ADRENALIN AND PITUITRIN—A STUDY IN INTERACTION AND INTERRELATION.

By DOUGLAS COW.

(*From the Pharmacological Laboratory, Cambridge.*)

THE action of extracts of the posterior lobe of the pituitary body in increasing the tonus and movements of the uterus, as described by Dale(1), is well recognized. Similarly there is general agreement that extracts of the medullary portion of the suprarenal gland produce that effect on the uterus which is obtained by stimulation of the hypogastric nerve. In certain animals, such as the rabbit, the uterus always responds to adrenalin by contraction(2): in another class, represented by the cat, the virgin (or non-pregnant) uterus is inhibited whilst the pregnant organ is contracted by adrenalin(3): in yet a third class, including the guinea-pig and the rat, the effect of adrenalin is to inhibit uterine movements whether the organ is pregnant or not(4). The brothers Gunn(4) give in tabular form the reactions to adrenalin of the uterus of the usual laboratory animals and of certain others, culled from previous literature.

The explanation usually given to account for these differences is that motor fibres (or nerve-endings) predominate over inhibitor in the hypogastric nerves of those animals in which the uterus is contracted by adrenalin, and that the reverse holds good in those animals in which adrenalin inhibits the uterus, whilst in the case of the cat it is supposed that the proportion of motor and inhibitor fibres is so evenly balanced that a hypothetical greater increase in the motor fibres than in the inhibitor during pregnancy is sufficient to change completely the reaction to adrenalin of the uterus.

Whilst these broad statements as to the qualitative reaction of the uterus to adrenalin hold good no doubt in most cases, one occasionally finds a uterus which responds to adrenalin in what must be considered an abnormal way, if one subscribes to the theory of preponderance of motor over inhibitor fibres (or *vice versa*) as the sole determining factor. I have on occasion observed such an "abnormal" response in the case of the guinea-pig's uterus, and have recorded such a response in a previous communication(5), though it has been suggested to me since

then that the mere fact that the uterus responded by contraction in this instance is sufficient to show that, whatever else may have caused the contraction, it was not adrenalin.

Further if one postulates this preponderance of one type of nerve-ending over the other in the uterus as the sole determining cause of the reaction of the uterus to adrenalin, it is necessary to imagine different mechanisms for the operation of parturition in the different types of animals, at all events if it is allowed that the glands of internal secretion, particularly the suprarenals, play any part. For example, if suprarenal secretion is evoked, perhaps by painful uterine contraction, in the first stage of parturition, the effect on the uterus of the rabbit would be diametrically opposite to the effect on the uterus of the guinea-pig. That such differences in the effect of an important activating agent can exist in two animals as alike as the rabbit and the guinea-pig would seem unlikely on general considerations—true as regards parturition there is one great point of difference in these animals; the young rabbit is born in a comparatively early stage of development, whilst the new-born guinea-pig has already reached a stage of development considerably more advanced, so that one might perhaps concede that whilst in the guinea-pig, where the size of the foetus is large compared with that of the mother, periodic intermissions in the contractions of the uterus may be necessary in order to allow time for the due expansion of the pelvic parts, separation of the pubic symphysis and so on, such intermissions are unnecessary in the rabbit, in which the relative size of the foetus at full term is very considerably smaller. On the other hand it must be borne in mind that all animals whose uterus is contracted by adrenalin do not normally bring forth their young at a correspondingly undeveloped stage: the human uterus for example behaves to adrenalin like the uterus of the rabbit.

In consequence, then, of the "abnormal" response referred to above and of the difficulty in postulating the preponderance of one type of nerve-ending over the other as the sole determining cause of the kind of reaction of the uterus to adrenalin, I have carried out the experiments recorded in this communication with the idea of showing that other factors may be involved.

These experiments were (*a*) on the isolated uterus, (*b*) on the uterus *in situ* in the intact animal, (*c*) feeding experiments followed by experiments on the uterus either isolated or *in situ* (sometimes the same uterus was used for experiment first in the intact animal and then as an excised organ).

Experiments on the isolated uterus.

