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# A REVIEW OF NEUROENDOCRINOLOGY, 1966-67†

This review covers the literature in neuroendocrinology published during 1966 and 1967. A selected group of papers have been analyzed which, in the author's opinion, have contributed significantly to the field of neuroendocrinology during the past two years. This review is not intended to be a complete summary of the literature and the author assumes full responsibility both for the particular selections and for any omissions. Interest in neuroendocrinology has continued to grow and a number of excellent reviews have appeared during 1966 and 1967.[25,49,139,151,234]

## HYPOTHALAMIC-PITUITARY MORPHOLOGICAL RELATIONSHIPS

A technique has been described that permits examination of the rat hypothalamus and pituitary gland with the light microscope by using histological sections fixed in an osmium tetroxide solution. With this procedure further staining was unnecessary and the histology of the neurohypophysis was viewed with remarkable clarity. A possible neuro-endocrine role of the pituicytes was suggested by the authors.[260] The ultrastructure of the neurovascular link between the hypothalamus and anterior pituitary gland was studied in rats[8,313] and it was observed that many unmyelinated nerve fibers terminated on the capillaries of the hypophysial portal vessels in the median eminence. These nerve endings contain mitochondria and many vesicular or granular inclusions and provide the morphological basis for the concept of a neurohumoral control of the anterior pituitary gland. Holmes[160] studied the vascular patterns in the mammalian median eminence and found that the patterns in primates were much more complicated than in lower mammals. In the rhesus monkey, for example, five different types of vascular formations were observed. The presence of a muscular arteriole in some of the large complexes suggests that a measure of control of the blood flowing through these capillary beds is possible.

Adams, Daniel, and Prichard[3] carried out extensive investigations of the vascular arrangements of the pituitary gland in man, monkey, sheep, goat,

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and rat. It was found that in all these species the pars distalis derives its sole blood supply from the hypophysial portal vessels of which there are two main groups, the long portal vessels which run down the stalk and supply the greater part of the pars distalis and the short portal vessels which are situated at a lower level than the long ones and supply a relatively small area along the dorsal border of the lobe. It is suggested that specific cells of the hypothalamic nuclei are linked with specific areas of the anterior pituitary gland by the portal vessels so that an individual portal vessel can convey blood containing neurohumors derived from a specific group of hypothalamic cells to an area of the anterior pituitary that is especially rich in certain types of epithelial cells. Such a system would permit a more precise control by the hypothalamus of the output of individual anterior lobe hormones.[5] These authors carried out additional studies of the changes in the volume of the pituitary glands of adult female goats several weeks after pituitary stalk section. They observed a marked shrinkage of the volume of the pituitary gland following this procedure. This shrinkage was due largely to contraction of the scar which replaced the original massive infarct as well as to shrinkage of the surviving parenchymal cells.[4]

Morphological evidence indicates a basic difference between the perivascular structures in the neurosecretory nuclei and the other parts of the brain. For example, in the supraoptic nucleus the proximity between the blood vessels and the ganglion cells is striking and this relationship correlates well with its presumed physiological function.[222] Leveque and his colleagues[213] have shown that the ependymal cells of the supraoptic or prechiasmatic recess in the rat and mouse can be characterized by their affinity for periodic acid Schiff when viewed under light microscopy. The morphological characteristics of these structures suggests a glandular function and their location and synthetic activity implicates them in the control of gonadotrophic hormone from the pars distalis of the pituitary gland. Electron microscopic and fluorescence microscopic observations of the tuberal hypophysial tract show that the dense granulated vesicles in this region are the carriers of catecholamines.[328] Reserpine, which is a known releaser of catecholamines, caused a reduction in the number of small granules in the median eminence.[336]

In an electron microscopic study of the anterior pituitary gland,[205] it was concluded that the corticotroph is a unique cell type which differs from both the gonadotroph and thyrotroph since minimal changes were observed after gonadectomy or thyroidectomy. Other indices such as P32 uptake have been used to measure anterior pituitary activity. Total anterior pituitary P32 uptake was found to parallel TSH secretion and gonadotrophin

secretion whereas it was unaffected by changes in ACTH secretion.[382] Another parameter of anterior pituitary activity is the measure of RNA synthesis in explants of rat anterior pituitary tissue in vitro. Continued RNA synthesis was observed in the pituitary organ culture systems and interestingly enough, the rate of incorporation of tritiated uridine into RNA was not increased above control levels in glands exposed to hypothalamic extracts in vivo or in vitro.[161] Dehydration stimulated protein synthesis by the neurons of the supraoptic nucleus and a significant portion of this newly synthesized protein appeared to be structural in nature.[270] The uptake of radioactive rubidium by tissues of the body is proportional to processes that govern transcapillary transfer and include factors such as blood flow, capillary surface area, capillary pressure and metabolic activity of the tissue in general. The uptake of radioactive rubidium was profoundly influenced by stimulation of the posterior hypothalamus and mesencephalic reticular formation suggesting that powerful neural mechanisms modify those local factors that influence the uptake of rubidium-86 by many tissues throughout the body.[90]

Levels of 5-hydroxytryptamine (serotonin) were determined in the brain, the eye, and the whole embryo of the toad in an attempt to find specific events and structures that are related to 5-HT synthesis during various periods of embryonic development. Certain events, associated with the first spontaneous movements, were found to be periods of significant change in the synthesis of 5-hydroxytryptamine.[26] In the rat, the 5-hydroxytryptamine concentrations in the pineal organ, hypothalamus, sensori-motor cortex, and mesencephalon did not change after five days of treatment with cortisol or following adrenalectomy. It was concluded that changes in glucocorticoid levels do not appear to alter brain and pineal 5-HT concentrations and therefore 5-HT probably does not play a role in glucocorticoid influences on brain function.[343] Other studies have shown that unilateral section of the medial forebrain bundle in the lateral hypothalamus of the rat results in a decrease in the serotonin and nor-epinephrine content of the brain-half ipsilateral to the lesion. These changes first appear on the second to third postoperative day and appear to be related to degenerating axons from the medial forebrain bundle.[261] Metabolic changes in the hypothalamus and pituitary result from changes in body temperature;[345] changes in sensitivity to electric shock are observed after ventromedial hypothalamic lesions[272] and pituitary hormones from tumors exert profound effects on the hormone content of the host pituitary gland.[237]

Palka, Ramirez, and Sawyer[276] studied the distribution of tritiated estradiol after is implantation in the hypothalamo-hypophysial region of female rats. The distribution of radioactivity within the brain and other

tissues was determined by autoradiography and liquid scintillation counting. In rats with median eminence implants, measurable amounts of radioactivity could be counted as far as 2 mm. from the implant site in the brain, trace amounts were detected in plasma and in the uterus, and significant amounts of radioactivity were counted in the anterior pituitary gland. This is the first study which clearly demonstrates that central hypothalamic implants can be carried systemically to affect distant regions. Therefore the studies of other investigators on the local effects of hormone implants in the brain are subject to some question. It appears that estrogen exerts separate actions on the cells of the pituitary and median eminence. Estrogen stimulates the release of LH by a central action on the median eminence but induces pituitary hypertrophy by a direct action on the hypophysial cells to which it is carried by the hypothalamo-hypophysial portal system. The effects of hormones on the EEG and firing rates of hypothalamic units were investigated. Progesterone exerted generalized effects on EEG and unit firing rates whereas luteinizing hormone exerted more specific effects on basal hypothalamic neurone firing rates which were independent of EEG changes thereby suggesting that luteinizing hormone may act as an internal negative feedback agent on the hypothalamic neurones which control pituitary LH secretion.[296] Unit activity was recorded in unanesthetized animals with diencephalic islands and it was observed that a major difference from intact brain was the absence of rhythmic bursts in thalamic units normally seen in association with a synchronized EEG.[65] The electrical activity recorded from the pituitary stalk has been correlated with the reflex discharge of antidiuretic hormone (ADH) and oxytocin and it has been demonstrated that these impulses originate in the supraoptic and paraventricular nuclei.[164] Morphological, electrophysiological and metabolic manifestations of hypothalamic function have been investigated in such diverse species as rat,[221] mouse,[301] monkey,[316] oppossum,[396] and fish.[325] Additional evidence for an internal feedback from the adenohyphysis to the hypothalamus was provided by observation of changes in nucleolar size following the administration of pituitary trophic hormones. Female rats were hypophysectomized and with the appropriate target endocrine glands removed, were treated separately with ACTH, LH, FSH, and TSH. Since previous experiments had shown that endocrine gland extirpations resulted in an increase in nucleolar size presumably because of the release of the hypothalamus from negative feedback, an attempt was made to determine whether or not the adenohypophysial hormones produced smaller nucleoli in comparison with untreated control animals. Statistically significant differences were observed in animals treated with ACTH, LH or FSH. However, no changes were observed in those animals treated with TSH. These findings

lend support to the internal feedback hypothesis for it would appear that hypothalamic neurones show morphological changes in response to changing levels of the adenohypophysial hormones.[162] Selye, *et al.*[342] have shown that the intravenous injection of lead acetate combined with the subcutaneous administration of histamine produces a neurotropic form of calcergy with extensive calcium deposition throughout the autonomic nervous system of the rat. These changes can be totally inhibited by pretreatment with an adrenergic blocking agent.

ACTH-ADRENAL

Six hormones are produced in the mammalian adenohypophysis but there has been considerable difficulty in relating the production of each of these hormones to a specific cell type. In particular, the cellular site of production of ACTH remains somewhat obscure. By means of autoradiography and differential staining the chromophobe cells of the anterior pituitary were implicated in the synthesis of ACTH.[191] Under conditions of stress ACTH may be released for extended periods of time independently of new hormone synthesis.[100] These studies were carried out in puromycin-treated animals in which the incorporation of $C^{14}$ valine into the pituitary gland was studied. Although the pituitary content of ACTH was much lower in the puromycin-treated animals, indicating decreased synthesis of ACTH, nevertheless the rate of corticosterone secretion was the same in treated and non-treated animals, indicating continued release of ACTH. Dasgupta and coworkers[70] continued to report on the presence of precorticotrophin in the hypophyses of various mammalian species. Precorticotrophin, which is biologically inactive, is present in the mammalian hypophysis and at least 80 per cent of the corticotrophic activity of the pituitary gland exists in this form. After treatment with acid, precorticotrophin is converted to corticotrophin which is biologically active.[69] An extra adrenal effect of corticotrophin has been reported wherein it altered ovarian blood flow both in the normal and in the adrenalectomized dog and cat without affecting systemic blood pressure.[360] It has often been observed that whenever the pituitary is acutely stimulated by stress to secrete ACTH it simultaneously stops secreting TSH. Recent evidence[92] indicated that the inhibition of TSH secretion in response to stress is a coincidence rather than a consequence of ACTH release.

