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FURTHER EVIDENCE REGARDING THE ENDOCRINE STATUS OF THE NEUROHYPOPHYSIS

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It has been shown that lesions of the neurohypophysis or its nerve supply (the supraopticohypophysial tract) result in a state of diabetes insipidus (Fisher, Ingram & Ranson, 1938), and possibly disturbances of the labour mechanism (Fisher, Magoun & Ranson, 1938; Dey, Fisher & Ranson, 1941), and that stimulation of the neurohypophysis or its nerve supply results in inhibition of a water diuresis (Harris, 1947) and contraction of the oestrous uterus (Harris, 1947) or post partum uterus (Haterius & Ferguson, 1938; Ferguson, 1941). The final proof that the actions of posterior pituitary extracts represent true endocrine functions of the gland rests on the demonstration that secretion of the gland, with these reactions as a consequence, occurs as a result of 'natural' stimuli. This has only been established for the antidiuretic hormone (Rydin & Verney, 1938, and see O'Connor, 1947). There is little evidence that the increases in intestinal motility and blood pressure that follow injection of post-pituitary extract represent the actions of any pituitary hormone(s).

In this paper are described the effects on the intestinal motility and blood pressure of stimulating the supraopticohypophysial tract in the unanaesthetized rabbit.

THE NEUROHYPOPHYSIS AND INTESTINAL PERISTALSIS

Bell (1909), Gaddum (1928) and Melville & Stehle (1934) have shown that the intestine of the rabbit is stimulated to increased activity by unfractionated posterior pituitary extracts, or by the pressor fraction. The colon appears to be the most sensitive part of the intestinal tract to the action of such extracts, and the ileum is more sensitive than the jejunum. These results are, however, mainly of pharmacological interest and offer no evidence that the neurohypophysis plays any physiological role in the control of intestinal movements. Suggestive evidence that the neurohypophysis does affect intestinal motility may be found in the work of Wang, Clark, Dey & Ranson (1940) who reported an increase in gastro-intestinal motility in cats under light ether or chloralose anaesthesia after stimulation of the hypothalamus, anterior to the infundibular region. This response had the characteristics of one which was humorally excited (i.e. long latent period, persistence for several minutes after cessation of the stimulus) but was seen in slight form in only four out of eleven cats after spinal cord section. For this reason, the authors were unwilling to emphasize the possible participation of the neurohypophysis in the reaction.

Methods

The remote control method of stimulation in the conscious rabbit was used. The buried unit and method of insertion has been described previously (Harris, 1947). The primary circuits and coils used were of two types: (*a*) a heavy iron cored coil in series with a variable resistance across the a.c. (200 V.; 50 cyc./sec.) mains, and (*b*) a smaller primary coil passing 50 cyc./sec. d.c. pulses produced by the thyratron discharge of a large condenser bank (see Harris (1948*a*)). All stimuli were applied for periods of 1 min., the intensity of the stimulus being gauged by the proximity of the primary coil to the animal's head (bearing the implanted secondary coil), and by the movements observed in the orbital structures due to the spread of current to the adjacent oculomotor nerve. Observations on gastro-intestinal motility were made in the unanaesthetized animals by direct scrutiny of the intact abdominal wall. Rabbits, starved for 24 hr., were tied in the supine position and the fur over the abdomen clipped short, rather than shaved, because the cropped fur made any slight peristaltic waves more obvious. After careful observation of the abdominal wall for at least 10 min., stimulation was performed, or an intravenous injection of 'pituitrin' was given, and observation continued for another 10 or 15 min. The peristalsis normally visible through the abdominal wall of the intact rabbit is somewhat variable. In eleven normal rabbits, observed on many occasions, six showed no peristalsis; three showed occasional, very slight local undulations of the anterior abdominal wall; and only two showed rhythmical waves which started a few minutes after the animal was tied on the table.

