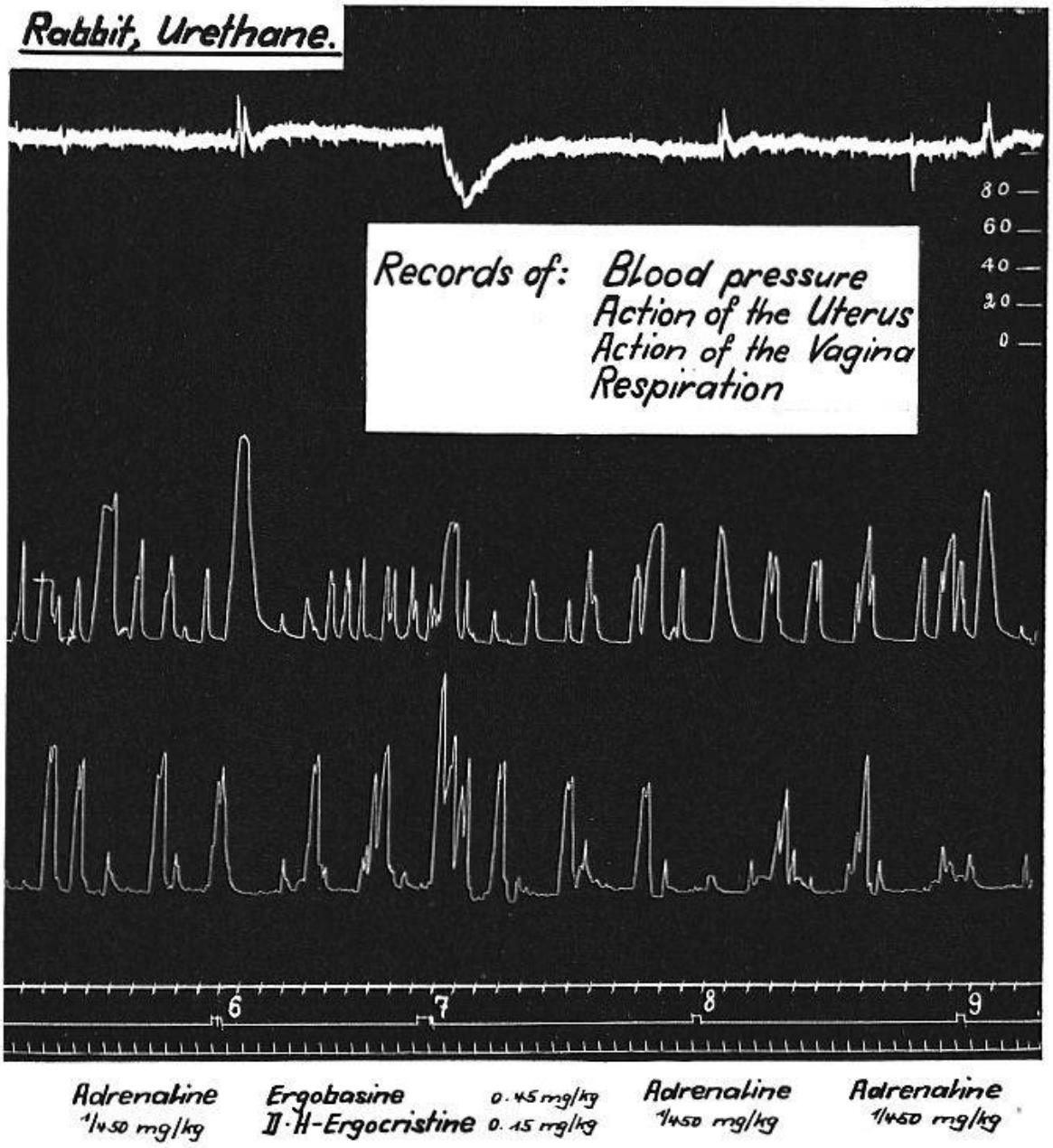


Fig. 7b.