The circadian rhythm of adrenocortical function did not alter the stress-induced increments in corticosterone levels.[309] Rats were subjected to novelty stimulation, electric shock, or ACTH administration at both the peak and trough of the adrenocortical diurnal cycle. It was observed that exposure to a new environment or novelty contributed significantly to the adreno-

cortical response which was often attributed entirely to the effect of noxious or painful stimulation.[123] Repeated stimulation of the pituitary-adrenal system results in a tachyphylaxis to ACTH if the stimulation of the adrenal gland is frequent. Under these conditions the release of steroids from the adrenal gland was impaired although the adrenal was still capable of synthesizing steroids.[171]

The action by which a number of different agents release ACTH has been investigated. Formalin, for example, appears to have a local action which is then transmitted via ascending nerve pathways to the spinal cord to activate the pituitary adrenal system.[230] When the rise in blood pressure which is usually produced by $\alpha$-ethyltryptamine is prevented by hemorrhage, no inhibition of ACTH secretion was observed in surgically stressed dogs. These results suggest that it is the rise in blood pressure which is produced by $\alpha$-ethyltryptamine that causes the inhibition of ACTH secretion.[125] Vasopressin induces steroidogenesis in man by an action which is due to ACTH secretion.[141] Pituitary adrenal activation in rats with hereditary hypothalamic diabetes insipidus was essentially normal so that it appears that vasopressin is not the physiological corticotrophin releasing factor (CRF) in the rat.[17] The pituitary adrenal response to acute stress was found to be impaired in animals with alloxan diabetes. It was concluded that the metabolic stress of diabetes resembles other chronic stressors which impair the secretory mechanism at the hypothalamo-hypophysial level.[197] The sympathetic nervous system is essential for the maintenance of body temperature of cold-exposed rats[228] and chemical sympathectomy or total adrenalectomy produced the same effects in these animals. The effects of adrenalectomy were attributed to a breakdown of sympathetic response at end organs due to the steroid deficiency. The glucocorticoids restored responsiveness to catecholamine administration, suggesting that the adrenalectomized rat may be considered a functionally sympathectomized animal because of impaired responsiveness of effector systems that normally are activated by sympathetic function.[229] Studies of the maturation of the hypothalamic pituitary adrenocortical system were carried out in rats[11] and it was observed that the animals responded to ether stress or to the administration of ACTH with increased plasma corticosterone concentration two weeks before diurnal variation in plasma corticosterone appeared. These data suggest that maturation of the central nervous system's ability to regulate rhythmic ACTH secretion is delayed well beyond the time when the pituitary is capable of secreting ACTH and the adrenal cortex is capable of secreting corticosterone.

Rats were subjected to stress during the trough or peak of the circadian rhythm in order to study the effects of the circadian rhythm on adrenocorti-

cal function.[399] The same increments in corticosterone were produced when the stress was applied at different times of the day during the diurnal cycle. It was concluded that the acute pituitary adrenal responses are not altered by marked diurnal variation in the plasma corticosterone levels. It was also found that intracerebral dexamethasone implantation preferentially suppressed circadian rather than the stress-induced ACTH release. These studies further implicated the brain, especially the hypothalamus, as the site of steroid feedback action.[400] Other studies of the diurnal rhythm of corticosterone secretion indicate that the concentration of corticosterone correlates directly with the length of light exposure.[339] The chronic administration of a number of central nervous system acting drugs did not influence the circadian rhythm in normal subjects.[198] Other reports indicate that there appears to be a diurnal variation in plasma glucocorticoid levels in the horse.[401]

Studies were carried out on the effect of ether and pentobarbital anesthesia on pituitary adrenal function in the dog.[95] Ether and pentobarbital anesthesia did not modify the ability of the pituitary and adrenal to secrete their respective hormones following stimulation by operative trauma. Ether was an extremely potent but variable stimulus to pituitary adrenocortical secretion. The stimulating effect of ether was markedly altered by the simultaneous administration of a barbiturate. Morphine evoked increased ACTH secretion only in doses that also sedated the animals, and repeated doses of morphine caused a depletion of pituitary ACTH that was sufficient to reduce the magnitude of response on subsequent exposure of the animals to cold stress.[275] A similar effect was observed following chlorpromazine administration but it is believed that the mesencephalic reticular formation plays a role in the action of chlorpromazine.[87] Reserpine is another drug that has a profound effect on brain stores of some neurotransmitter substances. This drug not only depletes serotonin and catecholamine stores in the central nervous system but it is also capable of inducing a long-lasting ACTH hypersecretion. By means of reserpine implants into the hypothalamus of rats, serotonin and catecholamines were depleted in this region. Nevertheless, the pituitary-adrenal response to stimuli for ACTH release was not impaired and it was concluded that monamines in the hypothalamus are probably not involved in the control of pituitary ACTH secretion.[355,111] Other investigators[188] have shown that reserpine counteracts the depressant effect of dexamethasone on adrenal weight and function. They interpret these results to indicate that the main effect of reserpine on the hypophysial adrenal axis is that of enhancing rather than depressing ACTH secretion and that the blocking action of reserpine is due to the effects of the enhanced blood levels of adrenal steroids which are

induced by the drug. Other drugs, such as α-ethyltryptamine inhibit stress-induced secretions of ACTH and it appears that this action is correlated with its pressor activity.[225]

Attempts have been made to determine the sites at which estrogen acts to produce increased plasma and adrenal corticosterone levels in female rats.[311] Estrogen implants into the arcuate nucleus, lateral mammillary area, and the anterior pituitary gland resulted in increases in plasma corticosterone levels whereas implants into other hypothalamic sites in and near the ventromedial nucleus, medial forebrain bundle, and medial mammillary area did not induce a rise in plasma corticosterone. The former sites respond to estrogen treatment by facilitating pituitary adrenal activity in the absence of detectable systemic action of estradiol. Similar experiments by other investigators[41] showed that implantation of thyroxine in different parts of the hypothalamus led to an enhancement of adrenal function when these implants were located in mid-posterior median eminence or in the posterior part of the arcuate nucleus. Implants in other hypothalamic areas or in the anterior pituitary did not change the corticosterone output of the adrenals. These investigators virtually exclude the possibility that thyroxine acts directly on the anterior pituitary tissue in the activation of ACTH release but instead propose a central nervous system action of thyroxine on the increased release of ACTH. Studies of the effects of conditioning on stress responses indicate that the reported differences in resting levels of plasma corticosterone in rats housed under different group conditions is not reflected in the response of such animals to stress.[322] It has been reported that the administration of ACTH completely blocked the conditioned avoidance reflex.[192] Further experiments along these lines[80,135] showed that the effect of ACTH, which results in a delay of extinction in the conditioned avoidance of the rat, is located in the N-terminal part of the peptide, presumably within the first ten amino acids.

The neural connections of the medial basal hypothalamus were partially or totally interrupted and the functional capacity of this neurally isolated region to regulate pituitary adrenal activity was investigated.[146] The diurnal rhythm in ACTH secretion was not evident after complete deafferentation of the medial basal hypothalamus whereas it was still intact after interruption of only the lateral, dorsal or posterior connections to the hypothalamus. In contrast, transection of only the anterior pathways disrupted the normal circadian rhythm of ACTH secretion. Therefore the anterior pathways appear to be essential for the maintenance of normal diurnal ACTH secretion. Despite complete deafferentation of the medial basal hypothalamus, elevated corticosterone levels in response to stress were nevertheless pos-

sible. The pituitary ACTH content was elevated in those rats with total interruption of neural afferents to the medial basal hypothalamus.[147]

The functional capacity of ectopic pituitary transplants has been somewhat clarified by the work from several different laboratories.[129,186,188,292] By increasing the number of pituitary transplants in hypophysectomized rats, maintenance of target organs and continued secretion of the transplants were demonstrated despite the separation of the pituitaries from the immediate environment of the hypothalamus. Ten heterotopic pituitary transplants maintained nearly normal adrenal weight and these animals showed corticosterone levels which were significantly higher than those observed in hypophysectomized controls. Continued secretion of ACTH from these pituitary transplants depended upon the presence of the subcortical portion of the forebrain.[188] A delayed release of ACTH was observed in animals with ectopic pituitary transplants. This delay was ascribed to an accumulation of a physiological corticotrophin releasing factor (CRF) in the peripheral circulation which subsequently stimulated the release of ACTH from the graft.[292] It has been shown that in rats with chronic hypothalamic lesions basal ACTH secretion is appreciable and can be further enhanced by severe hyperthyroidism.[66] It was postulated that this effect is accomplished through an extra hypothalamic route involving a humoral metabolic pathway since these animals did not release ACTH in response to stress or in response to electrical stimulation of the anterior hypothalamus. Hypothalamic lesions induced morphologic and functional deficits in pituitary target gland systems long after damage to the hypophysial portal vessels was ameliorated. Lesions directly in the pituitary stalk produced a triphasic disturbance in water metabolism. A short lasting polyuria was followed by an oliguric period of three days duration which then merged into a manifest diabetes insipidus. The activity of the pituitary adrenal system during the three phases of the diabetes insipidus remained at a constant basal level and the system was unresponsive to noxious stimuli. These effects were believed to be the result of damage to the portal vessel system.[209] However, when pituitary stalk section was carried out in dogs and an aluminum foil was inserted across the site of the transection to prevent portal vessel regeneration, the pituitary adrenal response to stress and nerve stimulation was observed for intervals up to five weeks after division of the stalk. These ACTH secretory responses observed in stalk sectioned animals could have been due to corticotrophin releasing factors that were produced in the hypothalamus and reached the pituitary through the systemic circulation.[403] Differential responses to histamine and adrenocortical deprivation were observed in animals with lesions either in the posterior hypothalamus or in the anterior hypothalamus. A functional dichotomy of the hypothal-

amus concerning the regulatory mechanism of ACTH secretion was therefore proposed.[179] Estrogen appears to alter the adrenal gland response in animals with mesencephalic lesions.[304] In the guinea pig the anterior and middle hypothalamus appears to be critical for the control of ACTH secretion[32-3] whereas in the cockerel the ventrotuberal area of the hypothalamus was shown to regulate pituitary ACTH secretion.[121] Facilitatory as well as inhibitory regions have been demonstrated in the diencephalon, midbrain and limbic system with regard to the secretion of ACTH.[97,249,358,374] Evidence has been obtained in the monkey for a negative feedback effect of injected hydrocortisone on the 17-hydroxycorticosteroid response to amygdaloid stimulation but not to hypothalamic stimulation. These results suggest the presence of a neural mechanism for negative feedback located functionally between the amygdala and the hypothalamus of the monkey.[241-2]