Results

Preliminary observations. In the course of some other work in which rabbits were tied supine, it was noticed that stimulation of the neurohypophysis or intravenous injection of 'pituitrin' caused an increase in the peristaltic waves as seen through the abdominal wall. These rabbits had all been subjected to the operation of vaginal transplantation, most of them to ovariectomy, and the subcutaneous implantation of a stilboestrol tablet. That the visible waves observed were not due merely to an increase in uterine motility was clear from their site, viz. to the right of a line drawn from the xiphisternum to the left iliac fossa. In this region the large gut is situated, the part of the intestine which has been described by many workers as being most sensitive to posterior lobe extracts.

It was difficult to make accurate observations on some of these animals, for any increased peristalsis due to stimulation tended to be masked by the very obvious waves present before the stimulus was applied. The prominent intestinal motility normally present in these cases was thought to be due to the oestrogenization, for later observations showed that this increased motility developed a few days or weeks after the operation of vaginal transplantation, ovariectomy and stilboestrol tablet insertion. Other explanations, such as the loss of weight after the operation rendering the peristaltic waves more obvious through a thinned abdominal wall, or interference with the nerve supply of the large intestine by transection of the vagina, were held to be unlikely.

It was therefore decided to investigate the effects of injecting various doses of posterior lobe extract on the peristalsis of normal rabbits and of stimulating various regions of the pituitary gland and hypothalamus by the remote control method.

The effect of intravenous injection of posterior lobe extract on the visible peristalsis of normal rabbits. Six injections of 500 mU. 'pituitrin', eight injections of 200 mU., six injections of 100 mU., three injections of 50 mU. and six control injections of normal saline were distributed amongst eleven normal rabbits. Only one injection was given on any day, except when control injections of saline were previously administered.

50 mU. of 'pituitrin' produced a definite increase in peristalsis in one out of three cases, 100 mU. in five out of six cases, and 200 mU. and 500 mU. in all cases. The responses to the injections were essentially similar in all the animals, and may be described as consisting of three phases:

Phase 1. A latent period of about half a minute.

Phase 2. A stage of increasing and then almost continuous intestinal movement for about two minutes. In most animals, a continuous rolling motion occurred in all parts of the abdomen, so that the general appearance could be likened to a 'bag of worms'. Sometimes short pauses were seen, in which the abdominal wall was still. These gave the impression that a series of waves, each of long duration, was in progress. Once the abdominal wall was observed to be raised into ridges during the pauses, perhaps indicating a state of spasm of the intestines.

Phase 3. A stage of decreasing rhythmical activity. In this phase, rolling motions of the abdominal wall were seen with a frequency of approximately one wave 30–120 sec. and a duration of 10–30 sec.

The effect of stimulation of the hypothalamohypophysial region on the visible peristalsis. Ten rabbits, intact except for the implanted coils, were used in these experiments. On each animal the effect of stimulation was studied on at least three separate occasions. The response of these animals to intravenous injection of posterior lobe extract was also investigated, so that the results of the two methods of stimulation could be compared on the same animal. The site of the stimulating tip of the electrode in these animals could be estimated with fair accuracy during life from a study of X-ray photographs of the head, and by the inhibition of a water diuresis produced by stimulation. It was established exactly, post-mortem, by means of serial sections.

These animals may be classified into three groups according to the position of the electrode: Group A, electrode more than 0·5 mm. from the supraoptico-hypophysial tract; group B, electrode within 0·5 mm. of, but not in contact with, the supraopticohypophysial tract, and group C, electrode in, or in contact with, the supraopticohypophysial tract.

