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HYPOTHALAMIC CONTROL OF THE ADENOHYPOPHYSIS*

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The anterior pituitary gland, adenohypophysis or lobus glandularis, is the portion of the pituitary gland derived from Rathke's pouch of the embryo. It is divided into three parts: The pars tuberalis, the pars intermedia and the pars distalis. (Figure 1).

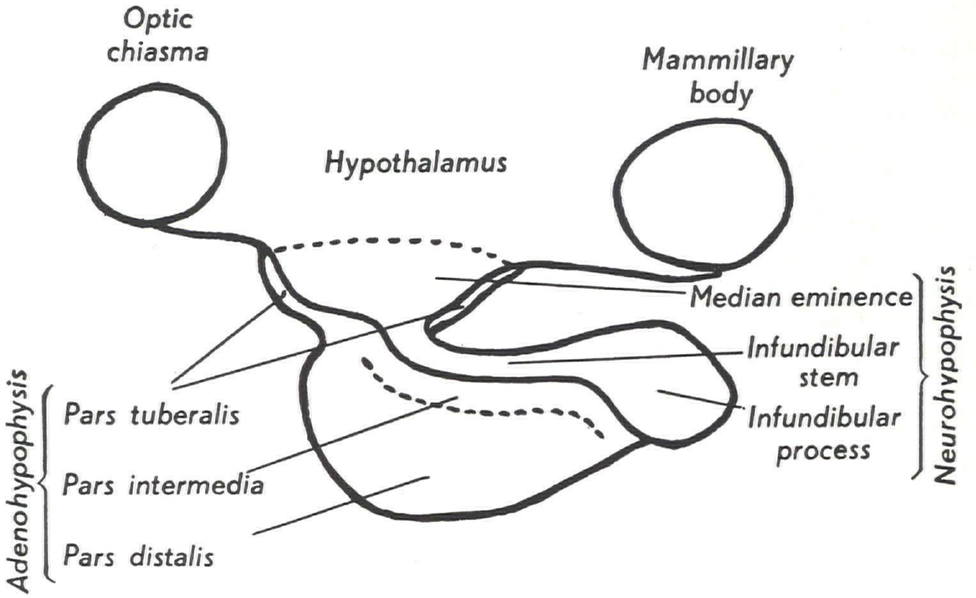

Figure 1

Diagram of a sagittal section through the pituitary gland of a rabbit. (Harris[3])

Over a hundred years ago, Bougery[1] described a nerve supply to the pituitary gland originating from the sympathetic plexus around the carotid artery. Since 1920, when first information concerning hormonal activities of the adenohypophysis was obtained, the nerve supply of this part of the pituitary has been the subject of extensive investigation. It has been suggested that it receives secreto-motor nerve fibers from three sources: sympathetic fibers from the plexus around the internal carotid artery, parasympathetic fibers from the petrosal nerves, and hypothalamic fibers from the median eminence and infundibular stem.

In 1913 Dandy[2] was the first to give a detailed description of the sympathetic pathway to the gland. His findings, as well as that of other workers since that time, have fairly well established that sympathetic nerve fibers pass to the pituitary gland from the surrounding perivascular plexuses, but it is not yet clear whether the main secreting mass of the adenohypophysis, the pars distalis, receives any of these

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fibers, or what the nature of such fibers may be; whether they are secreto-motor or vasomotor. It is very likely that the sympathetic innervation is destined mainly for the pars tuberalis, and that the pars distalis receives few, if any, fibers. This view would indicate that the fibers are vasomotor in nature, for the pars tuberalis is the most vascular region of the pituitary gland, and as far as is known has no definite endocrine function.

It has been shown that complete sympathectomy does not prevent normal reproduction in female cats and does not cause any very significant change in the metabolic rate of cats or rats. These experimental data demonstrate that sympathetic innervation of the pituitary plays no appreciable part in the control of secretion of the gonadotropic and thyrotropic hormones.

Furthermore, there is no sound evidence that parasympathetic innervation of the anterior pituitary gland plays any part in regulating the activity of this gland. It has been shown that removal of the sphenopalatine ganglion does not result in any abnormality of genital development or reproductive capacity in the rat. It has also been demonstrated that the reflex release of gonadotropic hormone which normally follows coitus in the rabbit still occurs after bilateral avulsion of the geniculate ganglion and after the destruction of the petrosal nerves at the geniculate ganglion.