Low steroid levels augment the release of ACTH during stress[308] and conversely the release of ACTH in response to stress can be prevented by large doses of corticosteroids. It has been assumed that the degree of impairment is directly proportional to the blood level of corticoids. The relation between plasma corticosteroid concentration and the inhibition of corticotrophin release was investigated in the rat and it was found that corticotrophin release in response to stress was not inhibited when the plasma corticosterone concentrations were highest.[158] On the other hand, release of ACTH was completely or partially impaired when the plasma corticosterone concentrations returned to resting levels. These results imply that the release of corticotrophin during stress is regulated by factors other than the total corticosterone concentration in the blood. A mathematical relationship was evolved between the plasma corticosterone response to a given stress, the dose of dexamethasone, and the duration of administration.[88] Other factors such as the binding of corticosteroids by plasma proteins seemed to interfere with the feedback inhibition of adrenocorticotrophin by corticosterone.[185,189] The intravenous administration of unbound corticosterone within one minute before the injection of histamine impaired the release of ACTH which was ordinarily provoked by the histamine. However, if the corticosterone was injected in the presence of corticosterone-binding proteins of plasma, the steroid failed to impair ACTH release following the histamine injection.[189] In studies of the feedback mechanisms that regulate pituitary ACTH secretion in rats bearing pituitary tumors, it was found that inhibition of ACTH secretion by maximal endogenous levels of blood corticoids is rather slow to develop. Furthermore, when high levels of blood corticoids persisted for a considerable length of time, the response to stress was not completely prevented.[361] Contrary to previous reports, it was found that norethandrolone was of no

value in overcoming cortisone-induced depression of pituitary ACTH release.[190] A new method of testing steroid-induced corticotrophin suppression was described[235] as well as a quantitative assay of corticosteroid depression in man.[154] An interesting but as yet unconfirmed report[396] states that small doses of corticosterone apparently stimulated ACTH secretion whereas higher doses were less effective or inhibitory. The site of corticoid action was presumably the anterior pituitary gland.[395] These conclusions are not supported by other investigators who feel that receptor sites for steroid inhibition are located in the central nervous system and in particular in the hypothalamus[73,111-13] as well as in the anterior pituitary gland.[57] Inhibition of stress-induced pituitary adrenal activity was not achieved with intracerebral dexamethasone although suppression of the circadian rhythm did occur.[400] No evidence could be obtained for the possible action by steroids on a CRF releasing enzyme in the hypothalamus.[188] Steroid sensitive neurons have been demonstrated both in the hypothalamus and in the midbrain.[217,354]

Administration of a purified preparation of CRF to rats with median eminence lesions produced a rapid increase in corticosterone secretion.[399] Blood flow to the pituitary of rats with median eminence lesions was not significantly different from pituitary blood flow in rats without lesions. Since CRF had no noticeable effect on local blood flow in rats with median eminence lesions, it was concluded that the inability of animals with median eminence lesions to respond to stressful stimuli was due to inability to secrete CRF rather than to deficiencies in pituitary blood flow. It was suggested that the activity of the pituitary adrenocortical system varies directly with CRF output and that CRF is involved in the minute to minute regulation of ACTH secretion.[399] Rats treated with morphine, chlorpromazine, dexamethasone, and Nembutal® were used for the assay of corticotrophin releasing factor (CRF) in order to provide a preparation which was reliable and somewhat easier to prepare.[18] Using an improved bioassay for ACTH,[380] significant increases in the amounts of adrenal corticotrophin releasing hormone in the peripheral blood were observed under conditions of physiological stress.[18] Evidence has been provided that vasopressin acts on the hypothalamus to cause the release of endogenous corticotrophin releasing factor[153] and it has also been reported that a pituitary factor other than ACTH is necessary for increased aldosterone secretion.[126]

It has been reported that there are changes in the electrical activity of the adrenal gland after its activation by ACTH.[208] However, other investigators failed to confirm these findings[388] and subsequently showed that adrenocorticotrophic hormone increased corticosteroid production without altering the membrane potential of the adrenocortical cells. No evidence

was found of a direct relation between production of cortical steroid by adrenocortical cells and the cellular membrane potential. Indeed the output of steroids appeared to be relatively independent of the polarization of the cell membrane. Studies of blood flow to the adrenal cortex and adrenal medulla showed that stress resulted in an increase in both regions of the adrenal cortex.[196] Certain steroids may inhibit adrenal steroid production by the inhibition of adrenal protein synthesis. This is consistent with a hypothesis of a local feedback inhibition of steroidogenesis by adrenal steroids.[263] On the other hand, low levels of adrenal steroids were found to directly stimulate the cells of the anterior pituitary to secrete ACTH.[286] The adrenocorticotrophic activity of synthetic $\alpha$-melanophore-stimulating hormone ($\alpha$-MSH) has been evaluated both in vitro and in vivo and compared with the effects of synthetic corticotrophin. It was found that $\alpha$-MSH stimulated corticosteroid secretion both in vivo and in vitro[77] but its activity was less than one tenth that of synthetic $\beta$-corticotrophin. No simple relationship was found between the specific activities of $\alpha$-MSH and ACTH with regard to the stimulating effect on corticosteroid secretion. Other investigators[55] showed that a nonspecific stressor such as carbon tetrachloride induced adrenocortical hypertrophy in the rat and that this effect could be prevented by the administration of ascorbic acid. Changes in adrenal ascorbic acid following stress or exogeneous ACTH were studied in rats, gerbils, and hamsters.[214] As expected, both ACTH and stress depleted adrenal ascorbic acid in the rat. The gerbil showed the same responses as did the rat but in the hamster adrenalectomy or stress had no significant effect on adrenal ascorbic acid or on cholesterol and only very large doses of ACTH showed cholesterol changes in the hamster adrenal. At least two peripheral regulators appeared to effect normal adrenal function during repeated stimulation with ACTH. There occurs a tachyphylaxis to ACTH if the stimulation of the adrenal gland is frequent and this may be due to alteration or saturation of the trapping mechanism for acceptance of ACTH by the tissue.[171]

Pituitary adrenal function differs in the newborn in comparison to the adult animal and these differences may be the result of incomplete development of hypothalamic pituitary relationships. Important factors may be the time of development of the primary portal plexus in the median eminence[58] and/or the ability of the adrenal gland to secrete its hormone.[214] It has been reported that the neonatal rat has the ability to synthesize adrenal steroids but is unable to release the steroid until a later time.[214] However, these conclusions are not supported by other investigators who found that the neonatal rat was indeed responsive to stress.[76,894] The stress results in an increase in liver enzyme activity in the infant rat whereas adult rats ex-

posed to the same stress do not exhibit this change. It was suggested that in the adult rat a mechanism exists that opposes the enzyme-inducing effects of cortisol and that this mechanism is nonfunctional during early postnatal life.[337] A method has been developed that makes it possible to collect all the effluent blood from the hypophyseal stalk in rats.[291] This procedure may make it possible to study the secretory rates of hypothalamic releasing factors. Moreover, it is now possible to quantitatively evaluate the local blood flow of the adenohypophysis in rats.[290] Neutralizing antibodies to ACTH have been produced and it has been shown that the structural requirements for the immunologic reactivity to ACTH is not always identical with those necessary for its biological activity.[118]

## TSH—THYROID

Thyrotrophin (TSH) has been measured in extracts of pituitary and body fluids for more than 30 years and during this time many bioassay methods for the estimation of TSH have been described. The McKenzie method has been used most widely and a number of improvements have been proposed that provide greater precision and sensitivity in the bioassay for TSH.[181] TSH is extremely stable[155] and is more effective by infusion than by single injection.[21] There is a diurnal variation in the plasma and pituitary concentrations of TSH[348] and this is accompanied by a diurnal rhythm in the level of thyroxin in the blood.[109] Circulating thyrotrophin levels are influenced by the estrus cycle and in the rat the TSH levels are highest during early estrus than during any of the other stages of the cycle.[40] Many authors have observed thyroid inhibition upon exposure of animals to various stressful stimuli. The fall of plasma TSH as a result of severe stress suggests that acute stress causes a rapid though transient inhibition of pituitary TSH secretion that appears to be closely related to the simultaneous release of ACTH.[320] The circadian rhythm of plasma TSH is opposite to that of plasma ACTH.[93] Acute stress generally decreases TSH secretion whereas chronic stress lead to increased levels of plasma TSH.[94] Although hypothalamic lesions impair TSH release whenever a higher demand for thyroid function is present, the pituitary gland appears to have some autonomy for both increased secretion and release of TSH[279] Lesions that were placed in the anterior hypothalamus of rats decreased TSH secretion by the anterior pituitary. Coincident with the decreased TSH release, a decrease was also observed in the oxygen consumption and $P^{32}$ uptake of the anterior pituitary.[383]

Morphine has been used to inhibit many neuroendocrine functions. The effects of morphine are believed to be mediated through the hypothalamic neural centers rather than by direct action on the pituitary gland itself.

Although morphine impaired TSH release from the pituitary gland, it was observed that the thyroid uptake of $I^{131}$ was only partially suppressed by the administration of morphine. These results suggest that the hypothalamus does not control TSH secretion completely.[300] Although thyroidectomy resulted in a decrease in the size of the nucleus of certain hypothalamic neurones as well as a reduction in the amount of neurosecretory material in certain regions of the hypothalamus, no sharply localized nuclear region for the control of pituitary thyroid function could be demonstrated since these changes were observed throughout many areas of the hypothalamus.[305] In birds, hypophysectomy significantly depressed thyroid function but thyroid hormonogenesis appeared to be maintained albeit at a slower rate. It was concluded that in birds, in the basal state, functional autonomy of the thyroid with respect to the hypophysis is low but nevertheless evident.[315] Central nervous system arousal or stress was shown to cause a decrease or failure of TSH secretion with a resultant thyroid inhibition.[108]

During cold exposure thyrotrophin reaches peak levels in the plasma very rapidly but these levels are not sustained for more than two hours[165] whereas during chronic exposure to cold, elevated levels could be sustained for long periods of time.[80] Electrical stimulation of the hypothalamus resulted in elevated plasma TSH levels 15 to 20 minutes from the onset of stimulation, reaching peak values after 30 minutes of excitation. This rapid response to hypothalamic stimulation was due to the rapid release of TSH from the anterior pituitary.[28] After partial or total interruption of neural afferents to the medial basal hypothalamus it was demonstrated that the hypothalamic region between the suprachiasmatic nuclei and the anterior border of the ventral medial nuclei, the so-called thyrotrophic area, plays an essential role in the hypothalamic control of pituitary thyrotrophin secretion.[144]

Ectopic pituitary transplants responded to a decrease in the level of thyroid hormone in the blood by hypersecretion of TSH.[134,298] Pituitary transplants are capable of secreting near maximal amounts of TSH when they are in direct contiguity with the hypothalamic median eminence but when such transplants are at distant sites TRF cannot attain sufficient concentration in the general circulation to cause secretion of TSH equal to that produced by transplants directly under the median eminence.[134] The subcortical forebrain appears to be necessary for the maintenance of TSH secretion of the heterotopic pituitaries. Presumably TRF is secreted by the forebrain and passes through the general circulation to stimulate TSH secretion of the ectopic pituitaries. Apparently the level of TRF reaching the heterotopic pituitaries through the general circulation can never attain the levels reached in the hypophysial portal system of the normal rat.[197]