The results of stimulation are given in Table 1. All the animals (except no. 40) were tested to see the effect of stimulation on a water diuresis, group A animals showing no effect, group B a submaximal antidiuretic response, and group C a maximal response. With regard to the effect of stimulation on peristalsis, similar results were obtained from the animals in both groups A and B. A negative result was observed in thirteen out of eighteen experiments, a doubtful positive response in four, and a marked response in one. The four doubtful responses consisted of a few, small and shortlived, localized undulations that appeared in the 10 min. after stimulation. These waves showed little similarity to those produced by the injection of 'pituitrin' into the same animals. It seems therefore unlikely that they were produced by the spread of current to the neurohypophysis, especially since in rabbits 30 and 32, any spread was insufficient to produce inhibition of a water diuresis which is a far more sensitive reaction. The significance of these four doubtful responses, and of the one definite reaction is unknown. In the group C animals, a definite excitation was observed in thirty-one out of thirty-two experiments, the character of the response being similar in nature to that evoked by intravenous injection of posterior lobe extract. The increased peristalsis occurred after a long latent period (0·5 min. or more after starting 1 min. stimulation), and then appeared as large, almost continuous, undulations mainly situated

TABLE 1. The effect on peristalsis of stimulating various areas in the hypothalamohypophysial region

Rabbit	Electrode site	No. of experiments	Effect of stimulation on peristalsis: 0	±	+	+ +
Group A						
30	Posterior part of tuber cinereum	3	1	2	.	.
32	Right posterior part of tuber cinereum	3	2	.	.	1
40	Zona tuberalis	3	3	.	.	.
Group B						
31	Lateral part of tuber cinereum and pars distalis on right of infundibular stem	3	2	1	.	.
33	Pars distalis below infundibular stem	3	3	.	.	.
34	Posterior part of tuber cinereum	3	2	1	.	.
Group C						
35	In contact with right side of infundibular stem	5	.	.	.	5
45	Median eminence slightly to left	4	.	.	2	2
51	Right side of median eminence	13	1	.	6	6
52	Junction of infundibular stem and infundibular process	10	.	.	2	8

The effect of stimulation on peristalsis is represented thus: 0, no effect; ±, a doubtful increase; +, a definite slight or moderate increase; and + +, a marked increase. All the rabbits responded to the intravenous injection of 100 mU. posterior lobe extract with an increase in peristalsis.

over the colonic area of the abdomen. These waves slowly decreased in frequency and amplitude during the next 5–10 min. The latent period of the response to stimulation was slightly longer than that to injection of 100 mU. of 'pituitrin' into the marginal vein of the ear. Also, as far as could be judged by observations on individual rabbits from day to day, the magnitude of the response to the standard 1 min. stimulation was less than that evoked by the intravenous injection of 100 mU. 'pituitrin' in the same animal. This latter point was observed most clearly in rabbit 52, in which visible peristalsis before stimulation or injection was very slight or absent.

In one rabbit, not included in the above series, after the abdomen had been opened under ether for another reason, the intestine and uterus were observed directly, whilst electrical stimulation of the infundibular stem was performed by the usual method. After stimulation for 45 sec. large peristaltic waves appeared suddenly in the large gut and uterus, both of which had been previously flaccid and quiescent. Though the stimulus ceased after 1 min. the waves continued for at least 4 min., but with decreasing amplitude and frequency. In another animal, observed under similar conditions, peristalsis was not excited by stimulation, possibly because this animal had been longer, or more deeply, anaesthetized.