The animals were killed by pithing or by a blow on the head: the vessels in the neck were cut and the animal rapidly bled: the uterus was removed and washed in Ringer's solution, afterwards being placed in a dish of Ringer's solution which was repeatedly changed until the solution ceased to be coloured by blood from the uterine vessels: the uterus was left in Ringer's solution at laboratory temperature until transferred to the bath of warm Ringer-Locke solution for the actual experiment. For experiment, one horn of the isolated uterus, or sometimes a longitudinal strip of uterine horn in the case of the pregnant organ, was suspended in a bath of Ringer-Locke solution at 38° C. so that it pulled on a counterbalanced lever which recorded contractions by an upstroke of the writing-point. The Ringer-Locke solution had a composition of:

NaCl	...	9·00 grams	in 1000 c.c. of glass-distilled water.
KCl ...	...	0·42 „	
$CaCl_2$	...	0·24 „	
$NaHCO_3$	...	0·50 „	
Dextrose	...	1·00 „	
Oxygen	...	saturated	

The bath contained 80 c.c. of this solution which was kept oxygenated by a constant stream of oxygen bubbling through it. The apparatus used was a modification of that described by Roth (6), the chief modification being that the outer water-bath was of considerably greater capacity in comparison with the capacity of the contained bath of Ringer-Locke solution, so that any slight variation in the temperature of the water supplied to the water-bath would have less effect on the temperature of the solution in the contained bath. In practice it was found that the temperature of the water-bath could be maintained without difficulty at a level constant within the limits of 0·5° C. In accurate work on the isolated uterus these details are of importance, as this organ is very sensitive to slight changes in temperature and in oxygen saturation of the solution. After suspension of the uterus in the warm Ringer-Locke solution, sufficient time (usually 15–20 minutes) was allowed for the tonus to become steady, so that at the time when the experiments actually started the tonus of the uterus was slightly above that of extreme relaxation and the movements were small. If the experiment is started before this stage is reached it is difficult to be certain of the degree of tonus existing in the uterus and the individual movements may be inconveniently large. In some cases the drugs were added to

the bath by means of a pipette in such a way that the drug was introduced away from the suspended organ and mixed with the solution by bubbling air through the bath: in other cases the drug already mixed with the Ringer-Locke solution to the required concentration was supplied from one of the containers within the water-bath.

In all some 130 experiments were performed: the organs were obtained from guinea-pigs, rats, cats and rabbits, and were in all stages of functional activity, virgin, non-pregnant, in different stages of pregnancy and taken at different periods after the termination of a pregnancy.

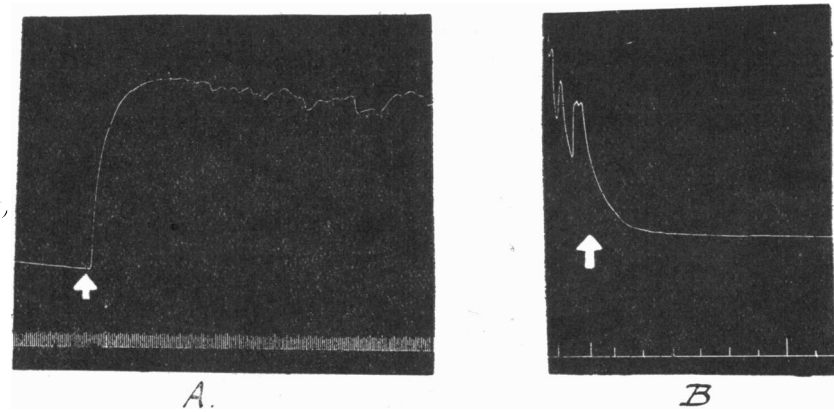

Fig. 1.

Isolated uterus of a guinea-pig (non-pregnant). Uterine movements (upstroke =contraction): Base-line and time-marking in seconds. At the arrow pituitrin was added to the Ringer-Locke solution to a concentration of 1–8000.

Isolated uterus of a guinea-pig (non-pregnant). Uterine movements (upstroke =contraction): Base-line and time-marking in 10 seconds. At the arrow adrenalin was added to the Ringer-Locke solution to a concentration of 1–1,000,000.

