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NEURAL CONTROL OF THE PITUITARY GLAND
I. THE NEUROHYPOPHYSIS*

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Most endocrine glands either lack a nerve supply or receive only a scanty innervation. The adrenal cortex is believed to be devoid of any nerve supply (Teitelbaum, 1942), whilst the nerve fibres described in the ovary, testis, thyroid, and adenohypophysis (anterior pituitary gland) are probably vasomotor in function. There is no sound evidence that these glands are dependent for their functional activity on a direct secretomotor nerve supply : such dependency seems to be true for only two endocrine glands—the adrenal medulla and neurohypophysis (posterior pituitary gland).

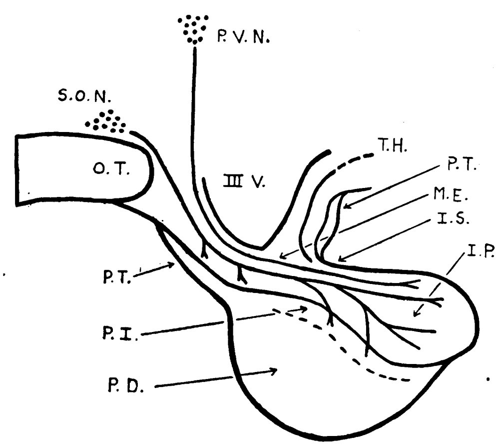

Diagram of a sagittal section through the hypothalamus and pituitary gland. The three parts of the neurohypophysis include the median eminence (M.E.), the constricted infundibular stem (I.S.), and the infundibular process (I.P.). The adenohypophysis also consists of three divisions—the pars distalis (P.D.), the pars intermedia (P.I.), and the pars tuberalis (P.T.). It is established that the neurohypophysis is innervated by the supraoptic nucleus (S.O.N.), situated above the beginning of the optic tract (O.T.). and the paraventricular nucleus (P.V.N.), which is in intimate relationship with the third ventricle (III V.). Other fibres constituting the tubero-hypophysial tract (T.H.) also run to the hypophysis, but their origin is unknown. (By kind permission of the Royal Society of Medicine.) .

The terminology adopted in this paper for the different regions of the pituitary gland will be that suggested by Rioch, Wislocki, and O'Leary (1940) (see accompanying illustration). The neurohypophysis is described by these authors as consisting of three subdivisions—the *median eminence* of the tuber cinereum, the *infundibular stem,* and the *infundibular process.* The first two parts may be collectively referred to as the *neural stalk.* This terminology emphasizes the important fact that the upper limit of secreting tissues is in the tuber cinereum. The adenohypophysis is likewise subdivided into three parts—the pars tuberalis, the pars intermedia, and the pars distalis.

Older Views on the Nature of the Neurohypophysis

Luschka in 1860 recognized the nervous nature of the neurohypophysis and proposed the name " nervendrüse " (nervous gland) for this structure. Peremeschko (1867), who studied the development of the neurohypophysis in various mammals, opposed Luschka's idea that this was a neural structure, and proposed the name " blutgefässdrüse " (blood-vessel gland). For approximately the next 30 years the view was held that the neurohypophysis was neuroglial in nature (see Truscott, 1944). In 1894 Berkley described nerve fibres in the neurohypophysis which he thought were sympathetic in nature, but it was left to Cajal (1894) to describe the important tract of supply to the gland, passing from a nucleus near the optic chiasma through the neural stalk to the infundibular lobe (" superior lobe " of Cajal). On histological grounds Cajal put forward the idea that the neurohypophysis was a sensory organ and that the hypothalamo-hypophysial tract conveyed afferent nerve impulses from the neurohypophysis to the hypothalamus. About this time the pharmacological activity of posterior pituitary (infundibular lobe + pars intermedia) extracts was being studied, and it was found that injection of such extracts had a pressor action (Oliver and Schäfer, 1895; Howell, 1898), a diuretic action in *anaesthetized* animals (Magnus and Schäfer, 1901; Schäfer and Herring, 1906), an antidiuretic and chloruretic action in *unanaesthetized* animals (von den Velden, 1913), a hyperglycaemic action (Borchardt, 1908), a stimulating action on intestinal peristalsis (Bell, 1909), an oxytocic action (Dale, 1909), a galactogogue action (Ott and Scott, 1910), and other effects. In 1928 this single extract with multiple activities was purified and separated into two fractions by Kamm, Aldrich, Grote, Rowe, and Bugbee, working in the research laboratories of Parke, Davis and Co. The names and probable activities of these two fractions are shown below :