Sympathicolytic Actions

Among the many possible tests suitable to demonstrate sympathicolytic i.e. adrenolytic action only a few will be described. Actually, these reactions are more uniform and distinct than those previously discussed because only quantitative differences seem to exist between the natural and dihydrogenated alkaloids. Table 3 presents the relative values of the adrenolytic action obtained with two tests on isolated organs, namely the uterus of the rabbit and the seminal vesicle of the guinea pig. In these assays the adrenolytic action of each alkaloid is compared with ergotamine as a standard. The mean deviation is $\pm 20\%$ and very many tests are required if quantitative values are sought. From the results given in table 3 we conclude:

Table 3

Isolated Uterus of Rabbit				Isolated Seminal Vesicle of Guinea Pig			
Natural		Hydrogenated		Natural		Hydrogenated	
Ergocornine	0,5	Dihydroergosine	2,0	*Ergotamine*	1	Dihydroergosine	6
Ergotamine	1,0	Dihydroergotamine	2,25	Ergosine	1	Dihydroergotamine	7
Ergosine	1,0	Dihydroergocornine	2,5	Ergocornine	2	Dihydroergocornine	25
Ergocristine	1,0	Dihydroergocristine	3,5	Ergocristine	4	Dihydroergocristine	35
Ergokryptine	1,5	Dihydroergokryptine	5,0	Ergokryptine	4	Dihydroergokryptine	35

(a) Applied to both test organs, the activity of the natural and dihydrogenated alkaloids differs widely, ranging between 1 and 35. The dihydrogenated derivatives are all more potent than the corresponding natural alkaloids.

(b) These tests allow a very accurate differentiation of the various degrees of activity of the natural and dihydrogenated alkaloids. In fact the isolated seminal vesicle of the guinea pig brings out the differences in activity of the various alkaloids, natural and dihydrogenated, much better than the isolated uterus of the rabbit. The test is extremely sensitive and enables the detection of amounts of biologically active alkaloid as small as 0,0018 γ/ccm (10).

The inhibition of the excitatory adrenaline effect on the *rabbit uterus in situ* can be regularly demonstrated. Fig. 8a and 8b illustrate such an experiment and table 4 gives a preliminary summarization of the relative potency of all alkaloids. Each alkaloid is compared on the same animal with ergotamine as a standard. The differences between the natural alkaloids are not very great, a fact borne out well by the results in vitro. Ergokryptine is the most active, while ergosine and ergocornine are

somewhat weaker than ergotamine. All dihydrogenated alkaloids act more intensively than the natural alkaloids. The results in vivo harmonize well with those in vitro. Although our comparative investigation is not yet concluded, we believe that the quantitative differences in the case of the dihydrogenated alkaloids will range in vivo in the same order as they do in vitro.