THE NEUROHYPOPHYSIS AND BLOOD PRESSURE

As regards the production of a pressor response to stimulation of the neurohypophysis in situ, a little evidence is available for animals in the anaesthetized state. Cyon (1898, 1900, 1901) observed a bradycardia and an increase in blood pressure after injection of pituitary extract, or stimulation of the pituitary gland either electrically or mechanically. He suggested that these results were mediated through the vagi. Chang, Chia, Hsu & Lim (1937) reported that stimulation of the central end of the cut vagus in dogs under chloralose anaesthesia, and with only vascular connexions between the head and trunk, gave a pressor response in the trunk. This response could be abolished either by interrupting the pituitary stalk or by removing the pituitary gland. The conclusion drawn was that stimulation of the central vagus induces a reflex secretion of the posterior pituitary principle. Rather more direct evidence is that of Clark & Wang (1939), who found that stimulation of the supraoptic region of the anterior hypothalamus gave a pressor response in seven out of ten anaesthetized spinal cats, the characters of the response being a long latent period ($\frac{1}{4}$–$\frac{1}{2}$ min.), a slow smooth rise of about 30 mm. Hg and a duration of approximately 2–4 min. They therefore thought it likely that the reaction was due to liberation of the posterior pituitary hormone. Sattler (1940) has confirmed, in the main, both the work of Chang *et al.* (1937), and Clark & Wang (1939). Ferguson (1941) records slight rises in blood pressure on stimulating the pituitary stalk in rabbits and cats anaesthetized with chloralose and urethane, and in which only vascular connexions remained between the head and trunk. In some cases, the pressor response was very slight (see his Fig. 2), although the oxytocic effect of the stimulus was well marked.

In view of the fact that the pressor response to injection of posterior lobe extract varies in the conscious and anaesthetized states, it was decided to investigate the effect on the blood pressure of stimulation of the neurohypophysis in the conscious rabbit.

Methods

Systolic pressures were measured on the vessels of the rabbits ears using the method of Grant & Rothschild (1934), care being taken that the vessels were thoroughly dilated by previous warming. With this precautionary measure rabbits gave readings which fluctuated by only a few mm. Hg over long periods. The full technique was as follows. A rabbit, with the outer surface of one ear shaved and the skin over the marginal vein of the opposite ear nicked with a razor, was placed in its cage over an electric heater for usually 4 hr., the temperature in the cage being 81° F. At the end of this period, the animal, with ear vessels well dilated and respiration occurring in shallow rapid pants, was removed from the cage, secured in the upright position in a duster to render it motionless, replaced on the heater and blood-pressure readings taken at about 5 min. intervals till a constant level was obtained. The intravenous injection of posterior lobe extract was then made into the marginal vein of the opposite ear through the previously nicked skin, or electrical stimulation applied for 1 min., and the blood pressure recorded after ½, 1½, 2½, 3½, 5 and 7 min. Stimulation was applied by the same method as used in the previous experiments on peristalsis (see above).

Results

The effect of intravenous injection of posterior lobe extract on the blood pressure of normal rabbits. It was necessary, before investigating the effect of stimulation of the neurohypophysis, to see if the conscious rabbit reacted to an intravenous injection of posterior lobe extract with a pressor response. Fifteen normal rabbits were chosen and, out of these, six different animals were tested at each dosage of 'pituitrin' (50, 100, 200 and 500 mU.), and also with injections of 1 c.c. 0·9 % NaCl solution. In some of the earlier readings the rabbits had been previously given small quieting doses of paraldehyde by stomach tube, but since these results did not differ from those obtained in the later experiments when no sedative was used, all the results have been grouped together. All the doses of 'pituitrin' produced a sharp rise in blood pressure lasting for 30–90 sec., and the pressure then fell more slowly over the next few minutes, the increase in pressure and its duration varying approximately as the dosage (see Table 2).

TABLE 2. The maximum increments in systolic blood pressure after intravenous injection of varying doses of 'pituitrin'

Dose of 'pituitrin' in mU.	500	200	100	50	Control injections
Rise in systolic blood pressure, in mm. Hg	30	28	12	10	5
	32	35	10	5	0
	35	40	10	17	0
	35	20	14	10	0
	33	25	25	10	0
	32	30	17	10	0
Average rise in systolic blood pressure, in mm. Hg	32·8	29·7	14·7	10·3	0·8

A marked bradycardia was also observed after injection of posterior pituitary extract. The figures given by Brown, McLean & Maegraith (1939), who measured the blood-pressure changes of rabbits, anaesthetized with nembutal, after injections of 'infundin' in doses of 0·12 and 0·06 U., varied from 18 to 43 mm. Hg, which are slightly higher than those obtained by the author in the conscious rabbit at an equivalent dosage. Brown *et al.*, however, used the carotid loop method of recording the blood pressure, which might well account for the higher figures, quite apart from their use of anaesthetized animals.