Many workers have noted scanty innervation of the pars intermedia by hypothalamic fibers from the infundibular process. The functional significance of this innervation is unknown since the only hormone known to be secreted by the pars intermedia is the melanophore-expanding hormone. The pars tuberalis also receives fibers from the hypothalamo-hypophysial tract but this highly vascular portion of the gland as far as is known has no definite endocrine function. The majority of workers have either found a complete absence of nerve fiber from the hypothalamic tracts in the pars distalis or the presence of so few that it seems very unlikely that they constitute a secreto-motor innervation for the gland. (Figure 2).

The anterior and posterior hypophysial arteries (a) and (b) are derived from the internal carotid arteries. The arterial twigs (c) to the pars tuberalis plexus are derived from the internal carotid and posterior communicating arteries. The venous drainage (d) passes to surrounding venous sinuses in the dura mater or in the basisphenoid bone. Another vascular system which is found in this region but not shown in this diagram is the hypophysial portal vessels which we will learn later plays a profound role in the hypothalamic control over the adenohypophysis.

The small arterial twigs seen at (c) in Figure 2 run to supply a rich vascular plexus situated in the pars tuberalis of the pituitary gland. From this plexus arises a multitude of capillary loops or tufts which penetrate into the tissue of the median eminence and these come into intimate relationship with the nerve fibers of the supraopticohypophysial, tuberohypophysial and other nerve tracts. These loops or tufts are collectively referred to as the primary plexus of the hypophysial portal vessels. The blood from the primary plexus is drained down the large portal trunks which lie mainly on the anterior or ventral surface of the pituitary stalk. The portal trunks in turn break up and distribute their blood into the sinusoids of the pars distalis of the adenohypophysis.

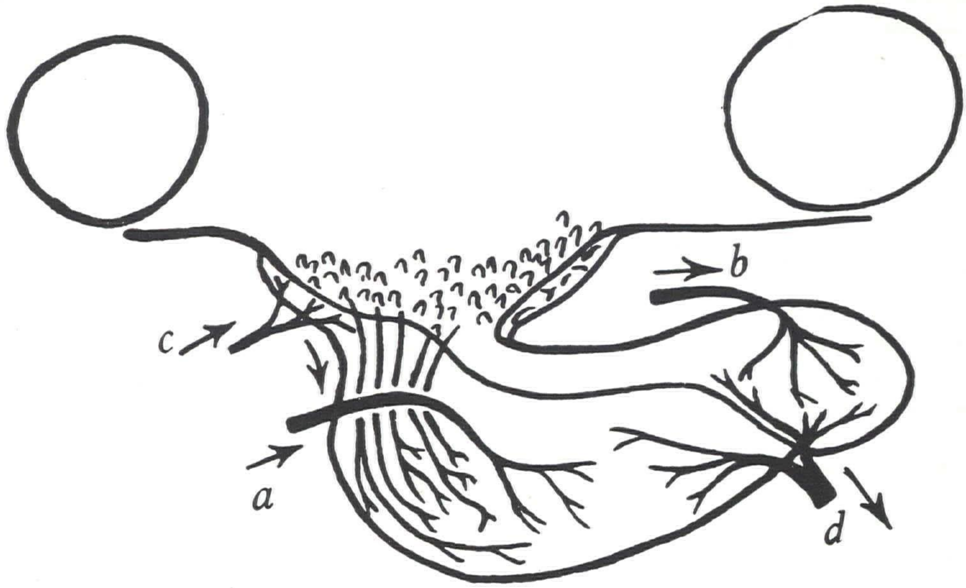

Figure 2
Diagram of a sagittal section through the pituitary gland of a rabbit illustrating the hypophysial blood supply. (Harris[3])

THE REGULATION OF GONADOTROPIC SECRETION

It is well known that changes in the external environment and psychological upsets may influence sexual processes. (Figure 3).

Some examples of exteroceptic factors are as follows:

1. When food is abundant sheep may breed twice a year whereas under-nutrition, if severe enough, may cause disturbance of the estrous and menstrual cycles.

2. The temperature and humidity of the environment seem to play a part in determining the sexual cycle in some forms. The female rat has been found to exhibit lengthened estrous cycles when maintained at low temperatures whereas the normally limited period of testicular activity in the male ground squirrel could be greatly extended by keeping the animals in a constant low temperature.