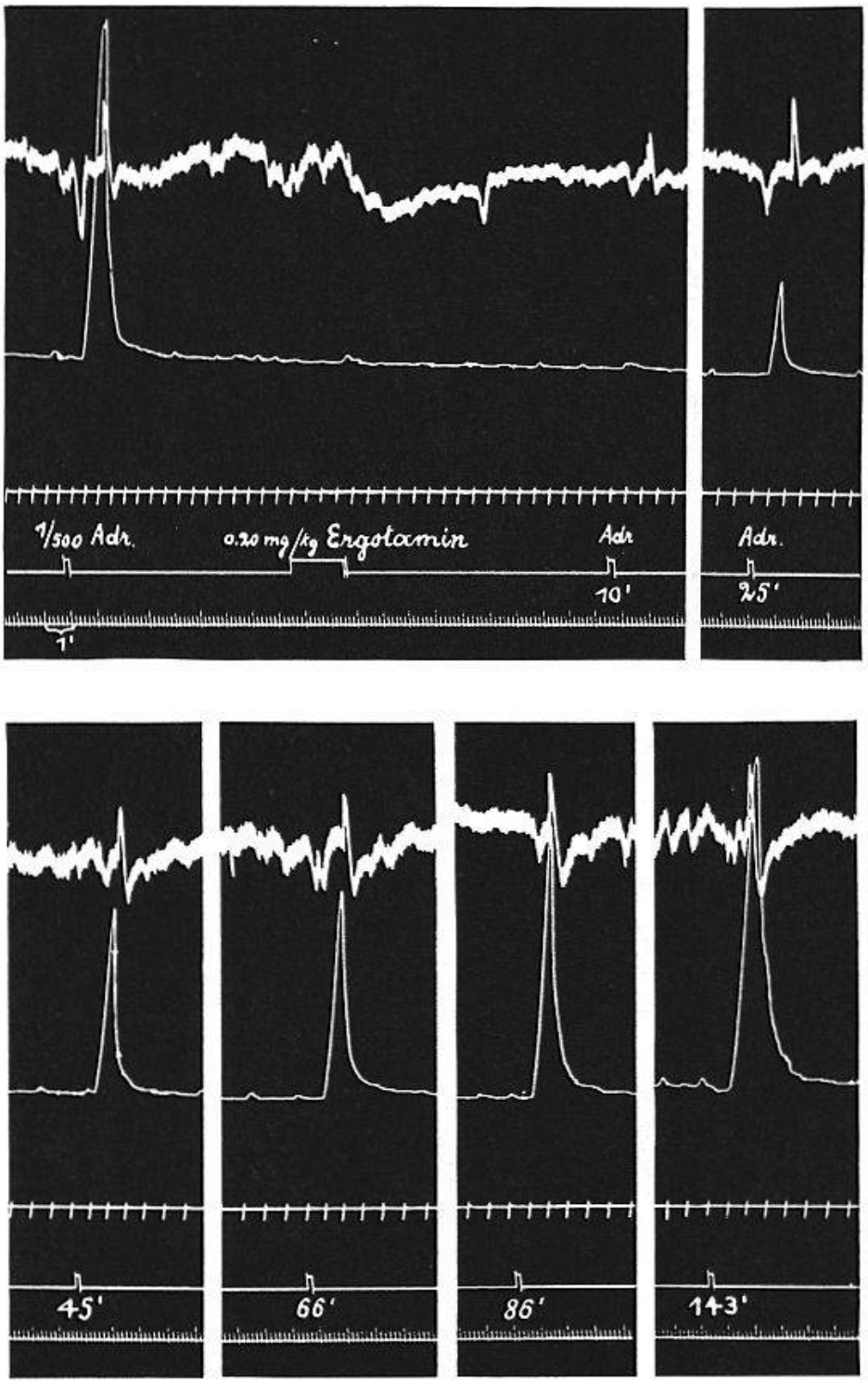


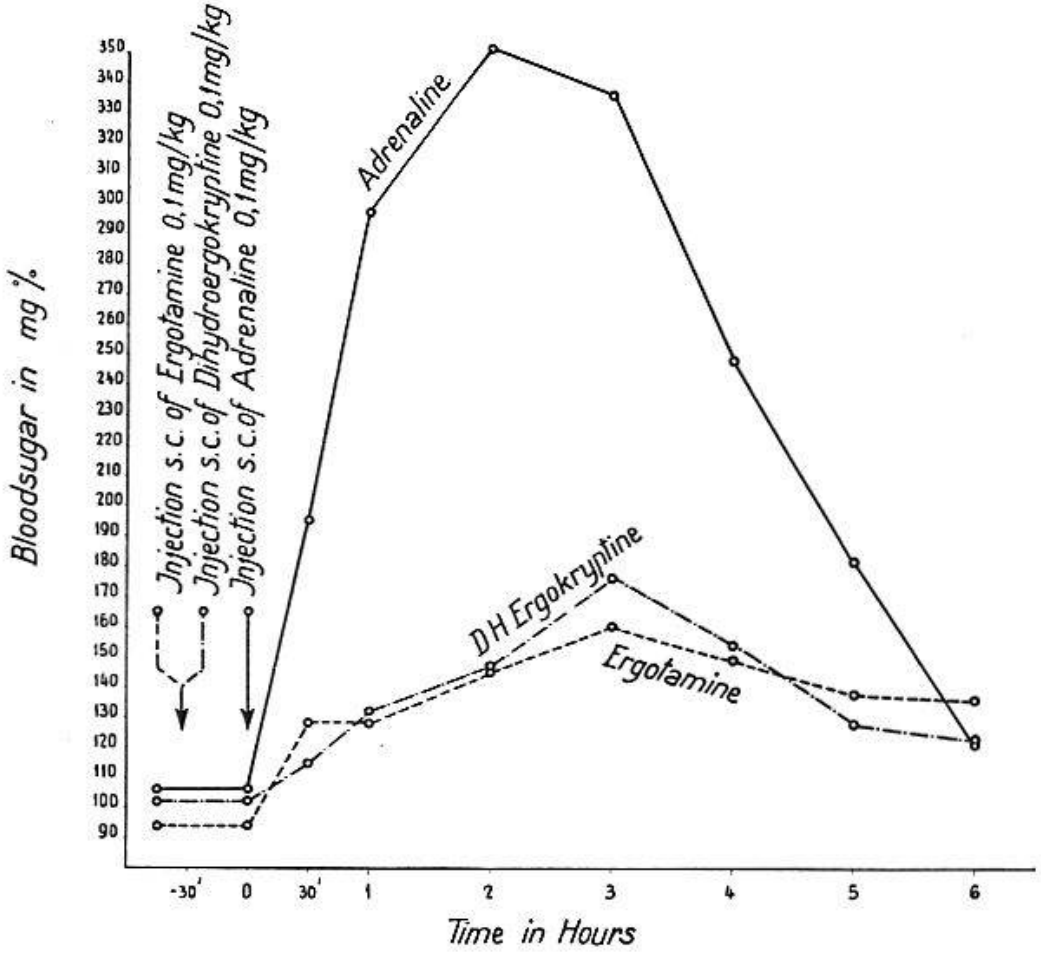
Fig. 8a and 8b. Record of the inhibition by Ergotamine of the Adrenaline effect on the Uterus of the rabbit in situ. Rabbit in Urethane narcosis.