TABLE 3. The maximum rises in systolic blood pressure after stimulation of various areas in the hypothalamohypophysial region for 1 min., and after the intravenous injection of 100 mU. 'pituitrin' in the same animals

		After stimulation		After injection	
Rabbit	Electrode site	Number of observations	Average change in systolic b.p. in mm. Hg	Number of observations	Average rise in systolic b.p. in mm. Hg
Group A					
30	Posterior part of tuber cinereum	3	−2·7	3	15
32	Right posterior part of tuber cinereum	3	−1·0	1	18
40	Zona tuberalis	3	+2·7	2	20
Group B					
31	Lateral part of tuber cinereum, and in pars distalis on right of infundibular stem	3	+2·3	1	25
33	Pars distalis below infundibular stem	3	−2·3	3	15·7
34	Posterior part of tuber cinereum	4	+8·3	3	18
49	Zona tuberalis	2	+2·5	2	6·5
Group C					
35	In contact with right side of infundibular stem	3	+8·3	1	14
45	Median eminence slightly to left	5	+6·8	5	16·6
51	Right side of median eminence	4	+4·3	2	15·5
52	Junction of infundibular stem and infundibular process	5	+8·2	4	16·8

The effect of stimulation of the hypothalamohypophysial region on the blood pressure. The effect of stimulation on the blood pressure was investigated in eleven rabbits bearing implanted coils. Three rabbits fall in group A with the electrode more than 0·5 mm. from the supraopticohypophysial tract, four in group B with the electrode within 0·5 mm. of, but not in contact with, the supraopticohypophysial tract, and four in group C with the electrode in contact with some part of the supraopticohypophysial tract. The results of these experiments are given in Table 3. It may be seen that the average variation in blood pressure after stimulation was very slight in all the animals classified as groups A and B except one (rabbit 34, group B). The four animals in group C seemed to show slight pressor responses (of the same type and time relations as those following injection of posterior pituitary extract), but it is doubtful whether these figures represent a significant physiological response to stimulation of the neurohypophysis. The results show clearly, however, that 100 mU. of whole posterior lobe extract injected intravenously produced greater pressor responses than stimulation of the neurohypophysis for 1 min.

OXYTOCIC RESPONSES ELICITED BY STIMULATION

Some of the rabbits used in the experiments described above were investigated to ascertain the effect of similar stimuli in eliciting the secretion of an oxytocic principle. Stimulation was applied for 1 min. in the usual way. The uterine responses of the unanaesthetized rabbits were recorded, from a permanent vaginal fistula, in animals that had been ovariectomized and implanted subcutaneously with a 50 mg. tablet of stilboestrol di-*n*-butyrate (see Harris, 1947, for a full description of the technique).

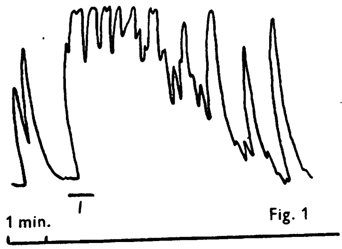
Rabbit 32 (group A) gave no uterine responses to stimulation.

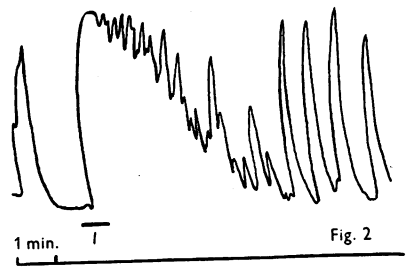
Rabbits 31, 33 and 34 (group B) showed definite uterine responses to stimulation, but smaller than those given by the animals in group C.