It seems well established that the hypothalamic regulation of anterior pituitary secretion of TSH is via the regulation of thyrotrophin releasing factor (TRF) and an excellent review has recently appeared dealing with TRF.[340] In vivo[296] and in vitro[359] assays have been developed for the determination of TRF and it has been shown that purified TRF is active in minute quantity.[302] Thyroidectomy enhanced hypothalamic synthesis of TRF[351] whereas thyroxin[302,351] inhibited the action of TRF on the anterior pituitary gland. Rat hypothalamic extract increased synthesis as well as release of TSH by the rat pituitary in vitro.[359] It was shown that the intrapituitary infusion technique was a sensitive method for testing thyrotrophin releasing factor provided certain precautions were taken to prevent nonspecific responses.[22] A competition appears to exist between thyroxine and TRF at the level of the pituitary gland in the release of TSH.[45,375] Although thyrotrophin secretion is controlled by the concentration of thyroid hormones in the blood, it was found that iodide had no effect on serum or pituitary thyrotrophin in vivo.[1] Triiodothyronine was about three times more active in suppressing the release of TSH than was thyroxine.[278]

Studies by Etkin, *et al.*[101-2] show that in amphibians there exists a thyroid feedback mechanism which stimulates a hypothalamic neurosecretory system. In the frog larvae, differentiation of the median eminence on the floor of the hypothalamus was dependent upon feedback action of thyroid hormone. However, the median eminence region was not sensitive to thyroxine until the animal reached a late tadpole stage. These results indicate that the time of metamorphosis depends on genetic factors that regulate the acquisition of sensitivity to thyroxine by the hypothalamus. Subsequent metamorphic changes, however, are regulated by the thyroid feedback system. The hypothalamus stimulates the pituitary which stimulates the thyroid which then feeds back again to the hypothalamus. Not only are hypothalamic structures involved in TSH secretion but it has also been shown that limbic structures such as the habenular nuclei are also involved in this regulation. These are believed to exert their influence on the TSH-thyroid system via the anterior hypothalamic structures.[344] The action of TSH on the thyroid gland appears to be the rapid coupling of freshly iodinated iodotyrosines to form iodothyronines.[346] Emotional stimuli can cause increased thyroid hormone secretion in sheep but catecholamines do not appear to play a role in this secretion.[108] Although thyroid hormones can influence pituitary hypertrophy as well as the size of neurons in the central nervous system[365] no evidence of a special and privileged position in the pituitary hormone economy was observed with regard to thyrotrophic hormone activity.[190] Fetal and neonatal rats were able to form goiters in response to goitrogen administration at a time when the hypothalamo-

hypophysial portal system was not fully developed.[119] Brain maturation and the development of electrical activity in the brain is influenced by thyroid hormones which may play an important role in the myelination of nerve fibers.[152] The administration of testosterone to neonatal rats resulted in a significant decline in the thyroid hormone secretion[204] whereas thyroid gland function was increased following the administration of gonadotrophins or of estrogen in the adult rat. The ovulatory surge of gonadal hormones may be accompanied by an increased secretion of thyrotrophin from the anterior pituitary gland.[47]

GONADOTROPHIN-GONAD

The difficulties involved in the assay of hypophysial gonadotrophins in plasma are generally recognized as a major impediment to a more complete understanding of pituitary-gonad physiology. Recently parabiotic rats have been employed for the evaluation of plasma gonadotrophin levels.[167-8] Changes in luteinizing hormone (LH) content of the pituitary is one of the earliest indexes of sexual maturation[262] whereas changes in pituitary content of follicle stimulating hormone (FSH) are frequently related to changes in progesterone secretion.[59] Anterior pituitary levels of LH, FSH, ACTH, and LTH were determined in female rabbits at various times after they were mated. LH, ACTH, and LTH decreased rapidly after mating but FSH was not significantly influenced by copulation. These results indicate that the mating stimulus was not specific for ovulating hormone release and suggest that other pituitary trophic hormones may affect reproductive function at the time of ovulation.[78] It has been reported that slight contamination of certain FSH preparations with luteinizing hormone can produce ovulation by causing the secretion of progesterone which then can facilitate the release of ovulating hormone from the pituitary gland.[246] In the intact rat prolactin maintains the secretion of the corpora lutea but after hypophysectomy the corpora lutea are unable to be maintained in a functional state by exogenous prolactin and continued administration of prolactin causes morphological leutolysis.[232] The secretion of prolactin is influenced by many diverse sensory stimuli.[136-7] Studies of a rat pituitary tumor which secretes large amounts of prolactin indicate that hormone secretion by the tumor can be altered by the direct action of a hypothalamic extract in vitro even though the tumor appears to be free of hypothalamic control in vivo.[350] In tumor-bearing rats it has been shown that high prolactin levels in the blood can increase the production of the hypothalamic prolactin inhibiting factor (PIF) and thereby depress pituitary secretion of prolactin.[56]

Rennels[309] has studied the ultrastructure of luteal cells from PMS and PMS-HCG treated immature rats with heavily luteinized ovaries. He also measured the pituitary content of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in these animals. Pituitary hypertrophy was observed prior to ovluation and was evidently brought about by estrogen stimulation. The secretion of estrogen appears to be of primary importance in the positive feedback which stimulates the release of ovulating hormone prior to ovulation.[310] Exposure of female rats to continuous light eventually induces a condition known as persistent estrus which is characterized by prolonged vaginal cornification and cystic follicular ovaries devoid of corpora lutea. However, the administration of progesterone can induce ovulation in persistent estrus animals.[349] On the other hand under certain conditions prolonged illumination can inhibit the secretion of gonadotrophin in the ferret and thereby block the manifestation of an inherent rhythm of sexual activity.[90] Rats deprived of light by blinding or by placement in continuous darkness continue to have regular estrus cycles when this procedure is carried out when they are 21 days of age whereas rats deprived of light when they are about 90 days of age begin to show prolonged cycles or even cease cycles entirely in a relatively short time. Thus if cycles begin under conditions of light deprivation they can continue normally without light but if cycles begin in the presence of light their continuation appears to be dependent upon light and its deprivation has an immediate profound effect on most rats.[159] A diurnal fluctuation in the content of ascorbic acid and progesterone in ovaries of intact and hypophysectomized immature pseudopregnant rats has been reported.[75] In intact animals these fluctuations may be explained by the surge of LH during the afternoon whereas in hypophysectomized rats these effects probably result from the predominance of catabolic processes at this time. A circadian rhythm in ovarian cholesterol has also been observed to be related to ovulation.[59]

It has been commonly considered that brain mechanisms which control ovulation and pseudopregnancy are the same but recent evidence indicates that these two processes are distinct and are regulated by different parts of the nervous system. Induction of ovulation involves a comparatively brief surge of gonadotrophic luteinizing hormone secretion from the adenohypophysis whereas maintenance of the corpus luteum requires prolonged secretion of luteotrophic hormone (LTH). By techniques of brain stimulation it was found that neural mechanisms that initiated pseudopregnancy in rats could be distinguished from other neural mechanisms that controlled ovulation. Stimulation of the preoptic area did not usually induce pseudopregnancy although ovulation was routinely elicited whereas pseudopregnancy was regularly evoked by stimulation of the tuberal region at sites

and with electric parameters not commonly yielding ovulation.[105] Estrus behavior did not depend upon the surge of ovulating hormone[104] nor did lighting conditions alter the effectiveness of pentobarbital blockade of ovulation.[106] Small quantities of exogenous estrogen induce precocious puberty but this effect could be inhibited by the administration of pentobarbital. Although the prevention of estrogen-induced puberty by anesthesia is consistent with the concept that estrogen exerts this effect through the central nervous system, the observation that estrogen has a direct effect on the vaginal cornification and is inhibited by pentobarbital suggests the possibility that pentobarbital administration may accelerate the biological inactivation of the hormone.[143] Reduction in the concentration of hypothalamic catecholamines usually resulted in a decrease in the secretion of luteinizing hormone with a concomitant increase in the secretion of luteotrophic hormone.[89,218,362]

The importance of the hypothalamus and of an intact portal circulation to the pituitary for normal gonadotrophic function has been well established. Pituitaries transplanted under the kidney capsule become undifferentiated and are unable to secrete gonadotrophins. Retransplantation of the pituitary under the median eminence causes redifferentiation and reinitiation of gonadotrophin release in female rats. Increased illumination stimulates the secretion of FSH by the in situ pituitary, an effect presumably mediated through the hypothalamus. Hypophysectomized rats bearing subcutaneous pituitary transplants showed elevated gonadotrophin secretion when they were exposed to continuous illumination, hence indicating the passage of a hypothalamic neurohumor via the systemic circulation.[284] Other studies have also shown that humoral substances which originate in the hypothalamus and maintain the secretion of ectopic pituitary glands can be blocked by hypothalamic implantation of testosterone.[357] Selective hypothalamic stimulation can induce pseudopregnancy. The pseudopregnancy could be immediate or delayed depending upon the nature of the stimulation.[105,294] Castrated young adult male rats bearing ovarian transplants were subjected to electrical stimulation of the hypothalamus. When stimuli were delivered to the preoptic area or to the median eminence the histological changes which were induced in the ovarian grafts indicated a discharge of ovulatory amounts of gonadotrophins.[259] Further studies along these lines showed that progesterone or pentobarbitone could influence the likelihood of ovulation following hypothalamic stimulation.[398]

The effects on gonadotrophin secretion of partial or total transection of the neural connections to the medial basal hypothalamus have been investigated.[145] After complete deafferentation of the medial basal hypothalamus, ovulation did not occur. Transection of the posterior lateral connections

did not interfere with ovulation whereas when only the anterior connections to the basal hypothalamus were interrupted, ovulation did not occur. These results indicate that neural afferents to the medial basal hypothalamus are required for ovulation. Employing electrical stimulation techniques in the rat, other investigators proposed a dual control system of adenohypophysial gonadotrophin secretion.[369] The first level of control is assumed to be located in the medial basal tuberal region and this regulates the tonic discharge of gonadotrophin secretion. This in turn is controlled by a second level which is responsible for initiating the ovulatory surge of gonadotrophins. The second level appears to be located in, or to operate through, the septal preoptic area.