		Probable activities
Whole posterior pituitary extract (" Pituitrin," Parke, Davis and Co.)	Pressor fraction (" Pitressin," Parke, Davis and Co.)	Pressor Antidiuretic Chloruretic Stimulation of intestinal peristalsis Hyperglycaemic
	Oxytocic fraction (" Pitocin," Parke, Davis and Co.)	Oxytocic Galactogogue

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Owing to the fact that the neurohypophysis has little resemblance to a glandular structure, it was at first thought that the active substance present in extracts was formed in the pars intermedia of the adenohypophysis. It was believed that cells, or cellular secretion, passed from the pars intermedia posteriorly into the infundibular lobe, where they were transformed into hyaline masses (Herring bodies) containing the active material. The Herring bodies were thought to migrate up the pituitary stalk and to exert an effect on hypothalamic nerve centres, or to pass into the cerebrospinal fluid of the third ventricle (Cushing, 1932). It can now be stated that (*a*) the active substance present in posterior pituitary extracts is formed in the tissues of the neurohypophysis, though the particular cells involved are unknown; (*b*) that the formation and liberation of any active material by the neurohypophysis is under the direct control of the hypothalamo-hypophysial tract; and (*c*) that any hormone liberated passes into the blood stream; there is no evidence that the pathway is up the stalk to the hypothalamus.

Nerve Supply of the Neurohypophysis

The original observation of Ramón y Cajal (1894), made on immature mice, that a large number of unmyelinated nerve fibres pass from the hypothalamus to the neurohypophysis, was confirmed by his pupil Tello (1912) on human material. Pines (1925) and Greving (1926) further localized the origin of this tract, as arising largely in the supraoptic and paraventricular nuclei of the hypothalamus, and were responsible for drawing the attention of physiologists and clinicians to this profuse innervation of the neurohypophysis. Fisher, Ingram, Hare, and Ranson (1935) subdivided the hypothalamo-hypophysial tract into two component parts, the supraoptico-hypophysial tract running in the ventral or more rostral wall of the neural stalk and the smaller tubero-hypophysial tract in the dorsal or more caudal wall of this structure. The exact cells of origin of the tubero-hypophysial tract are doubtful. The importance of the supraoptic and paraventricular nuclei in giving rise to the greater number of fibres in the supraoptico-hypophysial tract has been clearly demonstrated by studies of the retrograde degeneration that occurs in these nuclei after lesions placed in the pituitary stalk or tuber cinereum. For example, estimates have been made that in man there are normally about 100,000 nerve fibres present in the supraoptico-hypophysial tract and about 60,000 nerve cells present in each supraoptic nucleus. Following section of the pituitary stalk at the level of the diaphragma sellae in a man 46 years old, only about 9,000 cells were found in each supraoptic nucleus (Rasmussen, 1940). Many data of this type are available also for the rat, dog, and monkey.

The supraoptico-hypophysial tract appears to be the largest, and functionally the most important, innervation of the neurohypophysis. It takes origin largely in the supraoptic and paraventricular nuclei, runs in the ventral wall of the neural stalk (about 10,000 fibres, rat; 60,000, dog and monkey; and 100,000, man) and terminates in probably all three parts of the neurohypophysis—the median eminence, infundibular stem, and infundibular lobe.