Table 4

Inhibition of the Adrenaline Effect on the Uterus of the Rabbit in situ by the Natural and Dihydrogenated Alkaloids of Ergot

Ergotamine as standard compared with	Number of assays	Dose i.v. mg/kg	Duration of the inhibition in relation to Ergotamine		
			shorter	equal	longer
Ergosine	9	0,15 –0,2	7	1	1
Ergocristine	12	0,1 –0,2	2	8	2
Ergocornine	11	0,025–0,2	5	4	2
Ergokryptine	11	0,15 –0,2	2	5	4
D·H-Ergotamine . .	9	0,02 –0,05	1	2	6
D·H-Ergosine	8	0,15 –0,2	1	1	6
D·H-Ergocristine . .	11	0,15	0	2	9
D·H-Ergocornine . .	11	0,125–0,15	1	4	6
D·H-Ergokryptine . .	12	0,15 –0,2	0	1	11

Fig. 9 Effect of Ergotamine and Dihydroergokryptine on the Adrenaline-Hyperglycemia of the Rabbit. (mean of 3 animals for each group)



A very striking sympathicolytic test is the inhibitory effect of these alkaloids on the *adrenaline-hyperglycemia* in the rabbit. Fig. 9 shows this phenomenon on the hyperglycemic effect of 0,1 mg/kg adrenaline after 0,1 mg/kg of ergotamine and dihydroergokryptine respectively. The alkaloids are injected subcutaneously 30 minutes prior to the administration of adrenaline. The blood sugar then remains practically unaltered. The blood sugar of the control animals on the other hand rises to a level of 350 mg% after the administration of 0,1 mg/kg adrenaline. The effect lasts for about six hours. Following the administration of ergotamine and dihydroergokryptine respectively the adrenaline-hyperglycemia is markedly inhibited. In table 5 almost all the alkaloids, natural as well as dihydrogenated, are compared with ergotamine as a standard. It becomes evident that, of all the natural alkaloids, ergotamine has the strongest inhibitory effect upon adrenaline-hyperglycemia. With the exception of dihydroergocornine—which seems to be weaker—the dihydrogenated alkaloids are but little stronger than the natural alkaloids.

The differences between the natural and the dihydrogenated alkaloids as regards their effect upon adrenaline-hyperglycemia are very small when compared with the differences in the response to adrenaline in the uterus. On the other hand, the doses of the alkaloids necessary for complete inhibition of the adrenaline-hyperglycemia are smaller than those required for the inhibition of the excitatory action on the uterus of adrenaline. It should be remembered that in the hyperglycemia test the alkaloids are injected subcutaneously, whereas in the uterus test, they are given intravenously.

Table 5

Inhibition of the Hyperglycemic Effect of Adrenaline on the Rabbit by the Alkaloids of Ergot

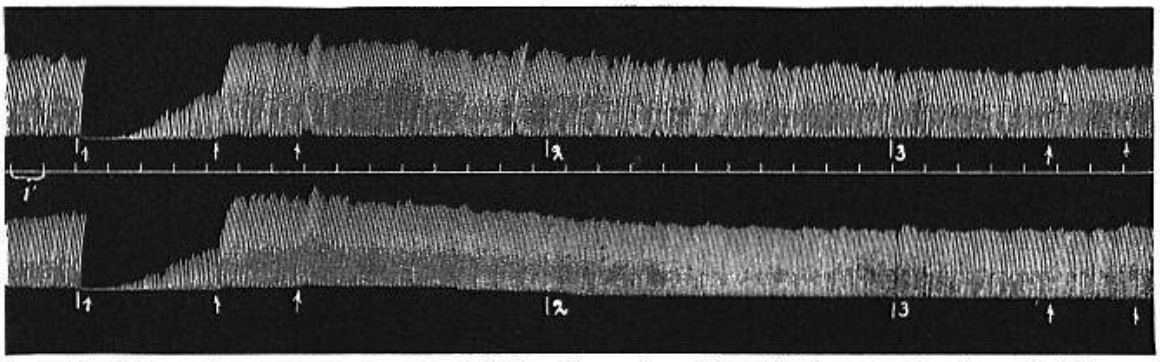
1. Preceeding administration of *0,15* mg/kg Alkaloid subc.
2. 30 Minutes later *0,10* mg/kg Adrenaline subc.