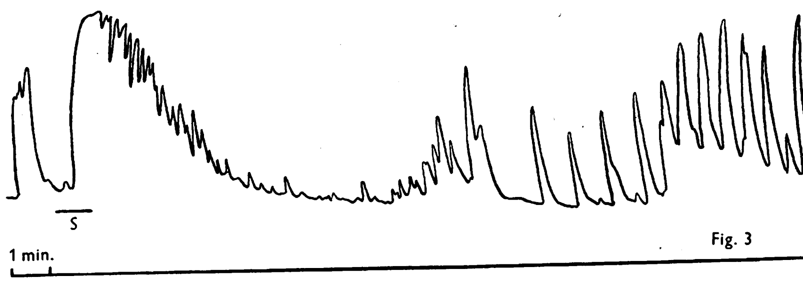
Rabbits 35, 51 and 52 (group C) showed definite uterine response to stimulation. The characters of such uterine effects and the evidence that they are due to secretion of an oxytocic principle from the neurohypophysis have been described previously (Harris, 1947). For the present purpose the comparison between the uterine responses to the standard 1 min. stimulation of the supraopticohypophysial tract, and to the injection of various doses of posterior lobe extracts, is of interest. Rabbits 35 and 52 gave uterine contractions, following the standard 1 min. stimulation, equivalent to 200–500 mU. (Figs. 1–4). In the case of rabbit 51, however, the uterine response was equivalent to the effect produced by an injection of approximately 100 mU., and it is interesting to note that the effect of stimulation on the peristalsis and blood pressure in this rabbit had also appeared to be less than that obtained in rabbit 52. The probable reason is that in rabbit 51 the electrode was situated in contact with the right side of the supraopticohypophysial tract in the median eminence where the tract is splayed out as a flat band of fibres, whereas in rabbit 52 the electrode was in the middle of the fibres where they are concentrated as a round bundle in the junction of the infundibular stem and infundibular process. It is likely then that only a proportion of the supraopticohypophysial fibres were stimulated in rabbit 51.

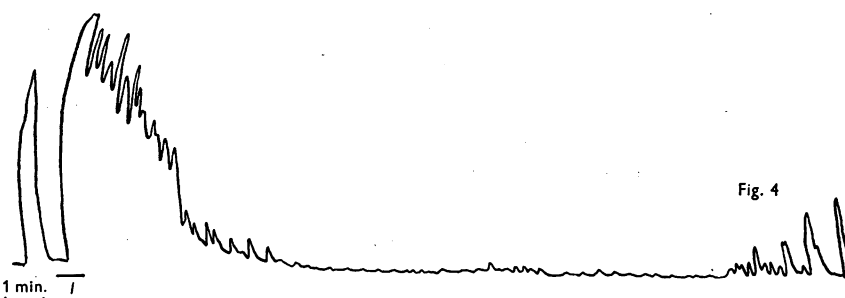
DISCUSSION

The results show that the conscious rabbit reacts to the intravenous injection of small doses of whole posterior pituitary extract with, amongst other effects, an increase in intestinal peristalsis and a pressor response. Stimulation of the









Figs. 1–4. Oxytocic responses of rabbit 52 (group C) to intravenous injection of posterior lobe extract, and to stimulation of the infundibular stem. In comparing these curves attention should be paid to the initial phase of contraction of the uterus, and in particular to the general shape of the curve, and the tendency to maintain a plateau at the height of the contraction. The phase of inhibition that follows the initial contraction, after stimulation of the neurohypophysis or injection of whole posterior lobe extracts, is discussed in the text.

Fig. 1. Intravenous injection 100 mU. 'pitocin', *I*.

Fig. 2. Intravenous injection 250 mU. 'pitocin', *I*.

Fig. 3. Stimulation of neurohypophysis, *S*.

Fig. 4. Intravenous injection 250 mU. 'pituitrin', *I*. (This curve is not quantitatively comparable with the other curves.)