Neural Control of the Neurohypophysis

Information regarding the functional relationship between the nervous system and the neurohypophysis has been arrived at in three main ways. Studies have been made of the effects of (*a*) lesions of the supraoptico-hypophysial tract in patients or experimental animals, (*b*) changing the external or internal environment in such a way that the secretion of the gland is increased (indirect stimulation), and (*c*) direct electrical stimulation of the nerve supply of the gland.

(a) Lesions of the Supraoptico-hypophysial Tract

Fisher, Ingram, and Ranson (1938) made an important advance in this field, following the rediscovery of the Horsley–Clarke stereotaxic instrument. This is a precision instrument, originally designed and used by Dr. R. H. Clarke and Sir Victor Horsley (1908) for the accurate placement of small lesions in different parts of the cerebellum. By the use of this instrument Ingram *et al.* made localized lesions in different parts of the hypothalamus. They noted in cats that lesions which bilaterally interrupted the supraoptico-hypophysial tract resulted in a condition similar to that of clinical diabetes insipidus. These lesions were situated in the hypothalamus and far enough from the pituitary gland to be sure that no direct damage to the gland or its blood supply had occurred. The normal urine output of a cat is about 100 ml./day, whilst in some of their animals the polyuria, when established, remained in the region of 500 ml./day indefinitely. The urine output of these animals could be brought down to normal levels by replacement therapy with posterior pituitary extracts. Post-mortem examination of the pituitary region revealed that atrophy of the neurohypophysis had occurred; the median eminence and the infundibular stem and process were shrunken and hypercellular, although the pars intermedia and pars distalis appeared normal. In cases of marked diabetes insipidus there was an almost complete absence of nerve fibres in the neurohypophysis. Extracts of these atrophic glands were tested for their pressor, oxytocic, and antidiuretic activity and found to be practically inactive. These results were confirmed on the monkey, both by placing electrolytic lesions in the supraoptico-hypophysial tract in the hypothalamus, and later by Magoun, Fisher, and Ranson (1939), who exposed the pituitary stalk in this animal by a subtemporal approach and made cuts in the median eminence or infundibular stem. Whereas complete transection of the median eminence, or of its anterior half, resulted in a marked polyuria, transection of the infundibular stem (leaving the median eminence part of the neurohypophysis still normally innervated) produced a less severe polyuria, if any at all. These results are enlightening with regard to the results of Mahoney and Sheehan (1936) on the monkey, and Dandy (1940) on the human, who found no, or only mild, polyuria following section of the pituitary stalk. It is probable that in these and other similar cases the tissues of the median eminence were still liberating antidiuretic hormone into the circulation.

The data regarding secretion of the oxytocic substance by the neurohypophysis following interruption of the supraoptico-hypophysial tracts are not so complete as that regarding the antidiuretic hormone. This subject has been reviewed previously (Harris, 1948c), and the position may be summarized by saying that a large proportion of animals in which the supraoptico-hypophysial tracts have been divided have a prolonged labour or deliver their young dead. Similar clinical reports are to be found in the literature (Marañón, 1947). However, a few animals in which the supraoptico-hypophysial tracts have been interrupted, as shown by a state of diabetes insipidus, have apparently normal labours. The meaning of these results is not clear. It is possible that oxytocic substance is formed elsewhere than the neurohypophysis, or that lack of oxytocic substance may be compensated for by other factors and so result in an apparently normal labour. To test the latter possibility, rats made diabetic by section of the pituitary stalk had either the muscles of the abdominal wall denervated or the nerve supply of the uterus interrupted (Colfer and Harris, unpublished). In some of these animals even these procedures did not prevent normal evacuation of the uterus. (Denervation of the abdominal wall often resulted in the last member of a litter being retained in the vagina, the other members of the litter having been " shunted " into the external world by their next of kin.)