(Planimetric Comparison)

Alkaloid	Inhibition in %	Alkaloid	Inhibition in %	Difference Ergotamine = 100%
1. Ergotamine . .	59,2	Ergocristine	42,4	—28,4
2. Ergotamine . .	57,3	Ergocornine	32,6	—43
3. Ergotamine . .	73,0	Ergokryptine	39,5	—46
4. Ergotamine . .	84,1	D·H-Ergotamine	91,6	+ 9
5. Ergotamine . .	72,3	D·H-Ergocornine	67,0	— 7,4
6. Ergotamine 0,10 mg/kg . .	71,5	D·H-Ergokryptine 0,10 mg/kg	76,0	+ 6,3
7. Ergocristine . .	60,0	D·H-Ergocristine	89,3	+49
8. Ergocornine . .	67,2	D·H-Ergocornine	90,0	+34

Intestine

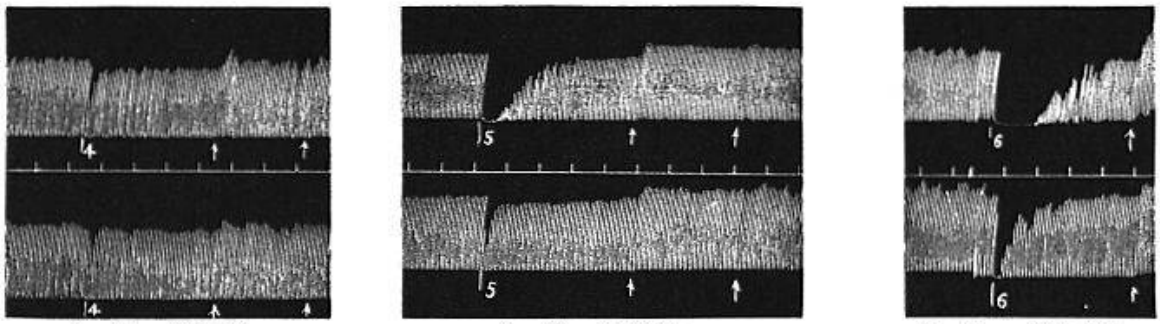
Of all the sympathicolytic actions of the ergot alkaloids the inhibition of the relaxing effect of adrenaline upon the intestine is of particular importance because the natural effect of adrenaline on this organ is not excitatory, but inhibitory. It has been assumed for a long time that the alkaloids of ergot inhibit exclusively the functions subject to the excitatory effects of adrenaline. In 1925 (11), however, we furnished convincing proof that ergotamine, in adequate doses, regularly inhibits the adrenaline effect upon small and large intestine in vitro and in vivo. This fact is of great importance and proves that the inhibitory properties of the ergot alkaloids include sympathetic functions which are excited as well as those which are inhibited by adrenaline. Thus the specific character of the sympathicolytic activity of ergot alkaloids becomes more significant and extensive. Both the natural and the dihydrogenated alkaloids possess this action on the intestine, as shown in fig. 10. There are significant quantitative differences among the various alkaloids, the dihydrogenated ones being stronger throughout than the natural alkaloids.



1 Adrenaline 1×10^6

2a D·H-Ergokryptine 16×10^6
2b D·H-Ergotamine 4×10^6

3 after 10 Min. Adrenaline 1×10^6



4 after 30 Min. Adrenaline 1×10^6

5 after 75 Min. Adrenaline 1×10^6

6 after 130 Min. Adrenaline 1×10^6

Fig. 10. *Record of the isolated small intestine of the rabbit.* Inhibition of Adrenaline by Dihydroergokryptine and Dihydroergotamine.

Finally, we should like to furnish readily convincing evidence of the adrenolytic property of the alkaloids of ergot. This appears desirable because the mode of action of these alkaloids is still explained differently or misunderstood by many. This is due to excessively schematic interpretation of the mode of operation of the autonomic regulatory system. Also, erroneous conclusions are sometimes drawn because the results obtained in different animals vary according to the species. In order to conduct this experiment we first determine the 100% lethal dose of adrenaline in white female rats. Intravenously this LD 100 is 0,3 mg/kg. Now the animals are given 2 mg/kg of an ergot alkaloid subcutaneously, followed again 30 minutes later, by a determination of the LD 100 of adrenaline. The new LD 100 of adrenaline, according to the adrenolytic potency of the different alkaloids, is from 10 to 100 and more times greater than prior to the administration of the alkaloid. In this test, the dihydrogenated alkaloids are far more active than the natural alkaloids. It is generally conceded that adrenaline represents the adequate physiological stimulus for the sympathetic system. In these assays the criterion is not merely a therapeutic dose, but the 100% lethal dose of adrenaline. Therefore, the conclusion would seem permitted that the outcome of this test is proof of a high adreno-sympathicolytic activity of the ergot alkaloids.