(In these and all other figures the tracings read from left to right.)

At first a few experiments were carried out applying one drug only, either adrenalin or pituitrin, to each uterus: in this way the capabilities of the apparatus were determined and a series of normal reactions to different concentrations of these drugs was obtained[1]. The usual effects of these drugs were obtained, viz. increased tonus and a series of gradually increasing movements starting in high tonus with pituitrin, and in the case of adrenalin relaxation of tonus and cessation of movements in the

[1] Various preparations were used of both adrenalin and pituitrin: all comparative results were obtained with the preparations of Messrs Parke Davis and Co. put up in bottles, not in ampoules: the contents of the latter are in my experience less reliable than the contents of stoppered bottles.

guinea-pig, rat and non-pregnant cat, increased tonus and movements in the case of the pregnant cat and rabbit. In the case of the guinea-pig, then, the effects of the two drugs are as opposed to each other as they can well be (Fig. 1).

If these two drugs are applied together, and so long as their relative proportions in the mixture are approximately correct (it is impossible to generalize as to the proportions which balance each other, as even with recently "standardized" preparations the variations in activity are somewhat large, so that the proportions were apt to vary with different

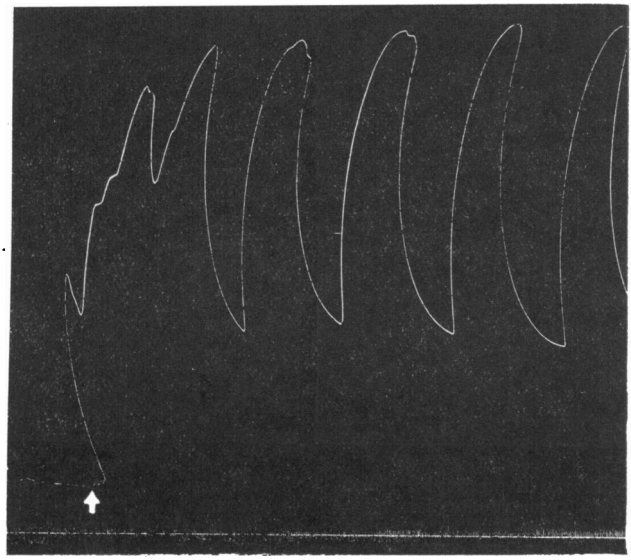

Fig. 2. Isolated uterus of a guinea-pig (non-pregnant). Uterine movements (upstroke = contraction): Base-line and time-marking in seconds. At the arrow a mixture of adrenalin and pituitrin was added to the Ringer-Locke solution to concentrations of 1–500,000 and 1–10,000 respectively.

batches of the drugs: further there appears to be considerable variation in sensitiveness to one or other drug between individual organs), the effect obtained is a very definite combination of the effects of the drugs when given separately: the uterus shows regular large movements the extent of which does not fall far short of that between complete relaxation and extreme contraction (Fig. 2). If the proportion of pituitrin in the mixture is unduly large the effect partakes more of the nature of a pure pituitrin response, that is to say the tonus is increased and increased movements are observed in a state of high tonus, but the

relaxations are more distinct than in the case of a pure pituitrin response (Fig. 3).

If the uterus is treated with adrenalin for some time before suspension and pituitrin is added subsequently, the effect is either the ordinary pure pituitrin effect or such an effect as is produced by a mixture of the two drugs. But if the uterus is first treated with pituitrin and then after suspension adrenalin is applied, one obtains, not the ordinary adrenalin effect of relaxation and cessation of movements, nor does one obtain an effect similar to that produced by a mixture of the two drugs,

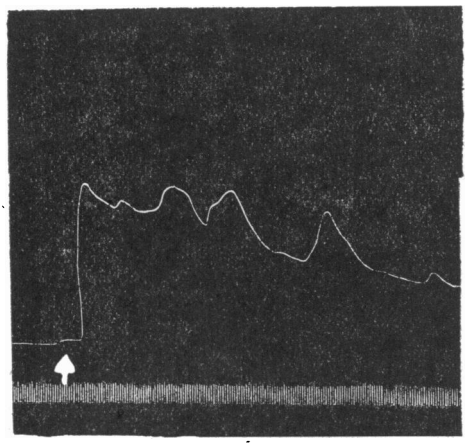

Fig. 3. Isolated uterus of a guinea-pig (non-pregnant). Uterine movements (upstroke = contraction): Base-line and time-marking in seconds. At the arrow a mixture of adrenalin and pituitrin was added to the Ringer-Locke solution to concentrations of 1–1,000,000 and 1–10,000 respectively.

