

ON THE ACTIVE PRINCIPLES OF THE PITUITARY EXTRACT

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The following experiments were undertaken to see if there was any obvious difference between the mode of action of pituitary on the uterus and blood pressure in the pithed cat.

The action of pituitary on the blood pressure was measured according to the method introduced by Dale and Laidlaw (1), with the extra precautions recommended by Hogben, Schlapp, and Macdonald (3). The only difference in my technique was that I destroyed the whole cord of the cat by pithing. The movements of the uterus were recorded in the following manner. The abdomen was opened in the mid-line and a silk thread tied to the ovarian end of one horn of the uterus. The horn was drawn through a slit in a piece of rubber sheeting which was fixed over the end of a glass cylinder ($1\frac{1}{2}$ inches in diameter). The cylinder was inserted into the abdominal opening and the abdominal wall was sewn up tightly around it. The cylinder was then filled with warm Locke's solution, and the movements of the uterus were recorded on smoked paper by means of a light lever. Most uteri are more or less fixed to the back of the cat so that it is rather difficult to lift them up and pull them into the glass-tube. But after cutting the ovario-pelvic ligament which attaches the uterus to the back the uterus can easily be made mobile without impairing its blood supply. The whole arrangement closely resembles Kehrler's method of preparing the isolated organ as the uterus is suspended vertically in a glass tube, surrounded by Locke's solution kept uniformly warm by an electric lamp, but nourished by its normal circulation. With such a preparation I generally obtained the best

results with cats which had had kittens some weeks before, in which the uteri were large, relaxed and very sensitive without showing big spontaneous contractions.

All experiments unless otherwise stated were performed with a standard extract of pituitary prepared according to Burn and

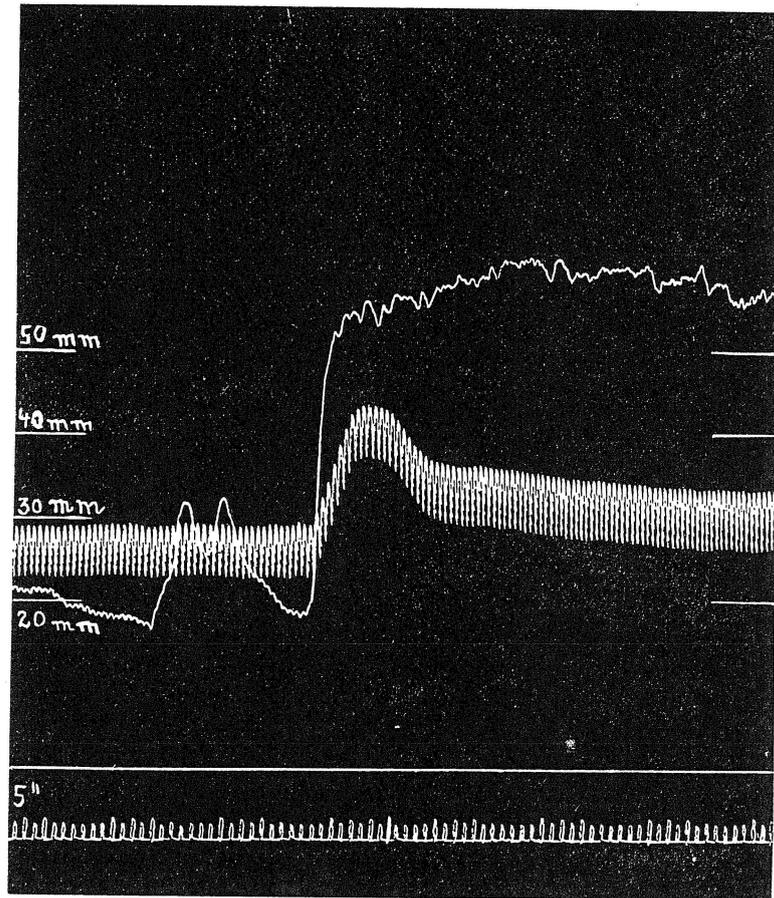


FIG. 1. CAT (KITTENS SOME WEEKS PREVIOUSLY), WEIGHED 3.5 KG., INTRAVENOUS (JUGULAR VEIN) INJECTION OF EXTRACT EQUAL TO 1 MGM. OF MOIST GLAND

Dale's (2) method. 1 cc. of this was equivalent to 25 mgm. of moist posterior lobe.