Elimination and Fate

We wish to make only a few remarks regarding the elimination and fate of the ergot alkaloids. The rate of elimination by the kidney was studied in white rats. The quantity of unaltered alkaloids present 24 hours after intravenous administration is only $^1/_{1000}$ of the dose administered. In the following 24 hours practically no alkaloid can be detected with even such sensitive tests as the seminal vesicle of the guinea pig.

When injected intravenously, the alkaloids disappear very rapidly from the blood. The following example demonstrates the speed of disappearance from the blood. The rabbit of 3,88 kg received 20 mg/kg of dihydroergokryptine:

	γ%	% of total
1. Concentration in blood after injection	30 000	100
2. Concentration in blood 2 minutes later	665	2,23
3. Concentration in blood 5 minutes later	166	0,56
4. Concentration in blood 30 minutes later	83	0,28
5. Concentration in blood 60 minutes later	41	0,14
6. Concentration in blood 120 minutes later	24	0,08
7. Concentration in blood 240 minutes later	12	0,04
8. Concentration in blood 360 minutes later	4	0,013

This behaviour is of great interest, since the alkaloids are neither eliminated nor do they remain in the blood. However, the alkaloids can be recovered in relatively great quantity in the liver, kidney, spleen, and muscles. They also have been found in the aqueous humour and in the cerebrospinal fluid, but not in the brain. Thus, it may be said that we possess a rather good knowledge of the distribution and elimination of these alkaloids in the organism. In respect to their biochemical fate, however there is still a gap which we are endeavouring to fill (12).

Discussion. The foregoing quantitative and qualitative differentiation of the pharmacological properties under various experimental conditions is presented in an attempt to explain the modes of action of the natural and the dihydrogenated alkaloids of ergot. We are aware of the complexity of the toxico-pharmacologic properties of these agents. The experimental findings prove that their field of action is very wide, extending to functions, the control of which is located partly centrally and partly peripherally in the effector organ itself. The peripheral and probably also the central actions of the alkaloids are bivalent, i. e. partly visible and partly latent. Even though both modes of action are of a direct nature, the latent action will become evident only in the course of active stimulation by the adequate stimulus of the function concerned, i. e. either by stimulation of the sympathetic or by adrenaline. Moreover, there are *qualitative differences* between the natural and dihydrogenated alkaloids as, for instance, in the behaviour of body temperature, where the fever producing effect of the natural alkaloids is converted, in the case of the dihydrogenated alkaloids, into a depressive effect. The bivalent action on the uterus of the natural alkaloids is evident in a visible muscular contraction and a latent sympathicolytic effect; that of the dihydrogenated alkaloids is evident in the relaxation of the uterine muscle and the even more powerful sympathicolytic effect. Fundamentally, the alkaloidal action on the blood vessels is similar. However, as far as the criterion of blood pressure is concerned, the appearance of a rise or a fall depends upon the competitive effects of the central depressive and the peripheral pressive actions of the alkaloid. A special situation is found in the intestine, which apparently, is neither excited nor relaxed. The relaxing action of adrenaline, however, is inhibited or abolished by the alkaloid. Thus the action on the intestine is only monovalent.

Because the ergot alkaloids exert an influence on both the excitatory and inhibitory sympathetic functions, their realm of action is very wide. It may be said that, because of this widespread sympathicolytic activity all functions regulated by the sympathetic nervous system are affected. Without doubt this is a most striking feature and the reason why these

alkaloids have achieved such great importance for the treatment of sympathicotonias and vegetative dystonias. It has been demonstrated in this paper that all the ergot alkaloids possess this specific sympathicolytic action although in different degrees. In animal experiments the dihydrogenated alkaloids are much superior in this respect to the natural alkaloids.

For the following reasons we recommend a thorough clinical trial of these new dihydrogenated alkaloids:

1. Better tolerance in comparison with the natural alkaloids.

2. More accentuated and clear-cut sympathicolytic action.

3. The possibility of thus gaining clearer insight into the clinical picture of autonomic imbalance by using dihydrogenated alkaloids not only for therapeutic but also for differential diagnostic purposes.