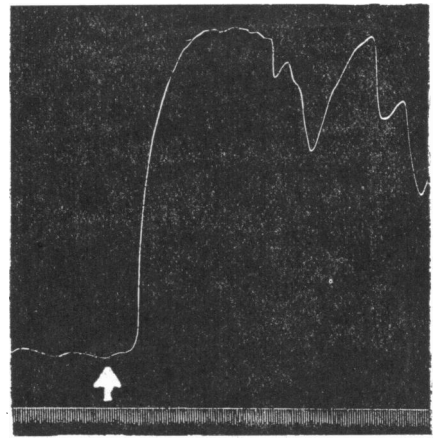

Fig. 4. Isolated uterus of a guinea-pig (non-pregnant). Uterine movements (upstroke = contraction): Base-line and time-marking in seconds. At the arrow adrenalin was added to the Ringer-Locke solution to a concentration of 1–1,000,000. This uterus had previously been left in a solution of pituitrin (1–10,000) for 60 minutes.

but an effect comparable with that produced by applying pituitrin, that is to say that under these conditions the effect of adrenalin is reversed (Fig. 4).

Since the uterus of the guinea-pig usually reacts to adrenalin in the same way whether pregnant or not—always by relaxation—one would expect that this reversed response to adrenalin in the uterus previously "sensitized[1]" by pituitrin would be obtained both in the pregnant and

[1] In a communication published in 1915 Blair Bell (7) describes his procedure of "sensitizing" the uterus with pituitrin during the last two or three months of pregnancy in cases of suspected idiopathic uterine inertia. Though he appears to have had no definite experimental data to guide him and though he advances no proof that this

non-pregnant organ of this species, and this was found to be the case. It appeared too that in the case of the pregnant uterus of this animal the reversed response to adrenalin was easier to obtain and with less sensitizing than in the case of the non-pregnant uterus.

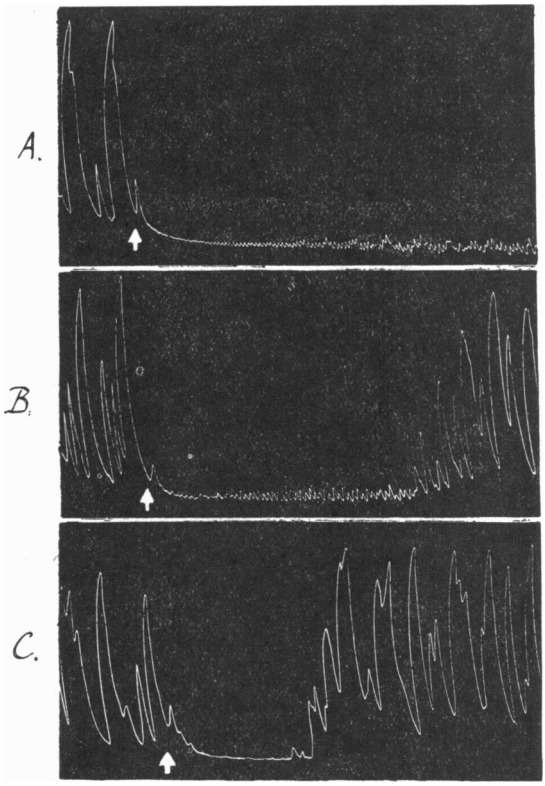

Fig. 5. Isolated uterus of a rat (pregnant about 10 days). Uterine movements (upstroke = contraction): Base-line. At the arrows adrenalin was added to the Ringer-Locke solution to a concentration of 1–500,000. A = normal uterine horn. B = the same horn previously "sensitized" in pituitrin (1–5000) for 45 minutes. C = the same horn further "sensitized" in pituitrin (1–5000) for a further 30 minutes.