Figure 1 shows more or less all the characteristic points of the results I obtained by using this method. The responses of

both blood-pressure and uterus after bigger doses of pituitary extract were approximately simultaneous and equally distinct. But while the blood-pressure fell to its normal level within a few minutes the uterus remained in a stage of higher tone, and often strongly contracting for a far longer time; this generally continued for one to two hours after the injection before it returned to the former degree of relaxation. Consequently, when using such a preparation for standardising pituitary extracts the uterus was not as convenient as the blood-pressure, for it took more time and was sometimes not equally exact.

The fact that the action of the pituitary extract on the uterus lasted so much longer than on the blood-pressure suggested the possibility that the circulatory system might be less sensitive than the uterus muscle. To test this, the least amount of pituitary which elicited a response from blood-pressure and uterus respectively had to be determined. I found that the minimal quantity of pituitary given intravenously required to produce a certain effect on the uterus was extract equal to 0.004 mgm. of moist gland per kilo whereas more than twice this amount (0.01 mgm. per kilo) was needed to produce a demonstrable rise of the blood-pressure.

Figure 2 illustrates the reactions of both blood-pressure and uterus induced by minimal doses of pituitary injected into the jugular vein. The first arrow represents an injection of 0.4 cc. saline; this was intended to detect its influence on the blood-pressure. The second arrow represents the injection of the same quantity of fluid but containing extract equal to 0.0125 mgm. of moist gland. This was followed by no distinct action on blood-pressure, but the obvious action on the uterus occurring later was almost certainly due in part to the second injection, as the response to such small doses of pituitary had a considerably longer latent period than that to larger doses. The third arrow shows the injection of another 0.4 cc. containing extract equal to 0.025 mgm. of moist gland which acted indubitably on both blood-pressure and uterus.

These facts show that there is at least an apparent difference between the sensitivity of the blood-pressure and of the uterus to

pituitary. But as the ratio is only 1:2.5, we have to consider several factors which may account for the difference between the pressor and the uterine response. There are the following possibilities:

1. A genuine difference of sensitivity of the circulatory system and the uterus to pituitary.
2. Some ability of the circulatory system to regulate or compensate the small constriction of its capillaries by enlarging

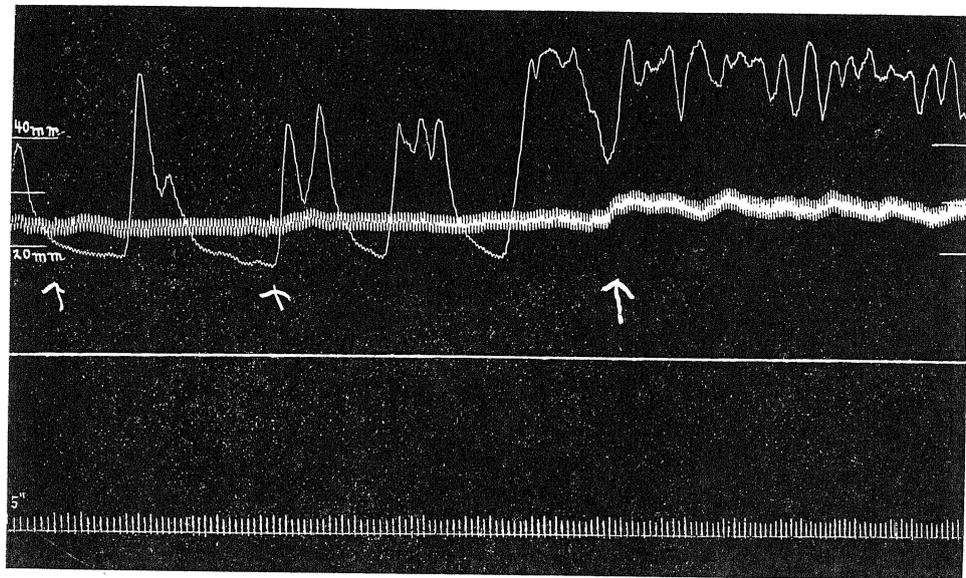


FIG. 2. CAT, WEIGHT 2.5 KGM.

1. Arrow: 0.4 cc. saline intravenously (jugular vein).
2. Arrow: 0.4 cc. containing extract equal to 0.0125 mgm. of moist gland.
3. Arrow: 0.4 cc. containing extract equal to 0.025 mgm. of moist gland.

other blood-vessels without necessarily showing a subsequent rise of the blood-pressure, while the slightest action on the uterus is inevitably visible.

3. The presence of two active principles in pituitary extract which have a selective action on the uterus and on the circulatory system respectively. The difference of action would depend on the relative amounts in which they were present and on the sensitivity of the corresponding organs.