(b) Indirect Stimulation

Verney and his colleagues have investigated the mechanism by which the urine flow is affected following changes in the external or internal environment, such as administration of water, exercise, emotional stimuli (noise and pain), and changes in the osmotic pressure of the blood. All these factors appear to exert their effects on the urine volume by changing the rate of secretion of the antidiuretic hormone. The results of many years' work have been reviewed by Verney (1947, 1948), and these papers should be consulted for a detailed discussion and bibliography. It was found that the inhibiting effect of exercise on a water diuresis is due to the emotional accompaniment of that exercise. Dogs submitted to emotional stimuli alone, in the form of loud noises or cutaneous pain, showed similar inhibition of a water diuresis. Many control experiments showed that the antidiuretic response to emotional stress was not mediated by changes in blood pressure or renal blood flow, but was due to a stimulus humorally conducted to the kidney. Dogs in which the posterior pituitary gland had been removed, or in which the supraoptico-hypophysial tracts had been sectioned, showed that these procedures very largely abolished the emotional inhibition of a water diuresis. Thus there is very good evidence that emotional stimuli result in excitation of the supraoptic nuclei, an increased rate of secretion of the antidiuretic hormone, and therefore an inhibition of any concurrent water diuresis. It is of interest that injection of a small dose of adrenaline just before the emotional stimulus prevented the usual antidiuretic response, probably by blocking some neural path leading to the supraoptic nuclei. Adrenaline did not prevent injected posterior pituitary extract from exerting its usual action. In some cases adrenaline liberated from the animal's own gland also appeared to inhibit the release of the antidiuretic hormone following emotional stress. (There are no data on whether adrenaline exerts a similar neural effect in blocking the liberation of the oxytocic substance. This would seem to be of importance in regard to disturbances of parturition and of milk ejection during nursing.)

Many years ago Verney hypothesized that the ingestion of water is followed by a diuresis owing to the fact that the absorbed water lowers the osmotic pressure of the blood and this in turn inhibits the secretion of the antidiuretic hormone by the neurohypophysis. The result is a state of " physiological diabetes insipidus." Direct evidence that changes in the osmotic pressure of the blood do regulate the secretion of the antidiuretic hormone has since been obtained. Short-period injections and long-period infusions of hypertonic sodium chloride solution into the common carotid artery have been shown to cause release of the antidiuretic hormone, with resultant inhibition of a water diuresis. The response was diminished by some 90% after removal of the neural lobe of the pituitary. The osmotic stimulus activates receptive elements situated somewhere in the vascular bed of the internal carotid artery. It is interesting to speculate that the receptive elements may be situated in the supraoptic nucleus, since this structure is so highly vascular and contains small vesicles which Verney has suggested might function as tiny osmometers. A detailed study of the effects of hypertonic solutions enabled Verney to state : ". . . Changes within the range and of the order of 1% in the osmotic pressure of the arterial blood lead, through the intermediation of the antidiuretic hormone, to changes in the rate of water excretion within the range and of the order of 1,000% : the maintenance of near constancy in the osmotic pressure of the internal environment is thereby achieved."

At least some of the fibres which synapse with the cells of the supraoptic nucleus appear to be cholinergic in nature. Pickford (1939) found that intravenous injection of acetylcholine into dogs inhibited a water diuresis, the response being abolished by removal of the neural lobe of the pituitary gland. It was later found that nicotine had a similar action in the human (Burn, Truelove, and Burn, 1945). Pickford (1947) localized the site of action of acetylcholine more exactly by finding that injection of 0.004 ml. (2–4 μg.) of acetylcholine solution direct into the supraoptic nuclei of dogs resulted in liberation of the antidiuretic hormone. It was then apparent that it was the cells of the supraoptic nucleus, and probably not the cells (if any) upon which the supraoptico-hypophysial tract terminates, that are sensitive to acetylcholine. This is supported by the fact that Feldberg and Vogt (1948) found very low values for the choline acetylase (enzyme system concerned with the formation of acetylcholine) content of the neurohypophysis. Recently Duke, Pickford, and Watt (1950) have been able to produce a reversible state of diabetes insipidus by injection of di-isopropyl fluorophosphate (D.F.P.), an inhibitor of cholinesterase, direct into the supraoptic nuclei of dogs. This procedure resulted in, first, a profound inhibition of urine flow, followed by a polyuria of 4–19 days' duration, and then return of the urine volume to normal values. It would seem, then, that the cells of the supraoptic nucleus are under the control of at least some cholinergic afferent fibres, but that the fibres of the supraoptico-hypophysial tract are not cholinergic in nature.