(Tracings of kymograph recordings $\times \frac{1}{2}$).

neurohypophysis causes a similar increase in peristalsis, but no marked rise in blood pressure. Before assigning a physiological role to the neurohypophysis in the control of intestinal peristalsis it would be necessary to demonstrate that lesions of the neurohypophysis interfere with the normal motility of the intestine, or prevent an increase in motility normally evoked by 'natural' stimuli. In this respect Cushing's (1932) observation that '...patients with tumors which have destroyed the pars nervosa or thrown it out of function by compression are, in many instances, notably victimized by chronic constipation', is of interest.

Evidence is accumulating that stimulation of the neurohypophysis in the conscious rabbit excites a secretion containing less pressor than oxytocic principle, as compared with unfractionated posterior lobe extracts.

(1) It has been shown (Harris, 1947) that when the oxytocic and antidiuretic responses are measured simultaneously, the oxytocic response elicited by stimulation of the neurohypophysis is greater relative to the antidiuretic than that evoked by injection of whole posterior lobe extracts. It is known that the antidiuretic activity of such extracts parallels the pressor activity.

(2) Stimulation of the neurohypophysis has been shown to produce an oxytocic effect equivalent to that produced by 200–500 mU. of whole posterior lobe extract, whereas similar stimulation in the same animals produces an effect on the intestinal peristalsis and the blood pressure less than that evoked by 100 mU. of whole posterior lobe extract. (It is likely that, in the rabbit at least, the peristalsis-stimulating action of whole posterior pituitary extracts is due to the pressor principle.) Further evidence on the amount of pressor substance liberated from the gland following stimulation for 1 min. is given by the fact that less antidiuretic hormone is excreted in the urine after such a stimulus than after the intravenous injection of 100 mU. 'pituitrin' (Harris, 1948*b*).

(3) Stimulation of the neurohypophysis excites an oxytocic response which is more closely simulated by intravenous injection of 'pitocin' than 'pituitrin' (Ferguson, 1941; Harris, 1947), the 'pituitrin' response showing a greater inhibition of the rhythmic waves after the initial contraction (see Figs. 1–4). The inhibitory phase following the response to stimulation is found to be intermediate in magnitude between that following injection of 'pitocin' and injection of 'pituitrin'. This inhibition is due to the pressor principle (Morgan, 1937; Harris, unpublished), probably causing spasm of the uterine arteries (Morgan, 1937). Thus the evidence derived from the uterine tracings alone strongly suggests that the pituitary secretion, excited by electrical stimulation, contains relatively less pressor principle than whole posterior pituitary extracts.

The evidence given above should not be used to support the 'unitary theory' or 'multiple hormone theory'. Two questions are involved here. First, does the gland manufacture a single substance with multiple actions, and secondly, if a single substance with multiple activities is formed in the gland, is it liberated as such into the blood stream, or as suggested by Van Dyke, Chow, Greep & Rothen (1942), are active fragments of the parent molecule discharged into the blood stream separately according to the requirements of the organism? It should be mentioned that Van Dyke *et al.* (1942) succeeded in isolating a protein from the dried posterior lobe of frozen gland material which behaved as a homogeneous substance and had oxytocic, vasopressor and diuresis-inhibiting activities present in ratios resembling those of the U.S.P. reference standard.