3. The principal stimulus relating reproductive rhythm to the environmental seasons appears to be light. The ferret is a long-day breeding animal having their breeding season from the middle of March to July or August. The recurrence of estrus in the ferret can be produced by extra illumination. The sheep is a short-day breeding animal which normally breeds from early October to late March. It is

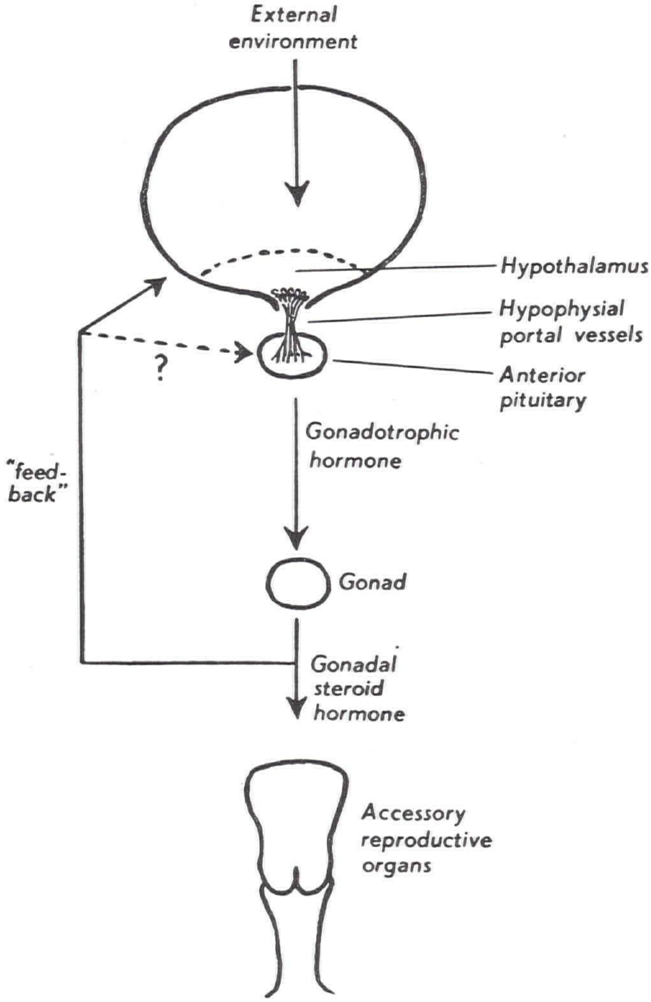

Figure 3

Relationship between the external environment and the reproductive organs. (Harris[3])

found that sheep can be brought into estrus if subjected to a gradually decreasing duration of light each day.

4. The presence of young, eggs, or a companion also play an important role. It is well known that for any one species of bird the number of eggs in a clutch is generally constant within narrow limits. The bird tends to lay a definite number of eggs and brood over them. If eggs are removed one or two at a time, as they are laid, the bird may continue to lay almost indefinitely. For example, a flicker was induced to lay 71 eggs in 73 days in this way.

5. It is well known that changes in the menstrual cycle are often associated with emotional upsets.

The most likely hypothesis to account for the fact that exteroceptive and psychological factors determine and modify the breeding, estrus, and menstrual cycles of so many forms is that the central nervous system controls the secretion of gonadotropic hormone from the pituitary gland. Since the anterior pituitary gland of the embryo, that is, Rathke's pouch, migrates from the roof of the mouth to become attached to the floor of the third ventricle, it would seem likely that the hypothalamus is the part of the central nervous system most directly concerned with the regulation of the anterior pituitary activity.

In 1937 Harris[3] found that stimulation of the tuber cinerum, posterior hypothalamus, or pituitary gland directly might result in ovulation or the formation of cystic or hemorrhagic ovarian follicles. More recently, researchers have shown that electrical stimuli which are ineffective in causing gonadotropic discharge if applied directly to the pituitary gland are fully effective in producing this result if applied to the tuber cinerum. On this basis it is likely that the stimulus from the hypothalamus is transmitted through the pituitary stalk but by structures that are not excitable to electrical stimulation. The component of the stalk which appears to fulfill these requirements is the hypophysial portal vessels.

It has long been known clinically in human beings that hypothalamic lesions may result in genital atrophy. Conclusions from such observations are uncertain since the hypothalamus is anatomically so small in size and consists of such an intricate mass of nerve fibers and scattered cell groups that even a small discrete lesion may affect many functions. Much more significant, however, are the experimental findings that hypothalamic damage may result in disturbance of the estrous cycle, such as persistent estrous in the normally cyclic species and the clinical finding that hypothalamic tumors may produce a state of precocious puberty.