(c) Direct Electrical Stimulation of the Supraoptico-hypophysial Tract

Until a few years ago electrical stimulation of the supraoptico-hypophysial nerve fibres, in order to study the effects of exciting the secretion of the neurohypophysis, was a difficult undertaking. Attempts were made (such as those of Haterius, 1940 ; Ferguson, 1941 ; Haterius and Ferguson, 1938), but the fact that anaesthesia itself affects the rate of urine secretion, the level of blood sugar, and so on, made stringent control procedures necessary before any conclusions cou'd be drawn from such experiments. The technical problems were much simplified, however, when it became possible to stimulate the basal regions of the brain, without anaesthesia, by using the remote control method. In a preliminary operation a small coil was buried between the scalp and skull and an insulated electrode, soldered to one end of this coil, carried down through the skull, corpus callosum, and other midline structures into some part of the hypothalamus or pituitary gland. After recovery from the operation the tissue surrounding the electrode tip could be stimulated by holding a primary coil carrying an alternating current over the animal's head, so that the embedded (secondary) coil was situated in an electromagnetic field. The strength of the stimulus varies inversely as the distance between the two coils, and is thus easily measured and adjusted.

Stimulation of the supraoptico-hypophysial tract by this method has been shown to result in liberation of the antidiuretic hormone and an oxytocic substance, with the following effects on the animal—inhibition of a water diuresis ; an increase in the relative, and sometimes absolute, urinary chloride ; a marked increase in uterine activity in the oestrous or oestrogenized rabbit, but no increase in the pseudopregnant animal or animal treated with progesterone ; an increase in intestinal activity and the appearance of an antidiuretic substance in the urine (Harris, 1947, 1948a, 1948b). Only slight rises in blood pressure were observed after stimulation, but these were of the same type as those following injection of posterior pituitary extract. No hyperglycaemic responses were obtained by stimulating the supraoptico-hypophysial tract or by stimulating different regions of the pituitary gland, though such a response had been claimed by previous workers using anaesthetized animals.

It is of interest that the oestrous rabbit possesses a mechanism (including the supraoptico-hypophysial tract, neurohypophysis, and oxytocic secretion) for increasing the activity of the empty oestrous uterus. Teleologically, there would appear to be no reason for such a mechanism to exist, except the possibility that it might be involved in sperm transport. Parker (1931) found the rate of entry of sperms into the rabbit's uterus too rapid to be accounted for by the rate of swimming of the sperms, and he quotes from an early paper by Heape (1898) in which it was suggested that sperms are drawn into the uterus of the rabbit by a sucking action of the uterus. Heape observed that this uterine activity was induced by stimulating the erectile tissue of the vulva. Krehbiel and Carstens (1939) have confirmed these observations. They found spermatozoa arrive at the utero-tubal junction of rabbits in as short a time as ten minutes after coitus, and, by *x*-ray studies, that various solutions placed in the vagina are carried to the tubal ends of the uterus in two to five minutes if the vulva is artificially stimulated. It seems clear, then, that the ascent of sperm is aided by the motility of the uterus, and that this motility is initiated or increased by vulval stimulation. Since coitus in the rabbit undoubtedly stimulates the adenohypophysis by a nervous reflex, it seems likely that the neurohypophysis may be stimulated by a similar reflex with a resultant oxytocic secretion and increased uterine motility. Since coitus in the rabbit does not result in the release of the antidiuretic hormone (Cross, 1950), then, if the above hypothesis is correct, it would seem that this stimulus causes the release of the oxytocic fraction from the neurohypophysis but not the antidiuretic (pressor) fraction.