Plasma and pituitary LH concentrations were estimated in rats with suprachiasmatic lesions of the type that induced hypothalamic constant estrus.[15] No detectable luteinizing hormone was found in the plasma of these rats and pituitary LH content was the same as that found in normal females in the estrus phase of the vaginal cycle. However, following spaying, plasma and pituitary LH levels increased in rats with large suprachiasmatic lesions and placement of these lesions in animals that had been spayed for two to three weeks failed to lower the plasma LH below the levels found in spayed sham operated controls. It was concluded that the negative feedback of gonadal steroids on LH secretion functions normally in rats with suprachiasmatic lesions and that the syndrome of hypothalamic constant estrus is probably caused by an interference with the cyclic timing mechanism that normally triggers ovulation. The effect of hypothalamic deafferentation on lactation was studied in rats[391] and it appears that a pathway for oxytocin release exists that is different from the supraoptico-hypophysial tract. Hypothalamic lesions in the median eminence hypophysial stalk or paraventricular nuclei of male rats produced lobulo-alveolar development and secretion of the mammary glands whereas lesions in the preoptic area and mammillary bodies were ineffective. From these results it was concluded that interruption of hypothalamic control results in increased prolactin synthesis and release in male rats and that the hypothalamus exerts a tonic inhibitory influence on prolactin secretion in the male as well as in the female.[79]

The earliest detection of the presence of luteinizing hormone releasing factor (LRF) coincides with the development of the primary plexus of the pituitary portal system and it has been suggested that LRF may have a trophic action on the anterior pituitary gland during the prepuberal phase of life.[54] LRF has been demonstrated in the hypophysial portal blood of proestrus rats,[115] is present primarily in the stalk median eminence region of the hypothalamus,[169] and is influenced by the levels of luteinizing hormone

and estrogen.[297] It has been reported that the primary effect of LRF is on LH release rather than on LH synthesis.[321] A highly purified preparation of LRF can induce ovulation in rats when administered in extremely small quantities.[20] The hypothalamic content of LRF can be influenced by castration or removal of gonadal hormones, as well as the administration of gonadal hormones,[283] and also by the stimulus of suckling.[252] Caution must be exercised in the assay of LRF since nonspecific responses have been reported.[74] A prolactin inhibiting factor (PIF) exists as a specific substance in the hypothalamus and the in vitro method is suitable for measuring changes in hypothalamic PIF content produced by different physiological states.[56,195,252,255,324]

Suppression of ovulation by progesterone has been known for a long time but within recent years it has become apparent that progesterone can also facilitate ovulation. This paradoxical effect has been observed in a number of species. The stage of the cycle when progesterone is injected appears to be critical in determining whether the action of the steroid will be inhibitory or facilitatory in nature.[86,181,271,295,397] A single injection of norethindrone blocked the release of LH following the intrapituitary infusion of hypothalamic extract. It was proposed that the effectiveness of norethindrone in blocking LH release depends on its capacity to block estrogen receptor sites in both the anterior pituitary and median eminence.[156] Pituitary luteinizing hormone stimulates the synthesis and release of certain progestins from rabbit ovarian interstitial tissue and these progestins act in a positive feedback fashion to prolong and heighten LH discharge in the mated rabbit.[157] As in the rat and rabbit the feedback action of ovarian hormones has also been demonstrated in the ferret.[91] It appears that a significant decline occurs in the output of gonadotrophin from the pituitary gland of aged rats.[206] Enovid®, a widely used contraceptive agent, is estrogenic in nature and the hypothalamus appears to be its major site of action.[251] The synthetic steroid, cyproterone, is a testosterone antagonist which competes with receptors in the central nervous system that regulate FSH secretion.[274,385] Systemic administration of Nembutal® can delay the PMS induced ovulation when the Nembutal® is given at the appropriate time. Direct application of Nembutal® to the preoptic area and the lateral septum of the hypothalamus also delayed the induction of precocious ovulation by PMS whereas injection into the mammillary body, basal part of the amygdala complex or frontal cortex had no apparent effect. The preoptic area and lateral septum appeared to be the site of positive feedback of the ovarian hormone.[142] It appears that the anterior hypothalamus is a direct target tissue for estradiol in the feedback control of gonadotrophin secretion[178] and this feedback effect can be influenced by the adrenocortical

steroids.[113] Studies have also shown that progesterone is taken up rapidly by the brain and pituitary.[210] Progesterone seems to differ from estradiol in that it is taken up rapidly by the brain, pituitary, uterus, and vagina in very small amounts which then disappear rapidly from the brain and pituitary and comparatively slowly from the uterus and vagina, whereas estradiol is incorporated and retained in the uterus, vagina, and pituitary. A comparison has been made of the effects of hypothalamic and pituitary implants of estrogen and testosterone on the reproductive system of female rats.[58] Implants of estrogen in either the median eminence region or the anterior pituitary gland can evoke a pseudopregnancy-like syndrome in the female rat. It appears that estradiol inhibits gonadotrophin secretion, FSH and LH in particular, but augments prolactin secretion by a central action on the hypothalamo-hypophysial unit whereas testosterone inhibits gonadotrophin secretion without altering prolactin secretion.[58] When an antiandrogen such as cyproterone was chronically implanted into the hypothalamus of male rats a specific stimulation of the male reproductive system was observed.[39] Neural implants of estrogen produced changes in neurosecretory material in the median eminence region of the hypothalamus[220] and the unit activity of certain hypothalamic neurons were influenced by the blood level of estrogen.[216-17]

Although much attention has been given to the concept that the ovarian steroids play an important role in the feedback control of gonadotrophin secretion via actions exerted directly on the pituitary gland or indirectly via the hypothalamus, until recently little attention has been directed toward determining the role of the pituitary gonadotrophins in the control of the hypothalamic gonadotrophin releasing factors. Evidence for a direct feedback system or internal feedback loop has been obtained by demonstrating that implants of luteinizing hormone in the median eminence decreased the level of luteinizing hormone in the pituitary gland itself. These results imply that the implanted LH induced an inhibition of pituitary LH synthesis via a negative feedback effect on LRF.[62,71] LH may therefore play a role by itself in the negative feedback control of its hypothalamic regulator.[61] Similar studies have also demonstrated an internal feedback effect of FSH on its respective hypothalamic activator.[63] These investigations strongly suggest that the pituitary gland participates in the regulation of its neural controller. Unit activity of hypothalamic neurons were responsive to changing levels of luteinizing hormone[183] and secretion of LH was generally accompanied by an increase in thyroid gland activity.[46,48]

Hypothalamic areas of the brain are involved in many neuroendocrine and homeostatic mechanisms. These functions can be presumed to be mediated directly or indirectly by changes in the pattern of action potential

activity. In these areas and in most other parts of the brain neurons display a continuous level of action potential activity (spontaneous activity) and from this activity functional changes have to be deciphered. Unit activity of the neurons in the hypothalamus, septum, and preoptic area of the rat were studied and the effect of estrogen on the spontaneous activity of these neurons was investigated.[216] The administration of estrogen appears to reduce the levels of spontaneous activity in the neurons of the anterior hypothalamus, preoptic and septal areas, whereas ovariectomy generally increased the spontaneous activity in these regions. Reciprocal effects were observed in the lateral hypothalamic area in response to these procedures. Most of the units in the lateral hypothalamic area were excited by pain, cold, and cervical stimuli whereas light sensitive units were found mainly in the lateral, septal, and anterior hypothalamic areas.[217] The responses to pain, cold, and cervical stimuli of the hypothalamic units corresponded to that of associated EEG activation suggesting that they were nonspecific arousal effects whereas those units that responded to estrogen treatment or deprivation appeared to be sensitive to the changing hormonal levels. DC and EEG frequencies were recorded in several hypothalamic regions of acutely prepared rats, and the results appeared to confirm the dominant role of the mid-hypothalamic structures in sensing and controlling pituitary gonadal interrelationships in sexual behavior. A possible function of the slow EEG potential changes in the region of the median eminence may be that a change occurs or that the threshold of neuroendocrine cells is reset thereby increasing the production of anterior pituitary hormones. A further consequence might be selective sensitization of this system to implants from cerebral as well as peripheral sources of stimulation relevant to reproductive activity.[211] The effects of sex hormones and antifertility steroids on brain thresholds in the rabbit have been studied.[184] In most instances the EEG arousal threshold changes were closely related to estrus behavior while the EEG after-reaction threshold changes indicated that the antifertility steroids exerted at least part of their ovulation blocking effect on central nervous system control of the adenohypophysis.[184] It appears that the amygdala may exert an inhibitory influence on those hypothalamic structures that activate the secretion of gonadotrophins.[98,96,271] Investigations into the afferent fibers that regulate hypothalamic pituitary activity failed to demonstrate a role of midbrain hypothalamic afferents in reproductive processes.[261]

Sedative doses of chlorpromazine can block ovulation in the rat. However, recent data has been presented to show that coitus resulted in ovulation in rats presumably blocked with non-sedative doses of chlorpromazine.[150] Further evidence showed that coitus acts through the central nervous

system to trigger the release of luteinizing hormone from the adenohypophysis of chlorpromazine blocked female rats.[149] Neither reserpine nor chlorpromazine blocked the milk-ejection response whereas both blocked ovulation and activated or maintained prolactin secretion.[202] An investigation was made to see whether the presence of the adrenal gland was necessary for cyclical activity of ovarian transplants in adult male rats that had been castrated at birth. It was found that the presence of the adrenal gland was not necessary to support cyclical activity in ovarian tissue transplants.[6] It has also been shown that goldthioglucose can damage hypothalamic centers that control prolactin release independently of those that regulate appetite.[50]

Sexual behavior in most vertebrates occurs only when the gonads are secreting sex hormones. This suggests that hormone sensitive neural elements exist and that a specific hormonal stimulus results in a specific overt behavioral act. Intracerebral implantation of testosterone resulted in reappearance of the complete pattern of male sexual behavior in the absence of any histologically demonstrable stimulation of the accessory sex organs in the castrate rat. It was concluded that sexual behavior in the male may be virtually independent of androgen sensitive peripheral mechanisms for it was elicited by the local action of testosterone on structures confined to the hypothalamic preoptic region of the brain.[72,210,277] Androgens and estrogens appear to function in the same neurological area to activate patterns of estrus behavior. Evidence has been obtained that progesterone plays a role in triggering sexual receptivity in a spontaneously ovulating mammal such as the rat.[273] It is possible that estrogen and progesterone may interact in different areas of the central nervous system or they may compete for steroid receptors in the ventromedial premammillary hypothalamus. When progestins were implanted into the ventromedial premammillary area in ovariectomized rabbits estrus behavior was not generally inhibited by small threshold doses of systemically administered estrogens.[278] Sterility was not consistently obtained when female rats were treated with small doses of testosterone on the fifth day of life[90] but testosterone pretreatment in adults could influence sexual behavior during conditioned fear.[193] In the monkey, male sexual behavior is influenced in some way by the level of secretory activity of the female.[249-50] It has been demonstrated that the reproductive activity in sheep is influenced by hypothalamic mechanisms upon which the gonadal steroids act.[295]

## GROWTH HORMONE

Studies of the regulation of growth hormone secretion have been handicapped by the lack of sensitive and specific methods for its measurement

in plasma. Bioassay methods, such as the growth of tibial epiphysial cartilage are relatively insensitive and nonspecific.[10] The development of radioimmunoassay techniques has made it possible to measure growth hormone levels in small animals such as the rat and it is now possible to study growth hormone levels in the plasma under various experimental conditions chosen both to validate the method and to study factors that regulate growth hormone secretion.[328] Hypoglycemia was found to be a potent stimulus for the release of growth hormone and it appears to act via the release of the hypothalamic growth hormone releasing factor (GRF) which triggers growth hormone secretion from the pituitary gland.[180,268] In the unanesthetized rhesus monkey, growth hormone secretion occurs in response to a number of noxious stimuli. Sudden perturbations in the environment as well as painful stimuli were associated with abrupt increases in plasma growth hormone levels. Growth hormone concentration can be increased following a variety of otherwise unrelated stimuli which are known to augment ACTH secretion.[202,247] It appears therefore that growth hormone secretion is very labile and is influenced by a variety of stresses as well as by alterations in the supply of available carbohydrate.