Similarly, preliminary sensitizing with pituitrin produced a contraction response to adrenalin in the virgin or non-pregnant uterus of the cat: in the pregnant uterus of this animal no change was observed, as was to be expected, since when pregnant the cat's uterus normally responds to adrenalin by contraction.

"sensitizing" takes place, the rationale of his treatment seems to be identical with what I am describing: consequently I have thought well to retain the term "sensitize."

Again in the case of the rabbit's uterus, which normally responds to adrenalin by contraction whatever its functional state may be, no change was observed as a result of preliminary sensitizing with pituitrin.

Though the uterus of the rat responds to adrenalin in the same way as that of the guinea-pig—by relaxation in all states of functional activity—a difference was noticed between the organs of the two species in connection with this reversed response to adrenalin: the guinea-pig's uterus, as has been shown, can readily be made to respond to adrenalin by contraction: the uterus of the rat on the other hand is less amenable to this treatment; only with the greatest difficulty can the sensitizing process be carried to the necessary extent; the usual effect of progressive sensitizing, even in the pregnant organ of this animal, is that the degree of inhibition produced by subsequent application of adrenalin becomes less and less marked as regards both duration and degree as the process of sensitizing lengthens (Fig. 5).

A few experiments were carried out with the object of determining whether the presence of products of conception within a horn of pregnant uterus made any difference in the response. No difference was noticed in any case, a longitudinal strip of the horn of a pregnant uterus responding in exactly the same way to adrenalin and to pituitrin as did the intact pregnant horn. Again in one or two instances records were taken of the movements of a pregnant horn intact and later of the same horn with the contents removed. Confirmation was obtained in yet another way: on one or two occasions a bicornuate uterus was found to be pregnant in one horn and non-pregnant in the other: each horn was found to react to both adrenalin and pituitrin in exactly the same way.

On a few occasions rings of circular muscle were taken from the uterus of a guinea-pig, cut through and suspended as strips of circular muscle. It was found in certain instances, particularly in rings cut from the vaginal end of the uterus, that pituitrin produced a definite relaxation.

Experiments on the uterus in situ *in the intact animal.*

Non-pregnant female cats were the animals used: they were kept under observation in the laboratory so that their reproductive history was known for at least one month before experiment: some were fed with pituitary preparations and received subcutaneous injections of pituitrin during this period; others received no such treatment. For experiment, the animals were anæsthetized with A.C.E. mixture and then with urethane (in a few instances the animals were decerebrated instead); a respiration tube was tied into the trachea; a cannula was

tied into the jugular vein; the carotid blood-pressure was recorded by a mercury manometer; one hypogastric nerve was isolated and placed on suitable electrodes; the uterine movements were recorded by placing a thread, connected over pulleys with a counterbalanced lever, beneath both horns of the uterus, which remained intact and *in situ*. The edges of the abdominal wound were propped up with small glass supports, so that the wound formed the rim of a deep cup formed by the abdominal cavity, which was filled with warm Ringer's solution completely immersing the uterus. Those animals which had received no preliminary treatment with pituitrin received first an intravenous injection of

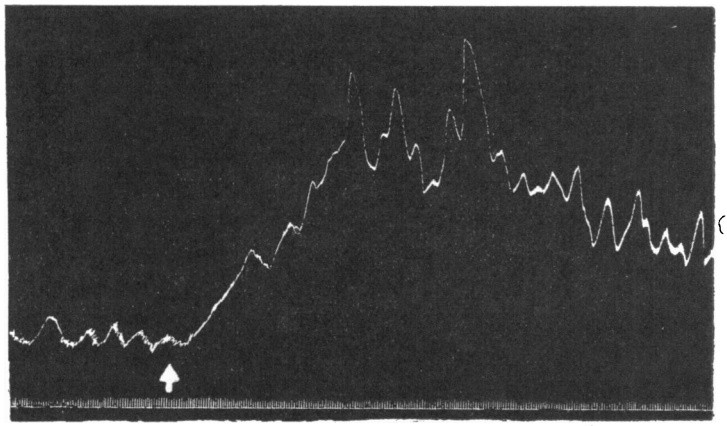

Fig. 6. Cat (non-pregnant): urethane. Uterine movements (upstroke = contraction): Base-line and time-marking in seconds. At the arrow 0·5 c.c. adrenalin (1–10,000) was injected intravenously. The animal had previously received daily doses of pituitary preparations by the mouth and subcutaneous injections of pituitrin over a period of six weeks. The animal was known not to have been pregnant for five months. (In this exp. the blood-pressure tracing continually obliterated the tracing of uterine movements, so the former was discontinued.)