In recent years attention has been turned to the relationship between the neurohypophysis and lactation. The process of lactation may be divided into two main phases (Folley, 1947)—first, milk secretion by the cells of the alveolar epithelium, and, secondly, milk discharge or withdrawal from the mammary glands by the suckling young. The first phase of milk secretion is clearly related to the function of the adenohypophysis. It has been suggested by Petersen (see Petersen, 1944) that normal milk discharge is dependent on the neurohypophysis. Petersen suggests that the sensory stimulation of the nipples by the young evokes a nervous reflex in the mother which excites the neurohypophysis to secrete oxytocin. This in turn causes contraction of some muscular element in the breast giving the "let-down" or "draught"—i.e., the milk is positively expressed to the young by the mother. Until recently the evidence in favour of this view was of an indirect nature. Ely and Petersen (1941) showed that after cutting the motor nerves to one half of the udder of cows oxytocin excited, and adrenaline or fright inhibited, the "let-down" in the two halves of the udder alike. Petersen and Ludwick (1942) adduced evidence for the hormonal nature of the stimulus to "let-down" by showing that "let-down" in a perfused udder was excited by adding to the perfusing fluid blood taken from a cow in which "let-down" had been stimulated, but not by adding blood from an unstimulated cow.

A more direct attack on the problem has been undertaken by Cross and Harris (1950) in Cambridge, and Andersson (1951) in Stockholm, the results of these two independent researches being in good accord. Cross and Harris, working on lactating rabbits, found that electrical stimulation of the supraoptico-hypophysial tract under ether anaesthesia resulted in flow of milk up a glass cannula tied into one teat duct. The response was recorded on a kymograph, and was found to have all the characters of one humorally transmitted—long latency, 20–30 seconds, slow rise to peak, and slow subsidence (several minutes). When the stimulation of the supraoptico-hypophysial tract lasted only 15 seconds the response did not start until after the end of stimulation. These responses were similar to those produced by injection of 50–200 mU. oxytocin ("pitocin," Parke, Davis and Co.). Previous cauterization of the supraoptico-hypophysial tract in the median eminence or infundibular stem (Cross and Harris, 1951) abolished this response to stimulation, and also abolished "let-down," so that, despite vigorous suckling on the part of the young, they were unable to obtain more than a fraction of the milk present in the maternal mammary glands. If the mother in which such a lesion had been placed received an injection of oxytocin immediately before suckling, then the milk yield approximated to that obtained before placement of the lesion.

Confirmation of this latter observation has been noted by Harris and Jacobsohn (1951) incidentally in the course of another investigation. Hypophysectomized rats were grafted with anterior pituitary tissue. The grafted tissue was placed under the median eminence in a site where functional activity returns to the graft (this work is described in more detail below). These animals then lacked the greater part of the neurohypophysis but had apparently normal anterior pituitary function. Some of these animals were mated, had normal pregnancies, and delivered living young. In only one out of eight rats that delivered living litters was the litter reared normally. In the other cases milk secretion occurred, but a failure of milk withdrawal resulted in starvation of the vigorously suckling young. It was observed very clearly, however, that if an injection of oxytocin was made into the mother prompt withdrawal of milk by the young resulted. Repeated injections of oxytocin (three times daily) enabled the litter to be reared. The independent researches of Andersson (1951) were made on sheep and goats using the Hess technique of implanted electrodes to stimulate the hypothalamus in conscious animals. Andersson found that stimulation of some regions in the anterior hypothalamus, in the vicinity of the supraoptic nuclei, induced milk ejection from cannulated teats. The response, recorded by an electrical drop recorder and kymograph, was unaffected by denervation of one half of the udder or by completely anaesthetizing the sacral region of the goat.