It was stated (Harris, 1944, 1947) that if it could be shown that the proportions of pressor (and/or antidiuretic) and oxytocic activities as produced by stimulation of the neurohypophysis ran parallel under a variety of conditions (hydration and dehydration, anoestrus, oestrus, pregnancy, pseudopregnancy and post-partum, etc.), then strong evidence would be obtained for the 'unitary theory'. However, preliminary experiments indicate that such is not the case. It has been found that the reactions of the oestrogenized uterus to intravenous injection of a solution containing 'pitocin' and 'pitressin' may give a roughly quantitative assay of the 'pitocin' and 'pitressin' content of such mixtures. The 'pitocin' content is related to the initial uterine contraction, and the 'pitressin' content to the subsequent inhibitory phase. Stimulation of the infundibular stem for 1 min. produces a secretion equivalent (in action on the uterus) to a mixture of 250 mU. 'pitocin' and 50–100 mU. 'pitressin'. Now since administration of hypertonic saline has been shown to excite the liberation of the antidiuretic hormone from the posterior pituitary gland (Chambers, 1945; Verney, 1946), the effect of stimulation one hour after intravenous administration of hypertonic saline was investigated. Under these conditions the stimulus appears to produce a secretion equivalent in action to the same amount of 'pitocin', but less 'pitressin'. Since the hypertonic saline does not alter the uterine reactions to intravenous injection of posterior pituitary extracts, the simplest explanation seems to be that the injection of hypertonic saline has depleted the neurohypophysis of its pressor content, but not the oxytocic. Further work is in progress on this subject.

The effect of whole posterior pituitary extracts, or of the pressor principle, in causing a phase of inhibition of uterine motility following any initial contraction appears to be due to the production of a state of spasm of the uterine vessels (Morgan, 1937). If this explanation is the true one, the fact that stimulation of the neurohypophysis is followed by a similar, though smaller, reaction demonstrates that the secretion of the gland can produce an effect on, at least, the uterine blood vessels. The question then arises as to why an effect on the general vascular tree was not demonstrable as a definite pressor response. Of many possible explanations the most likely appear to be (*a*) that the uterine vessels are specifically sensitive to the action of the pituitary secretion, (*b*) that nervous reflexes mask a pressor response otherwise due to a general vasoconstriction (though a bradycardia has not been observed to follow stimulation of the neurohypophysis), and (*c*) that the uterine responses were recorded in oestrogenized rabbits, whereas the pressor effects were investigated in non-oestrogenized animals. There can be no doubt that oestrogens sensitize the uterine musculature of the rabbit to the action of whole posterior pituitary extract and to the secretion liberated by stimulation of the neurohypophysis. They seem to cause also an increase in the intestinal peristalsis of the rabbit as seen through the intact abdominal wall, which would appear to be an effect exerted on the plain muscle of the intestine. With regard to a possible sensitization of vascular muscle, Byrom (1937, 1938) found an increased sensitivity of the blood vessels of rats to the pressor principle by the previous administration of oestrogens. This increase in sensitivity was of the order of a tenfold, or greater, increase. A few observations were made on the effect of stimulating the neurohypophysis of rabbit 35, after the operation of vaginal transplantation, ovariectomy and subcutaneous insertion of a 50 mg. tablet of stilboestrol di-*n*-butyrate. In three experiments the systolic blood pressure showed a rise of 32, 20 and 24 mm. Hg (average rise 25·3 mm. Hg) as compared with rises of 15, 7 and 3 mm. Hg (average rise 8·3 mm. Hg) before the operation. Further evidence on this point is needed.

SUMMARY

1. Intravenous injection of posterior pituitary extract (50–500 mU.) causes an increase in the peristalsis visible through the abdominal wall, and electrical stimulation of the neurohypophysis causes an increase similar in type, though less in magnitude, to that produced by 100 mU. of such extracts in the same animals.

2. Intravenous injection of posterior pituitary extract (50–500 mU.) causes an increase in systolic blood pressure (10–30 mm. Hg), and stimulation of the neurohypophysis causes a slight rise of systolic blood pressure of doubtful significance, and clearly smaller, than that produced by 100 mU. of such extracts in the same animals.

3. Stimulation of the neurohypophysis (in the same and other animals as those used in the above experiments) produces an effect on the uterus equivalent to 200–500 mU. of posterior pituitary extract.

4. The nature of the substance liberated from the neurohypophysis by electrical stimulation is discussed.

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