Dey[4] and his collaborators were the first to make a systematic study of the effect of lesions in the hypothalamus or reproductive function. He found that relatively large anterior hypothalamic lesions in the guinea pig were followed by the development of persistent estrous. Lesions which interrupted the connections between the hypothalamus and pituitary resulted in gonadal atrophy whereas lesions directly in the pituitary and lesions in the posterior hypothalamus were without definite effect. Hillarp[5] has found that bilateral lesions placed anterior and ventral to the paraventricular nucleus result in a state of constant estrous. (Figure 4).

The anterior hatched area is the hypothetical location of the "timing center" controlling the cyclic release of gonadotropic substances from the pituitary, as described by Greer.[6] The medial hatched area exerts a modifying influence on the timing center and persistent estrous will result if this area is destroyed.

Since the sympathetic and parasympathetic nervous systems have been shown to have little effect on anterior pituitary activity, the pituitary stalk is the only anatomical pathway by which the hypothalamus can regulate the anterior pituitary secretion.

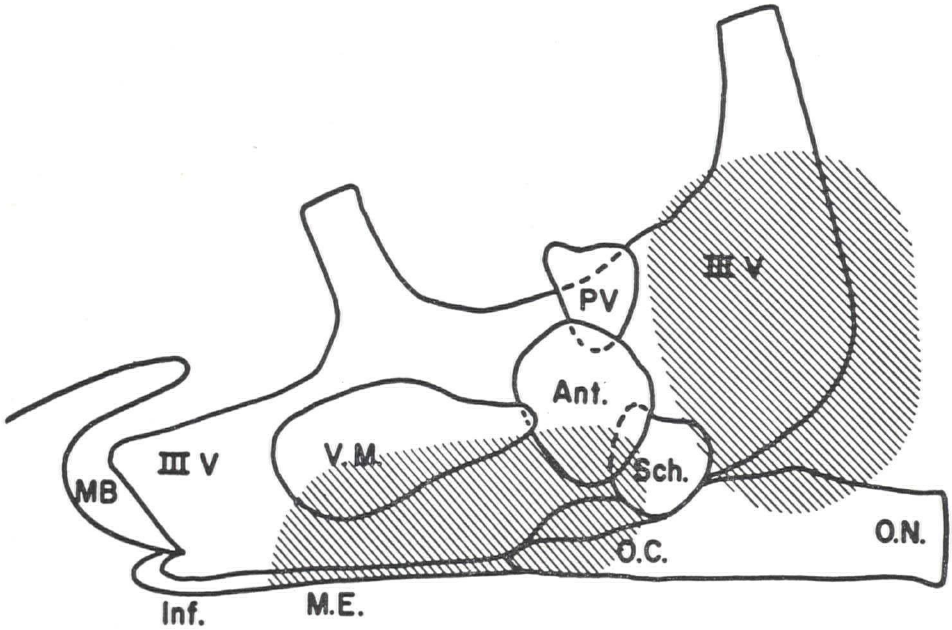

Figure 4

A Diagrammatic Representation of the Rat Hypothalamus. (Greer[6])

ANT = Anterior hypothalamic area.
INF = Infundibulum.
MB = Mammillary bodies.
ME = Median eminence.
OC = Optic chiasm.
ON = Optic nerves.
PV = Paraventricular nucleus.
SCH = Suprachiasmatic nucleus.
VM = Ventromedian nucleus.
III V = Third ventricle.

Many investigators have studied gonadotropic secretion and reproductive activity following cutting the pituitary stalk and observing pituitary function. Very highly discordant results have been obtained. Normal gonadal function has been reported on the one hand and gonadal atrophy has been reported on the other. Some researchers have noted prolonged estrous cycles whereas others have noted normal or absent estrous cycles. As the nerve fibers in the pituitary stalk lack a neurilemmal sheath, they do not regenerate once severed. Most investigators have held one of the following theories concerning the variable results of stalk section: First, it has been suggested that section of the stalk does not necessarily affect the pituitary secretion of gonadotropin; second, that animals which show normal reproductive functions after operation may have had incomplete severance of the stalk.