It would seem likely, then, that the neurohypophysis is concerned in the process of milk withdrawal by the young. Stimulation of the nipples by suckling appears to excite a reflex nervous release of oxytocin, and so contraction of the myo-epithelial cells (Richardson, 1949) around the mammary alveoli and ducts. It is not yet beyond doubt that oxytocin is alone involved as the humoral stimulus to milk withdrawal. However, if this is so, and the above results are confirmed, then the oxytocic *substance* will have been raised to the status of an oxytocic *hormone*.

It would be of interest to know whether cases of lactational failure in the human, in which the failure is one of disturbed milk withdrawal, would benefit by an injection of oxytocin just before nursing. The work of Newton and Newton (1948) would suggest that this is so. The dose required in the human would probably be in the order of $\frac{1}{2}$ to 1 unit of oxytocin. The results given above throw light on the old clinical observation that breast-feeding aids uterine involution in the post-parturient woman, and would also help to explain the observation of Gunther (1948), who noted an expulsion of milk from the breasts (of a lactating woman) with each labour pain.

Nature of the Secretion of the Neurohypophysis

A biochemical analysis of the active substance(s) present in an endocrine gland at any one moment throws little light on the way in which these substances are liberated into the blood stream. A major advance in the field of endocrinology will be made when it is found possible to assay the hormone content of venous blood draining particular endocrine glands. In lieu of blood analyses, the most promising approach to the question of what substance(s) an endocrine gland secretes is the observation of the effects of the secretion on the animal itself. In this respect it may be important that there is now available another simple and quick reaction (milk-ejection) by which the secretory activity of the neurohypophysis can be judged. For many years it has been debated whether the neurohypophysis liberates into the blood one hormone with multiple activities or two distinct hormones—one with pressor (and antidiuretic) activity, and the other with oxytocic activity. On the assumption, as seems likely, that it is the oxytocic fraction which is concerned with milk ejection, the following results are of interest with regard to the substance(s) secreted by the neurohypophysis. Cross (1950) has observed that if hydrated rabbits are allowed to suckle their young there is a slight inhibition of a water diuresis, which may be mimicked by injection of 0.5–1 mU. of antidiuretic hormone. Since the oxytocic secretion excited by suckling in the rabbit appears to be of the order of 50–200 mU. there would seem to be a quantitative dissociation between the secretion of the antidiuretic hormone and the oxytocic factor under these conditions. This would indicate the secretion by the neurohypophysis of more than one substance. On the other hand, the observation of Andersson (1951) that intracarotid injection of hypertonic sodium chloride solution, known to cause the liberation of the antidiuretic hormone (Verney, 1947), is effective in producing milk ejection in the goat would tend to link together the secretion of the substances underlying these activities. The conclusions drawn from these results of Cross and of Andersson are discordant, but their work is mentioned here to illustrate the belief that there is now available an important technique by which this problem may be approached.

Conclusions

Present views with regard to nervous control of the neurohypophysis may be summarized as follows. The glandular tissue of the neurohypophysis, which exists in the infundibular lobe, infundibular stem, and median eminence of the tuber cinereum, is richly innervated by the supraoptico-hypophysial tract of nerve fibres. If this tract is interrupted secretory activity of the neurohypophysis ceases, the gland atrophies, and a state of diabetes insipidus supervenes. In many cases denervation of the neurohypophysis is also followed by dystocia.

Excitation of the gland with release of the antidiuretic hormone follows emotional stress in the normal animal and the intracarotid injection of hypertonic sodium chloride solution; both responses are mediated by the supraoptico-hypophysial tract. Some, at least, of the afferent nervous pathways to the supraoptic nuclei are cholinergic in nature.

Electrical stimulation of the supraoptico-hypophysial tract causes liberation of the antidiuretic and oxytocic substance(s) into the blood, with the following results—inhibition of a water diuresis; increase in the relative, and sometimes absolute, urinary chloride; a marked increase in uterine activity in the oestrous or oestrogenized rabbit, but no increase in the pseudopregnant animal or animal treated with progesterone; an increase in intestinal activity; the appearance of an antidiuretic substance in the urine; and the ejection of milk from the cannulated lactiferous duct of a lactating mammary gland.