adrenalin which produced the normal effects both on blood-pressure and on the uterine movements. Then injections of pituitrin were given slowly and at short intervals over a period of 15–30 minutes, after which a second injection of adrenalin was given, when it was found that the uterus responded by increase in tonus and movements instead of by relaxation. An exactly similar change was noticed as the result of stimulating the hypogastric nerve before and after the injection of pituitrin. Some of the animals which had received preliminary treatment with pituitary preparations gave the reversed uterine response to hypogastric stimulation or to injection of adrenalin without any further injection of pituitrin (Fig. 6).

Feeding experiments.

Guinea-pigs and cats—all females and non-pregnant—were used. The cats received with their milk a daily dose of desiccated posterior lobe of pituitary body (Armour), starting with 0·05 gm. each daily, gradually increasing up to 0·5 gm. daily over a period of 5–7 weeks. During this period too they received subcutaneous injections of pituitrin, starting with 0·1 c.c. increasing to 0·4 c.c. or 0·5 c.c. Each animal received from 20 to 25 such injections during this period, the injection being omitted one day in every six or seven. The guinea-pigs received similar treatment varying in duration from 30 days to 18 weeks: the injections of pituitrin started with 0·05 c.c. for a dose, gradually increased up to 0·15 c.c., 0·2 c.c., 0·25 c.c., or 0·3 c.c. These animals too received by the mouth Armour's desiccated posterior lobe of pituitary body or Duncan and Flockhart's pulv. ext. pituitary in daily doses gradually increasing from 0·05 gm. to 0·3 gm.

The animals were then used for experiment, the guinea-pigs being killed and the uterus removed and treated as an isolated organ; the cats in some instances being anæsthetized and a record being taken of the movements of the intact uterus, and in other cases the animals being killed outright and the uterus removed and suspended as an isolated organ.

It was found in both instances that this form of preliminary treatment with pituitary preparations was sufficient to sensitize the uterus so that subsequent application of adrenalin, either intravenously in the case of the intact cat or into the Ringer-Locke solution in which the uterus was suspended in the case of the isolated organ, would produce the reversed uterine response to adrenalin: similarly in the case of the intact cat hypogastric nerve stimulation would evoke contraction instead of relaxation of the uterus.

It would appear from the foregoing results that an unwontedly generous supply to the uterus of the active principle of the posterior lobe of the pituitary body is sufficient stimulus to change in some way the reaction to adrenalin of the uterus of such species of animals as normally reacts to adrenalin (or to hypogastric nerve stimulation) by relaxation. It is known that in the case of the cat the uterus normally and without adventitious aid changes its relaxation response for a contraction response to adrenalin during pregnancy. It has further been shown that the pregnant uterus of the guinea-pig is more easily sensitized by pituitrin for this contraction response to adrenalin than is the non-pregnant uterus of this animal, and further that the uterus

of the guinea-pig is more easily sensitized than is the uterus of the rat, irrespective of the functional state of the organ. One can thus bring into line all species of animals; with the rabbit, dog, ferret, monkey and man at one end of the series, where the uterus is normally contracted by adrenalin in both pregnant and non-pregnant states; with the cat occupying an intermediate position; and with the guinea-pig and rat at the other end of the series. Further one can see that all that is necessary so to bring into line all types of uterus is a supply of the active principle of the posterior lobe of the pituitary body, a smaller supply in the case of the rabbit and a larger supply in the case of the guinea-pig and rat. What may be the exact significance of this variation in the amount of pituitary active principle which is necessary it is difficult to say.