A possible reconciliation of these variable results became apparent when it was found that the hypophysial portal system of vessels formed a constant anatomical feature of the pituitary stalk and that the flow of blood in these vessels was from the median eminence of the hypothalamus towards the adenhypophysis. Its seems possible that the influence of the hypothalamus on gonadotropic secretion is mediated via these vessels and that the variable results of pituitary stalk section may be explained in terms of variable degrees of portal vessel regeneration across the site of section.

An experiment was carried out in which the pituitary stalk was cut in 19 rats and small plates of paper were inserted between the cut ends of the stalk to prevent regeneration. Eleven of these remained anestrous, gonadal atrophy occurred, and histological examination showed absence of portal vessel regeneration. In eight, irregular or regular estrus cycles recurred and after death some regeneration of the portal vessels was observed around the edge of the misplaced plates.

It is felt that the changes observed could not be due to a reduction in the amount of anterior lobe tissue consequent to a diminished total blood supply for three reasons:

1. Smith[7] in 1932 showed that as little as 10% of the normal amount of anterior pituitary tissue in rats is sufficient to maintain some ovarian activity and that 3% can maintain normal sexual function.

2. The reproductive processes bore no relation to the amount of anterior lobe tissue present.

3. India ink injections showed that the pars distalis was still well vascularized in the animals in which portal vessel regeneration was completely prevented and which remained anestrous after operation.

As stated previously, light stimulation will produce estrus in the ferret. It is believed that this stimulus is mediated by the eyes, optic nerves and probably some nervous reflex pathway ultimately leading to increased pituitary secretion of gonadotropic hormone.

In 1953 Thompson and Zuckerman[8] severed the pituitary stalk in 17 ferrets. They believed that two ferrets, when exposed to light, became estrous even in the absence of any vascular connections between the median eminence and the adenohypophysis. They concluded that the hypophysial portal vessels do not form a part of the pathway by which light stimulates anterior pituitary secretion. In 1954 Donovan and Harris[9] repeated the experiments and obtained different results. He exposed the pituitary stalk of 24 ferrets. In four animals the stalk was left intact, in six, simple stalk section was performed and in 14, the stalk was cut and a paper plate inserted between the hypothalamus and the pituitary gland. After sacrifice, the vascular system was perfused with India ink and celloidin and sections cut serially through the pituitary region. It was found that the appearance of estrous could be correlated with the presence of vascular connections between the median eminence of the tuber cinerum and the anterior pituitary gland. No case of estrous was observed in the absence of such vascular connections.

Another important study concerns the effect of transplantation of the pituitary gland. In 1936 Greep[10] reported that young rats, bearing auto-and homografts of pituitary tissue in the sella turcica showed good anterior pituitary function as evidenced by growth, estrous cycles, pregnancy and lactation. In 1950 and 1952, Harris and Jacobsohn,[11] using hypophysectomized female rats, placed pituitary tissue either under the cut pituitary stalk or a few millimeters laterally under the temporal lobe of the brain where it could become revascularized by the hypophysial portal vessels. All animals regained a normal estrous rhythm and when placed with normal males, six became pregnant and delivered living young.

It has been noted by many observers, however, that if the anterior pituitary is transplanted into the anterior chamber of the eye or some other area distant from the sella turcica, the functional capacity of the anterior pituitary is markedly reduced. In 1949, Cheng, Sayers, Goodman and Swinyard[12] studied pituitary transplants in hypophysectomized rats and found that the decrease in the weight of the adrenals was in most instances as great as that which occurred in the hypophysectomized animals without grafts. There was also little evidence of secretion of growth hormone or gonadotropic hormone by the transplanted pituitary tissue.

In summarizing the above results, it may be said that there is no evidence that the anterior pituitary gland will maintain normal functions if transplanted to a distant site in the body, and that in this respect the adenohypophysis stands in marked contrast to the ovaries, testes, adrenal cortex, thyroid and parathyroids. However, very different results are obtained if the pituitary gland is removed from the sella turcica so that all vascular and nervous connections are interrupted but is then replaced in the sella turcica or in an adjacent site. Normal anterior pituitary function may then return to such grafted tissue.

ADRENOCORTICOTROPIC SECRETION FROM THE ANTERIOR PITUITARY GLAND.

Adrenocorticotropic Secretion from the Anterior Pituitary Gland.

Although systemic blood levels of adrenalin and of adrenal cortical hormones play a role in the regulation of adrenocorticotropic hormone, we will deal only with the hypothalamic control at this time. The most used indicators for ACTH secretion is the lymphocyte or eosinophil count, or the adrenal ascorbic acid or adrenal cholesterol content. (Figure 5).