We wish to state that all three of the afore-mentioned points have received clinical confirmation. Dihydroergotamine, the most thoroughly examined alkaloid, has given excellent results in the treatment of migraine, herpes zoster and herpes simplex. Promising results have been obtained in peripheral vascular disturbances of a spastic nature, such as essential hypertension, Raynaud's disease, Buerger's disease. From the pharmacological and clinical point of view, it would be desirable to determine the most suitable therapeutic application for each individual alkaloid. This task presents an ideal problem to be solved by team-work among pharmacologists and clinicians. It is already progressing satisfactorily, but the road is long and tedious.

Summary

The result of the toxico-pharmacologic study of the known natural and dihydrogenated alkaloids of the ergotamine and ergotoxine groups may be summarized as follows:

1. The toxicity of the natural alkaloids is considerably greater than that of the dihydrogenated alkaloids. Toxicity increases with progressive differentiation of the brain. Generally it may be said: the more toxic the natural alkaloid, the less toxic the corresponding dihydrogenated derivative.

2. The effects on the central nervous system of the natural alkaloids are more marked than in the case of the dihydrogenated forms. In the latter they are qualitatively different as shown by their action on body temperature and on the vascular centers. The latter action determines the effect on the blood pressure.

3. The peripheral actions of the ergot alkaloids are either directly visible or of a latent nature.

(a) The visible effects of the natural and dihydrogenated alkaloids vary. The natural forms specifically stimulate uterine contraction, the dihydrogenated forms inhibit uterine contraction; in other words, dihydrogenation inverses the quality of the natural effect. The vascular apparatus is constricted by all the ergot alkaloids but the natural forms exhibit this property more strongly than the dihydrogenated derivatives.

(b) The latent i.e. sympathico-adrenolytic property of the natural and dihydrogenated alkaloids is qualitatively identical. However, there are considerable quantitative differences. The sympathicolytic effect is not restricted only to functions excited by adrenaline but also to functions inhibited by adrenaline. Hence, the realm of action of these compounds extends to all functions which are subject to autonomic nervous control.

4. Elimination of the ergot alkaloids by the kidneys is insignificant. After intravenous administration, moreover, the alkaloids disappear very rapidly from the circulating blood. Their presence in various organs and body fluids may be demonstrated by biological methods.

Zusammenfassung

Die Ergebnisse der toxikologisch-pharmakologischen Untersuchungen der heute bekannten natürlichen und dihydrierten Alkaloide der Ergotamin- und Ergotoxingruppe lassen sich folgendermaßen zusammenfassen:

1. Die Toxizität der natürlichen Alkaloide ist wesentlich größer als jene der dihydrierten Alkaloide. Sie nimmt mit zunehmender Differenzierung des Gehirns zu. Allgemein gilt, daß je toxischer das natürliche Alkaloid, um so weniger toxisch das entsprechende Dihydroderivat.

2. Die Wirkungen der natürlichen Alkaloide auf das zentrale Nervensystem sind nicht nur stärker als jene der Dihydroalkaloide, sondern bei den letzteren zum Teil qualitativ verändert, so in Hinsicht der Beeinflussung der Körpertemperatur und der Gefäßzentren. Die Wirkung auf die letzteren bestimmt den Erfolg auf den Blutdruck.

3. Die peripheren direkten Wirkungen der Mutterkornalkaloide sind teils offensichtlicher, teils latenter Art.

a) Die offensichtlichen Wirkungen der natürlichen und dihydrierten Alkaloide sind verschieden, die natürlichen haben eine spezifisch fördernde, die dihydrierten Alkaloide hingegen eine spezifisch hemmende Wirkung auf den Uterus. Durch die Dihydrierung wird somit die Qualität der Wirkung umgekehrt. Die Gefäße selbst werden durch alle Mutterkornalkaloide verengert, dabei wirken die natürlichen Alkaloide stärker als die Dihydroderivate.

b) Die latente, d. h. sympathico-adrenolytische Eigenschaft der natürlichen und der dihydrierten Alkaloide ist qualitativ identisch. Es bestehen aber zum Teil sehr große quantitative Unterschiede. Die sympathicolytische Wirkung bezieht sich nicht nur auf Funktionen, die durch Adrenalin gefördert, sondern auch auf jene, die durch Adrenalin gehemmt werden. Somit erstreckt sich ihr Wirkungsbereich auf alle Funktionen, die der autonomen Regulation unterstehen.

4. Die Ausscheidung der Mutterkornalkaloide durch die Nieren ist äußerst gering. Andererseits verschwinden sie bei i.v. Verabreichung sehr rasch aus dem kreisenden Blut und können sowohl in den Organen wie in der Körperflüssigkeit auf biologischem Wege nachgewiesen werden.