To investigate the neural control of growth hormone secretion, the effect of hypothalamic lesions on growth hormone concentrations and the response of the animals to insulin-induced hypoglycemia was studied.[2] Resting levels of growth hormone were not altered by hypothalamic lesions, a finding that indicates a reasonable degree of autonomy of basal growth hormone secretion. On the other hand, hypothalamic lesions abolish the hypoglycemic induced growth hormone discharge. The influence of the hypothalamus on growth has been investigated in animals at various ages. Ventromedial hypothalamic lesions in weanling female rats resulted in a greater reduction of growth than placement of such lesions in older animals. The greatest reduction of growth followed placement of lesions in weanling rats and it was suggested that this effect is due to the greater requirement for hypothalamic factors which are necessary for the release of growth hormone and other pituitary hormones that affect growth.[35-6] A dose response relationship was observed between the depletion of pituitary growth hormone and the amount of hypothalamic extract that was administered.[180] It was also shown that following the administration of insulin a profound hypoglycemia resulted which was accompanied by a significant depletion in pituitary growth hormone and an even greater depletion in hypothalamic growth hormone releasing factor. It was therefore concluded that the hypoglycemic stimulus to growth hormone secretion acts via release of growth hormone releasing factor which then triggers growth hormone secretion from the gland itself.[180] This interpretation was not fully substantiated by

other investigators.[226] They found that stalk median eminence extracts caused an elevation of plasma glucose and insulin that preceded the rise in growth hormone. Furthermore, administration of glucose also resulted in elevated insulin plasma levels without a concomitant increase in plasma growth hormone. They suggest that the rise in plasma growth hormone levels is not a response to insulin but is a direct effect of a releasing factor in the stalk median eminence extracts.[226]

Growth hormone releasing factor has been detected in the blood of hypoglycemic hypophysectomized rats.[200,265] Some stressful stimuli such as cold exposure are capable of releasing growth hormone and induce this effect via the hypothalamus whereas other stresses like formalin injection which do not release growth hormone exert little effect on the growth hormone release mechanism of the hypothalamus.[266] The administration of exogenous growth hormone was capable of inhibiting the endogenous release of growth hormone, suggesting the existence of an auto-feedback mechanism[201,267,269] which probably acts via alterations in growth hormone releasing factor (GRF) in the hypothalamus.[326] Many agents appear to influence the release of growth hormone.[268] Chlorpromazine, reserpine, and $\alpha$-ethyltryptamine (Monase®) were able to suppress the release of growth hormone that had been induced by insulin whereas other drugs such as pentobarbital, morphine, amphetamine and iproniazid were unable to block the release of growth hormone induced by insulin. Corticosteroids suppressed the secretion of growth hormone and this action does not appear to be due to a reduced concentration of the hormone in the pituitary gland but to an impairment in its release from the gland.[280] Although these observations suggest that cortisol affects growth hormone release at the level of the hypothalamus, other investigators[38] suggest that some of the actions of corticosteroids on growth hormone release may be a direct effect on the pituitary gland itself. They observed a decrease in the release of growth hormone from the isolated pituitary incubated in vitro.

## HYPOTHALAMIC RELEASING FACTORS

It seems reasonably well established that the anterior pituitary gland is under the influence of the hypothalamus by means of chemical substances called releasing factors. The neuro-humoral mediators which have thus far been demonstrated in hypothalamic extracts of domestic and laboratory animals are corticotrophin releasing factor (CRF), thyrotrophin releasing factor (TRF), growth hormone releasing factor (GRF), follicle stimulating hormone releasing factor (FSHRF), luteinizing hormone releasing factor (LRF), prolactin inhibiting factor (PIF), melanocyte stimulating hormone releasing factor (MSHRF), and melanocyte stimulating hormone

release inhibiting factor (MIF). Many of these factors have also been detected in the human hypothalamus.[334]

Although corticotrophin releasing factor (CRF) has been demonstrated both in hypothalamic tissue[18,289] and in blood,[18] only recently has this substance been substantially purified.[82] A clear separation between CRF and growth hormone releasing factor (GRF) has finally been achieved[81] but it must be emphasized that these highly purified fractions are not yet completely homogeneous.

The presence of a thyrotrophic hormone releasing factor (TRF) in hypothalamic extracts of several species has been demonstrated[22,298,302,351-2,359] and investigations have been carried out concerned with its mode of action.[43,302,375] This field has recently been excellently reviewed.[340] Partially purified TRF active in very small doses[329] was inhibited by small amounts of thyroxine or triiodothyronine. Actinomycin D did not abolish the response to TRF, indicating that de novo synthesis of TSH is not required for TRF to exert its effect.[335]

Interesting and important observations have been reported by Guillemin and coworkers.[51,140] Their investigations indicate that hypothalamic TRF is perhaps not a simple polypeptide, as had been considered previously, for their material with TRF activity had less than 5 to 8 per cent amino acid content and was not affected by proteolytic enzymes such as pepsin and trypsin. These reports raise new questions and pose serious doubts concerning the accepted dogma of the nature of the hypothalamic releasing factors. A new look is in order concerning the peptide nature of the releasing factors and undoubtedly these recent reports will stimulate future work in this direction. Guillemin and his colleagues also showed that calcium ions were required for the stimulation of TSH release in vitro by hypothalamic TRF.[376] Furthermore, potassium stimulated the secretion of TSH in vitro and this effect like that of TRF requires the presence of calcium. The activity of both potassium and TRF could be inhibited by pre-incubation with thyroxine.[377] These important observations emphasize the similar effects of potassium and TRF on TSH release. Both require the presence of calcium for their activity in releasing TSH, and thyroxine can inhibit the TSH release induced by either potassium or TRF. These results are consistent with the hypothesis that a decrease in the membrane potential of the thyrotroph cells of the adenohypophysis may be involved in the mechanism whereby TRF stimulates the release of TSH.

Follicle stimulating hormone releasing factor (FSHRF) has been purified and is active in vivo at doses of the order of 10 nanograms.[336] It appears to exert actions, both on the release of FSH as well as on the synthesis of FSH in the pituitary gland.[173] FSHRF has been demonstrated in peripheral

blood under certain experimental conditions.[319] Luteinizing hormone releasing factor (LRF has been detected in the hypothalamus[20,54,169,252,288,297,321] and in the blood[115] and has been purified free of other releasing factors.[330] The action of a highly purified LRF preparation was studied on rat pituitary glands in vivo and in vitro. It was shown that a dose of approximately one microgram of LRF releases approximately five micrograms of LH per milligram of pituitary tissue. This is approximately twice the amount of this hormone originally present in the pituitary glands of these rats. It was therefore concluded that the excess of this hormone was probably synthesized during the period of incubation of the pituitary glands with the LRF preparation.[172] LRF was active in both male and female animals. In the male rat it caused an increase in LH secretion,[331] and in the male dog it caused a secretion of 17-ketosteroids by the testes.[389] LRF appears to be responsible for the changing rates of LH secretion during various stages of the estrus cycle.[14,114] A factor in the hypothalamus which inhibits prolactin release has been demonstrated and has been called prolactin inhibiting factor (PIF).[195] Changes in PIF have been observed at various stages of the estrus cycle and following suckling.[252,324] The administration of epinephrine and acetylocholine were observed to alter the PIF content of the hypothalamus.[255] The presence of PIF in the hypothalamus provides an explanation for the well known observation that when the pituitary is removed from close proximity to the hypothalamus and transplanted to a distant site elevated levels of prolactin secretion ensue.

Growth hormone releasing factor (GRF) has been demonstrated in the hypothalamus[180,226,266] and in the blood[200,265] but not in the posterior pituitary lobe.[19] Purified GRF is distinct from other substances known to be in the hypothalamus[81,338] and growth hormone synthesis as well as release were enhanced when GRF was incubated with anterior pituitary.[364] A hypothalamic melanocyte stimulating hormone releasing factor (MSHRF) has been obtained from the hypothalamus[366,368] and was capable of depleting the pituitary of its MSH activity.[83] Another hypothalamic factor which elevates pituitary MSH has been reported[332] and suggests the presence in hypothalamic extracts of a substance that causes inhibition of MSH release from the pituitary gland.[176,7] The significance of the melanocyte stimulating hormone releasing and inhibiting factors in the mammal remains to be elucidated.

A study has been carried out to determine the topography of the neurons that synthesize the various hypothalamic releasing factors.[245] The fact that the hypothalamic principles are found in high concentrations in the median eminence does not prove that they are synthesized in this hypothalamic region. By observing the effects of lesions in various parts of the hypothalamus it was demonstrated that a number of the releasing factors are not

synthesized in the median eminence but actually only stored there. Results of these studies indicate that FSHRF is synthesized in the paraventricular area whereas LRF was synthesized in the suprachiasmatic area. All lesions apparently reduced thyrotrophic hormone releasing factor (TRF) in the median eminence region, thereby suggesting that TRF is synthesized in a relatively large hypothalamic area. Corticotrophin releasing factor (CRF) stores in the median eminence were not modified following all types of lesions and thus far it has been impossible to localize those hypothalamic structures that synthesize CRF.

## NEONATAL ENDOCRINE ALTERATIONS

Many studies have confirmed the early observations that adult female rats show eventual cessation of estrus cycles and ovulation following implantation of testicular tissue or injections of androgen shortly after birth. Since the ovaries and pituitaries[9] of such androgen treated animals function normally when transplanted to untreated hosts, it is presumed that the effects of androgen are mediated through neural structures which regulate the secretion of the gonadotrophins. The rat is sensitive to the masculinizing effects of testosterone until it is five days old. Thereafter this sensitivity falls off rapidly and is largely lost by ten days of age. The dosage of testosterone administered and the presence or absence of the ovary do not appear to influence the duration of the sensitive period.[7] Testosterone appears to influence the maturation of certain parts of the nervous system[8] and the morphological changes of the pituitary gland in rats that had been neonatally sterilized resembles those that occur after castration.[233] In the rat, exposure to constant illumination, placement of appropriate hypothalamic lesions or injection of testosterone at five days of age, produce a condition of persistent vaginal cornification associated with small follicular ovaries devoid of corpora lutea. Since each of these treatments results in interference with cyclic release of LH and in view of the similarity of the ovarian and vaginal responses, it has been suggested that these three manipulations cause their effects via a common functional lesion involving neural structures concerned with secretion of gonadotrophins. Despite the similar ovarian and vaginal changes, constant light and testosterone produced effects on neural LH regulating mechanisms that differed from those caused by lesions.[44] Other studies which were carried out in rats before and after sexual maturation supported these findings.[287] Androgen sterilization could also be produced by intracerebral implants of testosterone in neonatal female rats[386] and furthermore in addition to its effect on sexual activity in the female it could influence the onset of puberty in the male.[356]