The undoubted difference between the responses of the plain muscle of the uterus and of the arteries to intravenous injection of pituitary could however hardly explain the striking difference between the duration of the action on the uterus and that on the blood-pressure. The only satisfactory explanation for this fact would be that the so-called blood-pressure principle is more or less destroyed by passing through the capillaries, while the oxytocic principle remains active and still circulates for an hour or more. This suggested a comparison of the effects of the same dose of pituitary given intravenously and intra-arterially on the same animal.

The results obtained by this method are shown in figures 3 to 5 and need no further description. The femoral artery was always used. A clip applied during the period of injection prevented bleeding, the substance was administered by means of a very fine needle attached to a syringe. When the fluid was injected in the direction of the blood-flow this method seemed very satisfactory.

It is evident that considerable quantities of pituitary injected into an artery would be unlikely to act only on the uterus without raising the blood-pressure. Both the quantity of the active substance of the pituitary and the quantity of the fluid itself require consideration. Extract equal to one-half to 1 mgm. (0.1 to 0.2 cc. fluid) of moist gland according to the size of the cat always acted powerfully on both blood-pressure and uterus when given intravenously, but it acted on the uterus alone when given intra-arterially. I repeatedly tried to inject 0.6 mgm. (per kilo cat) of moist gland intra-arterially, but saw a slight rise of the blood-pressure besides the action of the uterus, showing that a sufficient amount of the pressor substance passed undestroyed through the capillaries and still acted on the whole circulatory system. Yet I cannot say whether the larger volume of the fluid itself overburdened the capillaries of the limb or the increase of the active substance of the pituitary was the cause of the negative result as I did not repeat experiments using highly concentrated pituitary solutions under the same conditions. It would seem that like every other organ capillaries are limited

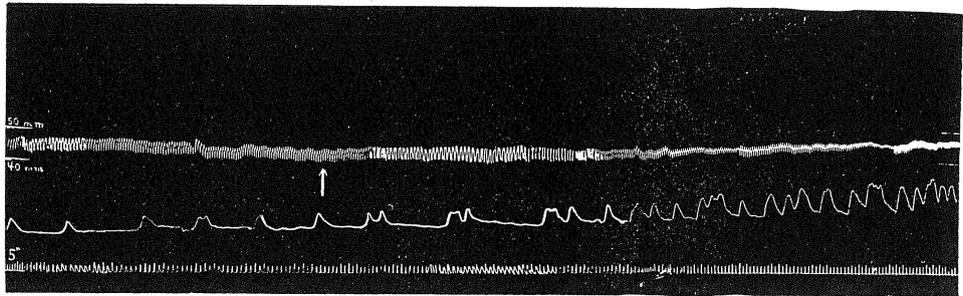


FIG. 3. VIRGIN CAT, WEIGHT 2 KGM.

1:30 p.m., extract equal to 0.5 mgm. (0.1 cc. fluid) of moist gland intra-arterially (a. femoralis).

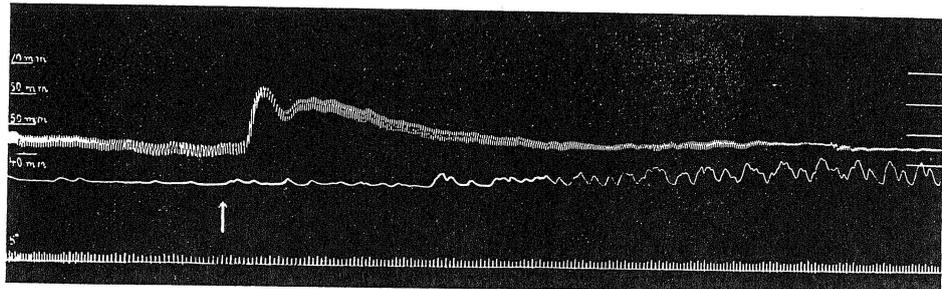


FIG. 4. THE SAME CAT

3:00 p.m., extract equal to 0.5 mgm. (0.1 cc. fluid) of moist gland intravenously (jugular vein).