It is recognized from the work of Erdheim and Stumme(8) and from the observations of Marek(9), Blair Bell(10) and others that during pregnancy the pituitary body undergoes a definite hyperplasia with the appearance of specialized "pregnancy cells" and the setting up of a degree of activity greater than is found in the non-pregnant animal. There seems, too, little reason to doubt that the pars intermedia and pars nervosa share in this increased activity, so that there is in the natural economy a provision whereby an increased supply of pituitrin is available during pregnancy.

There is then no necessity for the hypothesis, that during pregnancy the motor nerve-endings in the uterus multiply to such an extent that they come to outnumber the inhibitor nerve-endings, since we have all the factors necessary for this change in response without having to fall back on any such hypothesis.

An attempt was made to place this sensitizing action of pituitrin: in the first place a systematic series of experiments was undertaken on the isolated uterus of the guinea-pig, using other drugs instead of adrenalin and comparing the effects produced by these drugs before and after sensitizing with pituitrin. The drugs used were arecoline, pilocarpine, pituitrin, liquid extract of ergot, ergotoxine, tyramine and barium. It was found that preliminary treatment with pituitrin sensitizes the uterus for the subsequent action of pituitrin, arecoline, pilocarpine, ergot, ergotoxine and tyramine, but not for that of barium. That is to say after preliminary treatment with pituitrin subsequent application of these other drugs produces an effect, when in concentration lower than that necessary to produce an effect on the normal uterus: similarly the same concentration will produce a more note-

worthy result on the sensitized than on the normal uterus, so long as the concentration is such that a submaximal response is obtained.

It has been seen that this sensitizing action of pituitrin applies to adrenalin, a drug known to act by stimulation of sympathetic myoneural junctions: the action applies also to ergotoxine and tyramine, drugs again which produce their actions through the peripheral sympathetic system: again with arecoline and pilocarpine, drugs which stimulate the peripheral autonomic system, either sympathetic or cranio-sacral autonomic, the same holds good. With barium on the other hand, a drug which produces its action by a direct stimulation of the muscle, no such effect was produced.

It would seem, then, that the seat of this sensitizing action of pituitrin lies not in the muscle itself but in some part of the peripheral innervation: if there is no cranio-sacral autonomic innervation in the uterus, as some authorities hold, then this action of pituitrin would appear to lie in the peripheral sympathetic innervation: if there is also a cranio-sacral autonomic innervation in the uterus, then this sensitizing action would appear to lie in the peripheral parts of either sympathetic or cranio-sacral autonomic or both. The secondary application of pituitrin to the sensitized uterus throws little or no light on this point, since the seat of action of pituitrin itself is placed by different observers in different localities, thus Dale(11) places it in the end-organ independently of its innervation, or at any rate in some point nearer the periphery than the point on which adrenalin acts, whilst others consider that pituitrin stimulates autonomic nerve-endings or some particular innervation(12).

Kepinow(13) states that a preliminary injection of pituitrin affects the vasomotor mechanism of rabbits in such a way that the effect of a subsequent injection of adrenalin is exaggerated: he found too a similar augmented effect on the pupil of cats and rabbits. I repeated these experiments on the blood-pressure of cats, and found ample confirmation of Kepinow's statement. In one experiment, whereas before the application of pituitrin an intravenous injection of adrenalin (0·025 mg.) produced a rise in carotid blood-pressure from 71 to 158 mm. Hg, a similar injection after the animal had received 5 c.c. of 2·5 per cent. pituitrin, injected intravenously in 34 separate injections over a period of 25 minutes, produced a rise from 40 to 248 mm. Hg.

If this effect of pituitrin on the blood-pressure is the same as that already described on the uterus, it would appear to be an effect on either the sympathetic or the musculature. In another experiment

1 c.c. of a 0·5 per cent. solution of barium chloride was injected intravenously before and after 5 c.c. of 2·5 per cent. pituitrin given by slow injection lasting over a period of 30 minutes. In this case the rise in blood-pressure resulting from the injections of barium was identical—22 mm. Hg—in each case.