The initial appearance of FSH in the pituitary glands of infant female rats was observed by means of a fluorescent antibody technique. Such immunocytological observations showed that cellular FSH first appears in the pituitary gland of the rat within the first two weeks after birth but that a marked increase in the number of fluorescent FSH cells occurred after the third week.[345] Morphological changes were observed in the brains of adult male rats castrated in the neonatal period.[262] Normal male rats had heavier brains than either the neonatally castrated male or female rats. The anterior hypothalamic area of androgen sterilized female rats showed a significant increase in oxygen uptake when compared with untreated controls whereas the oxidative metabolism of the middle and posterior hypothalamus was similar in both groups of rats.[258] Administration of the antiandrogen, cyproterone, to infantile rats inhibited the action of testosterone on the neural centers regulating gonadotrophin secretion. However, larger doses of testosterone could overcome the inhibitory effect of cyproterone.[278]

Whether or not the neonatal rat responds to stress depends upon the type and severity of the stressor used and also upon such parameters as dosage, length of treatment, type of response measured, and time after exposure at which the measurement was taken. It has been shown unequivocally that the neonatal rat can respond to a variety of stressors whereas certain stresses were ineffective in the neonatal rat. It was postulated that so-called systemic stresses are effective in the neonatal rat whereas so-called neural stresses are not. This would tend to indicate that the pituitary adrenal axis is operative in the neonatal rat but that the neural component of the system is not yet functional at this stage.[393] Steroid sterilized animals exhibited normal stress-induced elevations of plasma corticosterone despite the presence of the anovulatory condition.[215] Neonatal rats that had received a single injection of cortisol were found to produce fewer antibodies in response to androgens when they were tested 60 or 70 days later.[338] A single injection of cortisol on the first day of life in rats could produce a fatal cachectic condition which was very similar to the wasting syndrome that follows post neonatal thymectomy. The survival time was longer and the mortality rate was less after administration of smaller doses of the steroid.[107] Reserpine failed to protect the female rat from the adverse effects of estradiol when these agents were given to neonatal rats. These animals were sterile when they reached adulthood.[402] When thyroxin was injected into the neonatal rat no significant changes in thyroid function were observed in adulthood.[341] The administration of hormones during the neonatal period of the rat may have profound effects on the hormonal, reproductive, and behavioral characteristics of adult ani-

mals. The reasons for these changes are unknown but it may well depend upon the development of the primary portal plexus at this time.[53]

## NEUROHYPOPHYSICAL HORMONES

It is well recognized that the mammalian hypothalamo-neurohypophysial complex plays an important role in the regulation of the osmotic composition of the extracellular fluid as well as the volume of the vascular compartment. Such regulation is accomplished to a great extent by the secretion of vasopressin. The demand for greater sensitivity in the determination of circulating vasopressin has led to development of several modifications of the standard hydrated rat assay for vasopressin and rats of the Brattleboro strain with hereditary diabetes insipidus have been employed for this purpose.[170,384] Rats with hereditary hypothalamic diabetes insipidus do not secrete vasopressin although they can secrete oxytocin. These animals were found to be much more sensitive to both vasopressin and to oxytocin compared to normal animals.[237] The isolation and purification of vasopressin has been greatly simplified by the development of a highly selective adsorbent for vasopressin. This adsorbent, a cellulose neurophysin resin, combines the advantages of a high degree of specificity with that of a solid phase adsorbent.[288]

Recent experimental evidence indicates that there is a readily releasable pool of neurohypophysial vasopressin which comprises about 10 to 20 per cent of the total hormone content of the gland. Once this readily releasable pool of hormone has been discharged, the neurohypophysis continues to release vasopressin in response to appropriate stimuli but at a greatly reduced rate.[318] Precursors of vasopressin are synthesized predominantly in the supraoptic nucleus and the resultant neurosecretory granules go through a maturation process during their passage from the hypothalamus to nerve endings in the neurohypophysis. Not until they reach the nerve endings do they contribute to the formation of the pool from which the hormone may be easily mobilized.[87,128,370] The neurohypophysial hormones must be freed from their attachment to the protein carrier, neurophysin,[84] before the vasopressin can act on the renal tubules[29] or on the blood flow to various organs by means of its vasoactive properties.[130,390] Hemorrhage appears to be one of the most potent stimuli for the release of vasopressin.[343]

The effects of ether anesthesia and hemorrhage on hormone storage and ultrastructure of the rat neurohypophysis showed that the posterior pituitaries of stimulated rats were characterized by a loss of the electron dense material from the granules of the neurohypophysial nerve fibers. The disappearance of the electron dense content of the hormone carrying granules does not appear to be related to the hormone content in the gland.[67] The

amount of neurosecretory material in the hypothalamic nuclei may well depend upon the amount of light to which the animal is exposed. Cell counts indicate that young normal rats may have more neurosecretory cells in the supraoptic nuclei than microphthalic females of the same age.[45] Ovariectomy decreased oxytocic activity but produced no significant changes in vasopressor activity.[27] After pituitary stalk section of rats the hypothalamo-neurohypophysial system was greatly depleted of vasopressor activity and the excretion of vasopressin in the urine was above normal.[208] In vitro studies show that acetylcholine can increase the rate of release of the neurohypophysial hormones.[68]

The hypothalamic nuclei are concerned with the production and release of oxytocin from the neurohypophysis[372] and changes in electrical activity of hypothalamic neurons were correlated with hormone secretion from the hypophysis.[240] The administration of serotonin to the rat results in a central inhibition of oxytocin release in response to suckling.[256] Solutions of growth hormone and luteotrophic hormone were shown to undergo degradation and to produce fragments with oxytocic-like activity that were initially absent in these preparations.[224] The ability to form peptides with uterine activity from larger molecules of other hormones is a most interesting and provocative finding.

## INTERMEDIATE LOBE, PINEAL GLAND, ETC.

The intermediate lobe of the hypophysis secretes melanocyte stimulating hormone (MSH) and this hormonal secretion appears to be under hypothalamic control. Extracts have been obtained from neural tissue that both increase or decrease MSH concentration in the pituitary. Therefore it has been proposed that there are two hypothalamic factors present that are concerned with MSH secretion. One factor stimulates MSH release whereas the other factor inhibits MSH release. Therefore, central nervous system activity can both stimulate or inhibit the release of this hormone. These substances have been termed melanocyte stimulating hormone releasing factor (MSHRF) and melanocyte stimulating hormone release inhibiting factor (MIF).[367-8] If these results are confirmed, it would be the first indication of the existence of two antagonistic neurohumoral principles that affect the liberation of a hypophysial hormone.

In rats pinealectomy results in an elevation of the MSH content of the pituitary glands, presumably because of the removal of the pineal substance called melatonin.[175] The stress of ether inhalation produced a significant decrease in pituitary MSH. This effect of ether was not blocked by pretreatment with dexamethasone or Nembutal.® Investigations of the effects of stress on MSH release indicate that under certain experimental

conditions the pituitary content of MSH and ACTH do not necessarily change in parallel.[174] The activity of the sympathetic nervous system appears to have an important influence on the secretion of melanocyte stimulating hormone (MSH).[166] In the reptile the vascular pattern of the intermediate lobe strongly suggests that it is under the direct control of the hypothalamus by means of a neurosecretory mechanism.[344]

Previous investigations have established that the synthesis of melatonin is highly specific for the pineal gland and it has been suggested that melatonin is a pineal hormone. It has also been observed that pinealectomy significantly increased the number of estrus type vaginal smears and in pinealectomized animals containing intramuscular implants of pineal glands, the effects of pinealectomy were reversed. These studies indicate that the pineal gland and its secretions may be intimately involved in reproductive function. It has been hypothesized that the pineal gland influences gonadal function via the secretion of melatonin and that melatonin causes a decrease of both ovarian growth in immature female rats as well as a decrease in the incidence of vaginal estrus in young mature females. Furthermore, rats deprived of their pineal glands were shown to have an increased incidence of estrus, and treatment with melatonin reduced this back to normal. It therefore appears that the pineal gland inhibits gonad function. Pineal cell proliferation has been studied by radioautographic techniques[85] and it was found that two days after birth the pineal parenchymal cells of mice had a high proliferative rate as indicated by a large number of labelled nuclei. On the other hand at 21 days of age DNA synthesis occurred in less than one per cent of the cells and by one month it had essentially ceased. The rate of DNA synthesis was lower in pineal parenchymal cells than in any other tissue of the adult mouse studied except for neurons of the central nervous system. No DNA synthesis was observed after injections of estrogen and progesterone into ovariectomized mice. Pinealectomy, when performed in male rats, resulted in a significant increase in the weight of the testes, prostate, and seminal vesicles and suggests that the pineal gland usually inhibits LH and FSH secretion. The principal effect of melatonin appears to be an inhibition in the secretion of luteinizing hormone and it was suggested that the pineal gland exerts an anti-FSH effect through compounds that are different from melatonin.[264] There is a marked 24 hour circadian rhythm in the serotonin content of the rat pineal gland which varies from a midday peak to a night-time trough. This rhythm is endogenous and persists in blinded rats and in rats kept in constant darkness. This rhythm is apparently under central nervous system control and can be abolished by removal of the superior cervical ganglia. It has also been observed that the circadian rhythm in the serotonin content of the rat pineal gland can be

inverted by 180° by reversal of the lighting regimen.[358] A 24-hour norepinephrine rhythm has been observed in the rat pineal gland. Norepinephrine levels are highest at the end of the dark period and fall during the light period. This rhythmic variation in pineal norepinephrine is abolished when animals are blinded or are kept in continuous light or darkness. It appears to be generated by nerve impulses that are initiated by photic stimulation of the retina. These impulses are carried to the brain by the inferior accessory optic tract and reach the pineal by a pathway that includes the preganglionic sympathetic trunk to the superior cervical ganglion.[388] The synthetic activity of the pineal gland is regulated by photic stimuli which reach the pineal gland by way of the postganglionic sympathetic fibers that originate within the superior cervical ganglia. In rats, blinding prevents environmental lighting from depressing melatonin synthesis within the pineal gland. Apparently in the absence of light the pineal gland is activated to synthesize and release substances that have antigonadotrophic effects. Therefore, blinding is followed by involution of the gonads due apparently to the augmented secretion of the antigonadotrophic factors by the pineal gland. Superior cervical ganglionectomy has the same effect as blinding in that the effect of light appears to reach the pineal via the superior cervical ganglion sympathetic nervous system. However, it has been observed that superior cervical ganglionectomy in the hamster is similar to pinealectomy and counteracts the effects of blinding.[307] Removal of the eyes causes regression of the reproductive organs, adrenal glands, and the pituitary gland of adult male hamsters. Pinealectomy or superior cervical ganglionectomy counteracts the effects of blinding. Removal of the pineal gland combined with superior cervical ganglionectomy in non-blinded hamsters had no effect on the size of the reproductive or endocrine organs studied.[307] Unless the pineal gland is triggered by an early exposure to light it will not exert its gonadal inhibitory effects under the influence of darkness.[308]