It is possible that reflex stimulation of the neurohypophysis follows coitus, and that the resultant increased uterine activity is one factor in the transport of sperm in the female genital tract.

Much evidence now exists that the transfer of milk from a lactating animal to her young is effected by a nervous reflex excitation of the neurohypophysis. The secretion of posterior pituitary hormone causes contraction of some element in the mammary gland and thus a positive ejection of milk from the mother to her suckling young. This milk-ejection response appears to be a function of the oxytocic substance of the neurohypophysis, and the reaction seems to offer a new technique by which the problem of the number of hormones liberated from the neurohypophysis into the blood may be investigated.

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The British European Airways ambulance flight at Renfrew airport (Glasgow) is the subject of a recent article in *John Bull.* It consists of two pilots and two radio-operators, forming two crews who alternate for 24-hour spells of duty. They fly old De Havilland Rapides with a normal cruising speed of 120 m.p.h. to Campbeltown or any of the service airports in the Hebrides, and (in daylight only) to any of 10 emergency landing strips in Highlands, Hebrides, or Orkneys. During 1950 they made 200 trips to carry cases of nephritis, poliomyelitis, fractures, acute appendicitis, and so on, and, since the air ambulance costs at least £16 a flying hour, it is called out only for real need. The aircraft are those used on the regular passenger service: four seats are taken out and replaced by a cradle to hold a stretcher.

CORTISONE AND A.C.T.H. IN HYPOPITUITARISM

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The isolation of A.C.T.H. has provided a method of replacing the pituitary secretion which influences the adrenal cortex ; cortisone provides a method of direct replacement of some of the adrenal cortical hormones. The natural practical application of these two products would therefore be the treatment of adrenal cortical deficiency, either primary, as in Addison's disease, or secondary, as in hypopituitarism. The early discovery that these two hormones have a wide range of other effects led, however, to their being diverted to the treatment of other diseases, and relatively few investigations have been made to assess their value in the treatment of hypopituitarism.

In the literature there are five reports on the treatment of true cases of hypopituitarism with A.C.T.H. The periods of treatment were usually about 6 to 10 days. There was nearly always some clinical improvement during the therapy, but the biochemical effects appear to have been rather variable. Pompen (1950) noted an increase in 17-ketosteroid excretion in the urine and also of oestrogenic substances, but not of corticosteroids. Knowlton *et al.* (1950) observed a slight increase in 17-ketosteroid excretion to 2.6 mg. a day, but no corresponding increase of oestrogen excretion. Bartter *et al.* (1950) treated three patients with A.C.T.H. ; all showed a rise in urinary corticosteroid excretion, but only one had an increase of 17-ketosteroid excretion. Seffer, Lestina, and Freeman (1950) observed an increase of 17-ketosteroid excretion.

The nitrogen and electrolyte balance was studied by Bartter *et al.*, who observed some retention of sodium and chlorine, with a loss of nitrogen and calcium and a transient loss of potassium. Knowlton *et al.* also observed the retention of sodium and chlorine, but no alteration in the metabolism of calcium or nitrogen, apart from some increase in the excretion of uric acid.

Schrock, Sheets, and Bean (1951) treated a patient who had a combination of rheumatoid arthritis and hypopituitarism with A.C.T.H. and also with cortisone. Unfortunately this patient was also given testosterone at the same time, so that it is difficult to evaluate the effects of the first two hormones. During the treatment with cortisone signs of myxoedema occurred. The case of "pituitary cachexia" treated with corticotrophic hormone by Hemphill and Reiss (1944) cannot be accepted as a true example of hypopituitarism ; there was nothing to suggest that any structural changes had occurred in the pituitary.

Present Cases

Five patients have been treated in the present study. All were typical cases of hypopituitarism due to post-partum necrosis of the anterior lobe (Sheehan and Summers, 1949). The symptoms and signs were of a severe degree of pituitary deficiency, with permanent