Résumé

Les résultats des recherches toxicologiques et pharmaco-dynamiques des alcaloïdes naturels et dihydrogénés, connus à ce jour, du groupe de l'ergotamine et de l'ergotoxine, peuvent se résumer comme suit:

1° La toxicité des alcaloïdes naturels est nettement plus grande que celle des alcaloides dihydrogénés et elle augmente au fur et à mesure que le cerveau est plus différencié. En général, le dérivé dihydrogéné correspondant est d'autant moins toxique que l'alcaloïde naturel est plus toxique.

2° Les effets des alcaloïdes naturels sur le système nerveux central sont non seulement plus fort que ceux des alcaloïdes dihydrogénés, mais ces derniers sont différents du point de vue qualitatif, comme le montre leur action sur la température et sur les centres vasculaires. Cette dernière action est responsable de l'effet sur la tension artérielle.

3° Les effets périphériques directs des alcaloïdes de l'ergot de seigle sont en partie visibles et en partie latents.

a) Les effets visibles des alcaloïdes naturels et dihydrogénés sont différents. Les naturels ont une action spécifique stimulatrice, les dihydrogénés par contre une action spécifique inhibitrice sur l'utérus. L'effet est donc inversé par dihydrogénation. Les vaisseaux sont contractés par tous les alcaloïdes de l'ergot de seigle, plus fortement par les alcaloïdes naturels que par les dérivés dihydrogénés.

b) Les propriétés latentes, c'est-à-dire sympatho-adrénalytiques des alcaloïdes naturels et dihydrogénés sont identiques du point de vue qualitatif. Mais pour certains, il y a de grandes différences quantitatives. L'action sympathicolytique ne s'exerce pas que sur les fonctions stimulées par l'adrénaline, mais aussi sur celles qui sont inhibées par l'adrénaline. C'est pourquoi leur domaine d'action s'étend à toutes les fonctions qui sont soumises au contrôle du système autonome.

4° L'élimination par voie rénale des alcaloïdes de l'ergot de seigle est extrêmement faible. D'autre part, administrés par voie veineuse, ils disparaissent très vite du sang circulant et peuvent être décelés aussi bien dans les organes que dans les liquides de l'organisme par des méthodes biologiques.

Riassunto

I risultati delle ricerche tossicologiche e farmacologiche sugli alcaloidi naturali e diidrogenati conosciuti fin'oggi e appartenenti al gruppo dell'ergotamina e dell'ergotossina, possono riassumersi nel modo seguente:

1.° La tossicità degli alcaloidi naturali è notevolmente più elevata di quella degli alcaloidi diidrogenati e cresce parallelamente all'aumentato grado di differenziazione del cervello dell'animale di sperimento. In generale, il derivato diidrogenato corrispondente è tanto meno tossico, quanto l'alcaloide naturale è più tossico.

2.° Gli effetti degli alcaloidi naturali sul sistema nervoso centrale sono non soltanto più forti di quelli degli alcaloidi diidrogenati, ma sono anche diversi dal punto di vista qualitativo, come è dimostrato dall'azione sulla temperatura e sui centri vascolari. Quest'ultima è responsabile dell'effetto sulla pressione arteriosa.

3.° Gli effetti periferici diretti degli alcaloidi della secale cornuta sono in parte visibili e in parte latenti:

a) I primi sono differenti per gli alcaloidi naturali e diidrogenati. I naturali hanno un'azione stimolante specifica, i diidrogenati un'azione inibitrice specifica sull'utero. L'effetto è quindi invertito dalla diidrogenazione. I vasi sono contrattati da tutti gli alcaloidi della secale cornuta, più fortemente però dagli alcaloidi naturali che dai derivati diidrogenati.

b) Le proprietà latenti, cioè adrenalino-simpaticolitiche degli alcaloidi naturali e diidrogenati sono identiche dal punto di vista qualitativo. Tuttavia esistono per alcuni grandi differenze quantitative. L'azione simpaticolitica si esercita non soltanto sulle funzioni stimolate dall'adrenalina, ma anche su quelle che sono inibite da essa. Per ciò, il loro campo di indicazioni si estende a tutte le funzioni sottoposte al controllo del sistema simpatico.

4.° L'eliminazione per via renale degli alcaloidi della secale cornuta è minima. D'altra parte, amministrati per via venosa, essi spariscono molto rapidamente dal sangue circolante e possono essere svelati tanto negli organi che nei liquidi dell'organismo mediante metodi biologici.

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