Other investigations seem to indicate that the regulatory function of the pineal gland with respect to reproductive function is a minor one. When neonatal female rats were pinealectomized and their reproductive functions studied when they matured, it was found that they did not differ from untreated or sham operated controls. However these females matured 8 to 9 days earlier as evidenced by the opening of the vaginal membrane. In males, pinealectomy had no influence on the testes development nor on the weights of the accessory sex organs.[189] It has also been reported that the inhibitory substance of pineal origin (melatonin) neither inhibits completely the actions of exogenous gonadotrophins on the ovary nor the action of estrogen on the uterus.[305] It has been claimed that there is a substance in the pineal

gland that inhibits the development of the mammary glands. Mammary development was studied in pinealectomized rats and the findings suggest that the pineal gland does not exert any inhibitory effect on the development of the mammary glands or on the release of lactogenic hormones. Increased mammary gland development was not observed following pinealectomy.[254]

The definitive study has been carried out by Reiter[306] on the effect of pineal grafts, pinealectomy and denervation of the pineal gland on the reproductive organs of male hamsters. His findings confirm that in blinded hamsters the testes and accessory organs undergo rapid involution, a response that is prevented totally if the animals in addition to being blinded are pinealectomized. By comparison the transplantation of pineal glands under the renal capsules of blinded pinealectomized hamsters failed to cause gonadal involution. The failure of such transplanted pineal glands to produce or release gonadotrophin inhibiting substances is presumably a result of the loss of sympathetic innervation of the grafted pineals since bilateral superior cervical ganglionectomy, like pinealectomy, prevents testicular regression in blinded hamsters.[306] The activity of hydroxy-indole-o-methyl-transferase (HIOMT), the melatonin forming enzyme in the pineal gland, is several times greater in rats kept in continuous darkness than in those kept in continuous light. Lesions which transect the median forebrain bundle in the lateral hypothalamus suppress these differences in enzyme activity and abolish the light induced changes in pineal weight. These findings indicate that the medial forebrain bundle may participate in the control of the pineal gland in response to environmental lighting.[24]

Hyperplasia of the thymus has been observed following removal of the fetal pituitary gland. This effect was abolished when ACTH was injected into the fetus. These observations suggest that the fetal pituitary is not acting directly on the thymus but acting through the fetal adrenals and that the thymus hyperplasia is secondary to the reduction in fetal adrenal activity.[21]

A salivary secretion factor has been extracted from hypothalamic tissue. A polypeptide that stimulates an increase in the volume and amylase activity of saliva after intravenous injection into rats has been detected and partially purified from bovine and rat hypothalamic tissue. This polypeptide has been named Sialogen and gives a dose response curve for volume and amylase activity of the collected saliva. If Sialogen proves to be of physiological significance it may function as a neurohormone participating with the nervous system in the regulation of salivary secretion.[212]

## REGULATION OF EATING AND DRINKING

The role of the central nervous system in regulating food intake is now well recognized. Experimental evidence indicates that there are two opposing mechanisms in the hypothalamus that regulate food intake: a mechanism in the lateral hypothalamus that initiates feeding and one in the medial hypothalamus that brings about cessation of feeding. Changes in the internal environment following feeding appears to present signals to the appropriate nerve centers and an extensive search is being made to discover the nature of these signals. The level of glucose utilization in the body was believed to be one important signal, but this relatively slow mechanism cannot account for the rapid changes observed in food intake. It is therefore likely that afferent nerve fibers which originate in receptors in the GI tract relay information to the central nervous system in the regulation of food and water intake. Lesions placed in the region of the ventro-medial nucleus of the hypothalamus generally produce hyperphagia characterized by gross overeating which results in obesity. The most widely accepted explanation of this has been that the area of the ventro-medial hypothalamus is a satiety center acting to inhibit the ventro-lateral hypothalamus or feeding center. Hyperphagia could therefore be interpreted as the result of removal of neural tissue that normally exerts inhibitory control over food consumption. An alternative hypothesis has been proposed which states that electrolytic lesions result in irritation of certain neuronal elements and it is the irritative foci resulting from the lesioning process that is responsible for hyperphagia. In an attempt to demonstrate that metallic deposition is not a necessary condition for hyperphagia, it was recently shown that suction ablation of the ventromedial hypothalamic nuclei produced the characteristic hyperphagic syndrome.[287] Hypothalamic lesions not only produced hyperphagia but also derangements of metabolism[124,289] and it is possible that the pituitary gland plays an important role in production of hypothalamic obesity.[209]

A discretely localized system within the hypothalamus for both food intake and gastric secretion has been demonstrated,[253] and changes in electrical activity of single neurons in the hypothalamic feeding centers were observed after gastric distention.[12] The demonstration of fiber connections between the medial and lateral areas of the hypothalamus provides the anatomical basis for the long and widely held concept that the medial hypothalamic (satiety) region can act as an inhibitor of the lateral hypothalamic (feeding) area.[16] Following lateral hypothalamic lesions in rats there is observed an initial aphagia and anorexia which is followed by recovery so that these animals begin to regulate their food intake in response to dietary deficiency as well as to low ambient temperature. However these

animals fail to eat more during insulin induced hypoglycemia. These results suggest that rats with lateral hypothalamic lesions suffer from a specific loss of a hypoglycemic control of food intake.[98] Evidence has been obtained that the anterior hypothalamus is involved not only with temperature regulation but also with physiological adjustments during heat and cold stress which include behavioral adjustments such as eating and running.[148] The effects of stress on the growth rate and food and water intake of rats has also been investigated. A variety of stresses caused a slowing of growth that was apparently not associated with decreased food and water intakes. Since food consumption was unchanged during stress whereas the rate of growth decreased, it was concluded that the rate of oxidative metabolism was probably increased by the effects of stress.[168]

Amphetamine depressed food intake in man and animals and its locus of action has been investigated. The anorexigenic action of amphetamine was not dependent upon an intact hypothalamic ventro-medial inhibitory system.[275] Evidence indicates that amphetamine and chemically related compounds clinically useful in decreasing appetite generally act by decreasing the excitability of the lateral hypothalamus and this hypothalamic region appears to be its specific site of action.[361]

Food and water intake can be observed following both adrenergic and cholinergic stimulation of not only hypothalamic areas but also of several parts of the limbic system.[42,64] Drinking occurs when carbachol is applied directly to the hypothalamus of satiated rats and the cessation of this drinking is influenced by feedback mechanisms activated by factors such as distention of the stomach resulting from drinking. The action of carbachol persists for periods up to two hours after its application since it still induces drinking when water is delayed for this period of time. However, when access to water is provided immediately after application of carbachol, the effect of the carbachol is rapidly cut off. The nature and mechanism of these negative feedback inputs are unknown.[110,363] Carbachol readily enters the cerebral ventricle and can act at sites distant to the site of application. These findings seriously question the accepted locus of action of carbachol with regard to drinking.[116] Cholinergic drugs affect not only drinking but also emotional behavior.[379] Observations have also been made which suggest that under physiological conditions the autonomic nervous system may play a role in the control of insulin secretion.[231]

## CLINICAL NEUROENDOCRINOLOGY

The basic concepts of neuroendocrinology are just now being introduced into the clinic. The tremendous increase in our knowledge of basic neuroendocrinology will undoubtedly become an important tool for the physician

of the future. Only a brief sampling is appropriate in this review and an attempt has been made to bring to the reader's attention those clinical applications based upon well-established neuroendocrine phenomena.

Endocraniosis is a pathological condition characterized by hyperostosis of the skull and signs of diencephalic lesions usually accompanied by hormonal alterations.[347] It occurs most often in adult women, rarely in men, and never in children. Hormonal disorders of women, primarily alterations of reproduction, represent a frequent and important manifestation of this syndrome. It is believed that some allergic manifestation which influences the hypothalamic centers and neuroendocrine regulation is involved. Endocraniosis is not considered as a strictly defined disease but as an abnormal condition that under unfavorable circumstances may lead to important endocrine, metabolic, and psychoneurotic disturbances.

After prolonged suppression of human pituitary adrenal function by cortisol-like steroids, there is frequently a delay of several months before normal function is regained. The course of recovery is characterized by an initial phase in which both ACTH and cortisol in the blood are subnormal. There is an intermediate phase during which ACTH increases to concentrations that are normal or greater, but adrenal cortical responsiveness to ACTH remains subnormal. In the final phase, normal adrenocortical responsiveness is regained so that cortisol is secreted in normal quantities in response to normal concentrations of ACTH in the plasma. Attempts have been made to hasten recovery from pituitary adrenal suppression by the administration of ACTH, but it was found that exogenous ACTH administration did not shorten the period of pituitary adrenal suppression that followed prolonged steroid treatment of patients.[117] The recovery of hypothalamo-pituitary adrenal function in patients after corticosteroid therapy showed that the basal steroid levels returned to normal more quickly than did the response to hypoglycemia and it was almost a year before a normal response to hypoglycemia was observed in all patients. These data suggest that steroid feedback sensitivity and stress responsiveness may not be restored to normal at identical rates and response to stress may lag considerably behind recovery of normal resting hydrocortisone levels.[223] The steroid feedback effect of dexamethasone was normal in patients with emotional derangements,[127] in patients with hypothalamic central nervous system dysfunction, and in patients with extrahypothalamic central nervous system disease.[199]

Patients with adrenal cortical insufficiency had an increased taste sensitivity to salt. As a result of this observation a so-called "taste sensitivity test" for adrenal insufficiency has been developed and the authors claim that it is a useful tool in the diagnosis of this disease.[194] A rapid test of the

hypothalamo-pituitary axis for the secretion of growth hormone and also for the secretion of cortisol has been described.[132] In all patients suspected of having hypothalamic or pituitary hypofunction, an impaired or absent growth hormone response to insulin was obtained. In some patients, this was the only endocrine abnormality detected. The impairment of growth hormone secretion after insulin is of diagnostic value since the appearance of this abnormality appears to precede evidence of gonadotrophin, adrenocorticotrophin, thyroid stimulating hormone, or antidiuretic hormone deficiency. The determination of plasma cortisol values throughout the insulin test had less diagnostic significance than the determination of growth hormone or free fatty acid levels. The response to insulin proved of value in differentiating patients with hypothalamic or pituitary hypofunction and those with anorexia nervosa.[207]

A study of the effect of central cooling in man on pituitary thyroid function and growth hormone secretion was carried out[34] and it was observed that a brief period of central cooling brings about a prompt increase in oxygen consumption in some individuals but that significant activation of the pituitary thyroid axis or of growth hormone secretion was not observed under these experimental conditions. Measurements have been made of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in pooled urine samples from prepubertal children aged two to six years and from male adults. It was revealed that sexual maturity is accompanied by a substantial increase in the excretion of LH accompanied by smaller increases in FSH excretion.[312] Attempts have been made to quantitate clinical unpleasantness or discomfort, and certain physiological variables associated with this state have been correlated. These include urinary excretion of catecholamines, pulse rate, blood pressure, and tissue resistance.[122]

Although the science of experimental neuroendocrinology is now well established, we are only beginning to appreciate the possible practical significance of neuroendocrine thinking in clinical medicine.

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