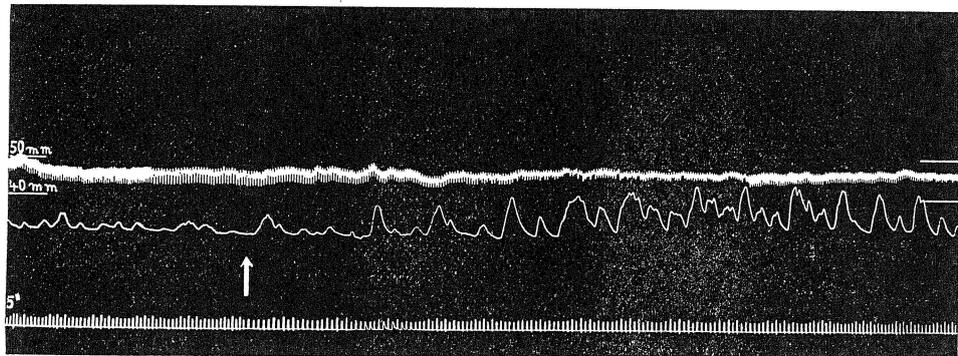


FIG. 5. THE SAME CAT

5 p.m., extract equal to 0.5 mgm. (0.1 cc. fluid) of moist gland intra-arterially (a. femoralis).

in the extent of this action, but tend to destroy the blood-pressure principle of the pituitary to a certain degree.

Furthermore, the whole active substance of the pituitary may be so reduced by passing through the capillaries that it still acts on the uterus, but not on the less sensitive blood-pressure. This was eliminated by determining the smallest dose of pituitary which acts on the uterus when given intra-arterially; extract equal to 0.01 mgm. (per kilo cat) of moist gland produced a marked action on the uterus. This is certainly different from the minimal dose by intravenous injections, but not very greatly so—a ratio of only 1:2.5. We have to consider the fact that the intra-arterial injection is more or less equivalent to a very slow intravenous injection, or in other words, the dilution of the active substance is certainly far greater when given intra-arterially than after a comparatively quick intravenous injection. This may explain the observed difference mentioned above. Consequently it does not seem that the oxytocic principle is destroyed to any large extent by a single passage through the capillaries as the small dose of extract equal to 0.01 mgm. of moist gland still acts on the uterus.

Minimal quantity (in milligram of fresh posterior lobe per kilo) of pituitary producing visible effect

	ON UTERUS	ON BLOOD PRESSURE	RATIO
1. Intravenous injection.....	0.004	0.01	1:2.5
2. Intraarterial injection.....	0.01	0.6	1:60

I also examined the effect of an intramuscular injection of pituitary on the circulatory system and on the uterus, and I include three tracings which show the pituitary action on both organs. Figure 6 obtained after an injection of extract equal to 1 mgm. of moist glands shows a more or less parallel rise and fall of both blood-pressure and movements of the uterus, apparently due to a fluctuating absorption of the pituitary from the tissue. Figure 7 is a record from another cat to which a larger dose, namely, 0.3 cc. of Parke, Davis pituitary extract diluted 1:5 had been given. It shows a definite action on the uterus together with

a slight rise of the blood-pressure. Figure 8 represents the response of the same animal to 0.4 cc. of Parke, Davis Pituitrin diluted 1:5 and indicates the consequences of an approximately therapeutic dose of pituitary. The contrast between the curve of the blood-pressure tracing after an intravenous and after an intramuscular injection of pituitary is evident, and suggests the prompt but short action of the quickly destroyed pressor principle given intravenously, and the gradually rising yet prolonged