It appears then that on two separate body mechanisms, each consisting essentially of a sympathetic innervation and a plain muscle end-organ, pituitrin produces a sensitizing effect for the subsequent action of adrenalin, but that whilst this sensitizing applies to drugs which act through the sympathetic it does not apply to drugs which directly stimulate the plain muscle.

A few experiments were then carried out both on the isolated uterus and on the blood-pressure of the intact animal with the object of determining whether or not this sensitizing process would take place on the mechanism previously treated with drugs known to paralyze peripheral nervous structures whilst leaving the muscle intact. It was found in both instances with ergotoxine and apocodeine that no such sensitizing occurred, though the musculature was shown to be normally active (or approximately so) to barium.

One is forced then to the conclusion that this sensitizing action of pituitrin, whatever be its real nature, is an action on some part of the peripheral mechanism central to the end-organ.

Fröhlich and Pick(14) have published the statement that extracts of hypophysis remove the paralysis of sympathetic vaso-constrictor nerve-endings produced by ergotoxine—in other words that pituitrin annuls Dale's vasomotor paradox. It appeared that this effect and the sensitizing action of pituitrin which I have described might have a common foundation. In three separate attempts on cats I have failed to obtain the effect which Fröhlich and Pick describe. Dale in a personal communication tells me that he too has failed to obtain the effect described by Fröhlich and Pick. Is it possible that in Fröhlich and Pick's experiments sufficient pituitrin remained in the cannula and vein to produce the effect which they ascribe to adrenalin? It is known that the pressor effect of pituitrin is unaffected by ergotoxine paralysis.

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Summary and Conclusions.

1. Experiments are described in which adrenalin and pituitrin in combination and following each other were applied to the uterus.

2. Preliminary treatment of the uterus with pituitrin produces a reversal of the normal adrenalin response of the uterus of the guinea-pig and of the virgin or non-pregnant cat.

3. The presence or absence of products of conception in the pregnant uterus makes no difference to the response of the uterus to either adrenalin or pituitrin.

4. Pituitrin under certain conditions may produce a relaxation of the circular muscle fibres of the uterus.

5. The suggestion is made that a determining factor of the response of the uterus to adrenalin is the amount of active principle of the posterior lobe of the pituitary body which has been available.

6. This "sensitizing" action of pituitrin appears to reside in the peripheral nervous mechanism probably of the sympathetic system: it does not reside in the end-organ.

7. A parallelism is drawn between this "sensitizing" action of pituitrin on the uterus and an, at first sight rather different, effect which it produces on the vasomotor mechanism.

8. The statement of Fröhlich and Pick that extracts of hypophysis remove the paralysis of sympathetic vaso-constrictor nerve-endings produced by ergotoxine is not confirmed.

References.

(1) Dale. This Journal, **34**. 163. 1906.
(2) Langley and Anderson. Ibid. **19**. 122. 1895.
Langley. Ibid. **27**. 252. 1901.
(3) Cushny. Ibid. **35**. 1. 1906.
Dale. Ibid. **34**. 163. 1906.
Kehrer. Archiv f. Gynäk. p. 169. 1906.
(4) Gunn and Gunn. Journ. of Pharm. and exp. Ther. **5**. 527. 1914.
(5) Cow. This Journal, **48**. 443. 1914.
(6) Roth. Journ. of Pharm. and exp. Ther. **5**. 563. 1914.
(7) Blair Bell. Proc. Roy. Soc. Med. **8**. 1915. (Sect. Obstet. p. 71.)
(8) Erdheim and Stumme. Berl. klin. Woch. **45**. 1031. 1908. Ziegler's Beitr. **46**. 1. 1909.
(9) Marek. Zntrlb. f. Gynäk. **35**. 1612. 1911.
(10) Blair Bell. Sex Complex, p. 55. London, 1916.
(11) Dale. Biochem. Journ. **4**. 427. 1909.
(12) v. Frankl-Hochwart and Fröhlich. Arch. f. exp. Path. u. Pharm. **63**. 347. 1910.
Fröhlich and Pick. Ibid. **74**. 92. 1913.
(13) Kepinow. Ibid. **67**. 247. 1912.
(14) Fröhlich and Pick. Ibid. **74**. 114. 1913.