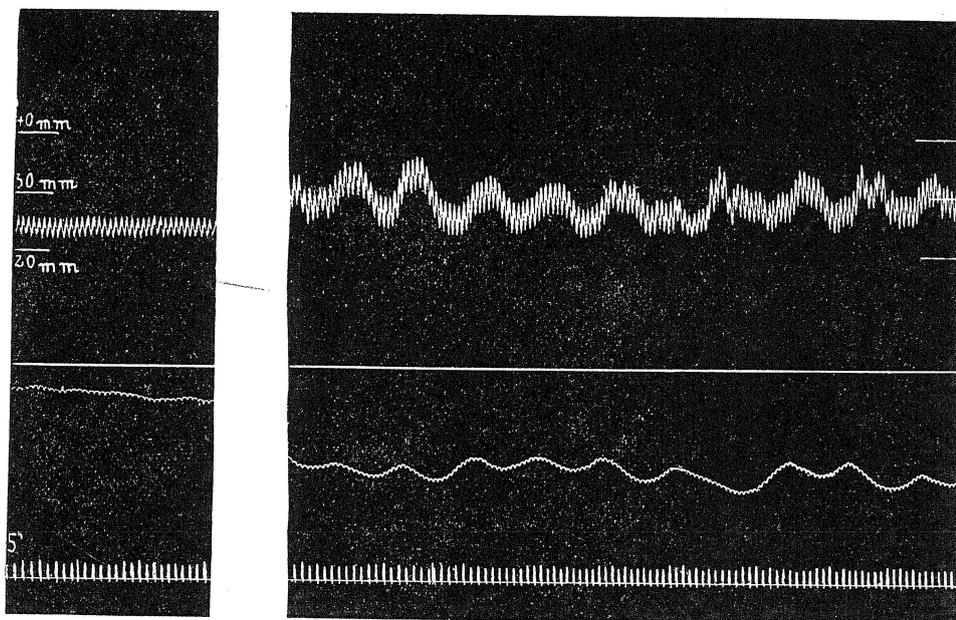


FIG. 6. VIRGIN CAT, WEIGHT 3 KGM., INTRAMUSCULAR INJECTION OF EXTRACT EQUAL TO 1 MGM. (0.2 CC. FLUID) OF MOIST GLAND

action caused by continual slow reception of the blood-pressure substance into the general circulation when given intramuscularly.

The facts shown in figure 6, 7 and 8 suggested a comparison of the effects of an intra-arterial injection with those of an intramuscular injection in general. The absorption of any substance is obviously slower given intramuscularly or hypodermically than given intra-arterially. Further, if a difference of sensitivity between the uterus and blood-pressure were the cause of the

different effects of the intravenous and intra-arterial injection, intramuscular injection should produce even less effect on the blood-pressure, than does intra-arterial injection, for the dilution of the pituitary in the circulating blood would be greater in the former than in the latter case. Nevertheless the figures show a marked action on both blood-pressure and uterus, which

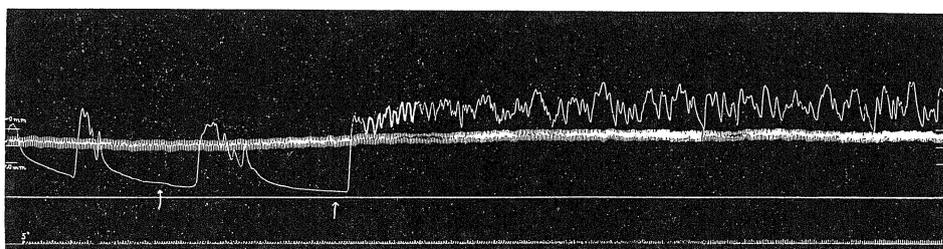


FIG. 7. CAT (KITTENS THREE WEEKS PREVIOUSLY), WEIGHT 3.5 KG.

1. Arrow: 0.1 cc. of Parke, Davis Pituitrin diluted 1:5, intramuscularly.
2. Arrow: 0.3 cc. of Parke, Davis Pituitrin diluted 1:5, intramuscularly.

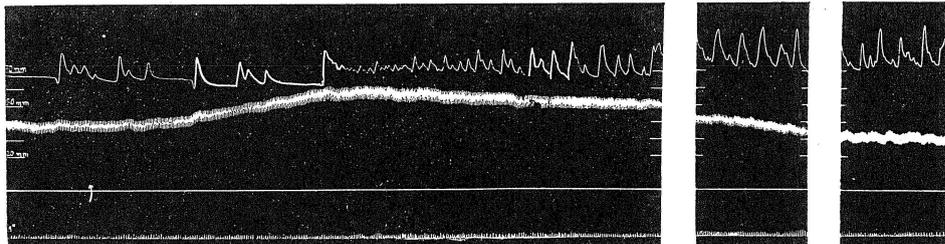


FIG. 8. THE SAME CAT AS IN FIGURE 7

- a. At the arrow 0.4 cc. of Parke, Davis Pituitrin diluted 1:5, intramuscularly.
- b. Taken forty-five minutes after the injection.
- c. Taken one hour and a half after the injection.

indicates that both the principles in spite of their slow absorption remained active.

The results recorded in this paper, particularly the ratio of the minimal doses of pituitary acting on the uterus and on the blood-pressure when given intravenously and intra-arterially respectively, appear to be most readily explained by the assumption that there are separate pressor and oxytocic principles in pituitary extract and that the pressor substance is rapidly destroyed by passing through the arterioles.

CLINICAL CONCLUSIONS

The experiments show that extract equal to 1 mgm. of moist posterior lobe of the pituitary injected intravenously produces in the pithed cat a strong action on the uterus lasting for at least an hour together with a marked rise of blood-pressure. The corresponding dose for a human being is extract equal to about 25 mgm. of moist gland and this appears to be the maximum dose that should be given intravenously.

Larger doses are permissible for hypodermic or intramuscular injection, especially as the absorptive capacity of the subcutaneous tissues is impaired during pregnancy.

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