As stated previously, pituitary transplants in hypophysectomized animals at a site distant from the sella turcica results in partial or complete atrophy of the adrenal cortex.

In 1950, deGroot and Harris[13] suggested that some neutral mechanism in the hypothalamus is largely responsible for maintaining and regulating the secretion of ACTH. They postulated that hypothalamic nerve fibers liberate some chemical transmitted into the hypophysial portal vessels which is carried to the anterior pituitary gland.

Colfer, deGroot and Harris[14] found that in the rabbit, as in other experimental animals, emotional stress stimuli evoked a lymphopenia. Hypophysectomy abolished this response to stress, though injection of ACTH was still followed by a lymphopenia in the hypophysectomized animal. Electrical stimulation of the posteroir region of the tuber cinerium or mammillary body resulted in a lymphopenia that was similar in time relation and magnitude to that following an emotional stress stimulus or intravenous injection of an appropriate dose of ACTH. Hume[15] in 1953 reported

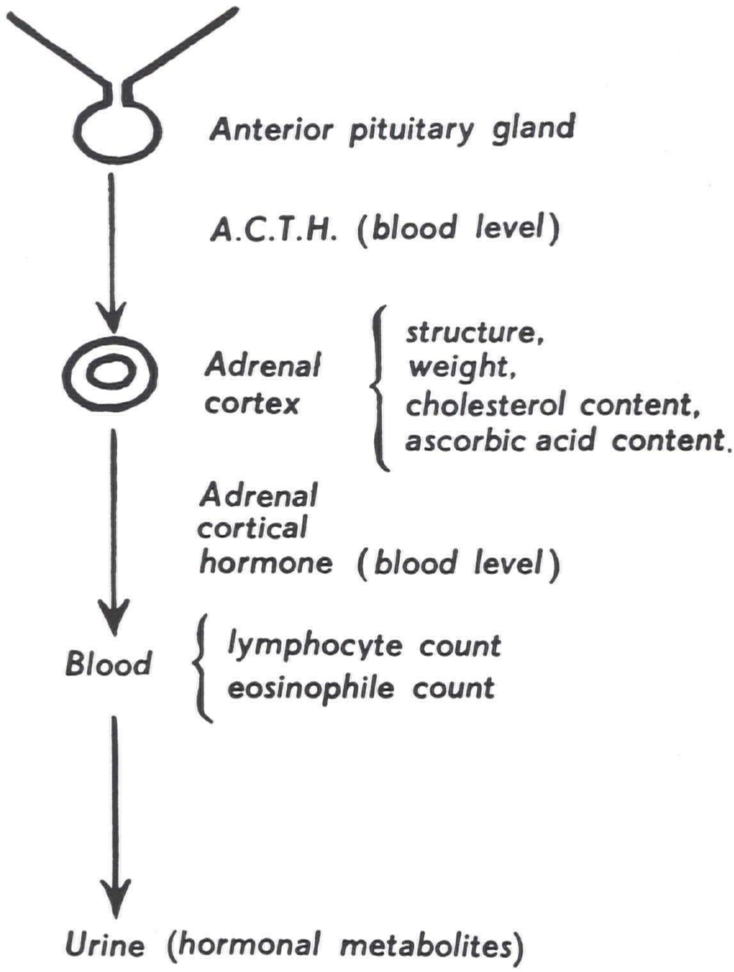

Figure 5

Methods used to measure the activity of the pituitary-adrenal axis. (Harris[3])

that the stimulation of the posterior tuber cinerium of the hypothalamus of dogs also resulted in an eosinopenia.

deGroot[16] in 1952 studied the effect of different types of stress stimuli at varying periods after cutting the pituitary stalk in mice. He found that mice respond to a stress stimulus with a lymphopenia most marked at the third hour after the stimulus. Following simple section of the pituitary stalk, this lymphopenia response was temporarily abolished but was slowly re-established between the 6th and 15th days due to portal vessel regeneration. When a waxed paper plate was placed between the cut ends, the lymphopenic response was abolished for the duration of the experiment. Marked atrophy of the adrenal glands was also noted.

Hume and McCann[17,18] in 1951 and 1953 have found that median eminence lesions in the dog, rat, and cat will interfere with adrenal activation following stress as evidenced by eosinopenia or a decrease in adrenal ascorbic acid content. Other workers have found that the posterior hypothalamus seems to be necessary for adrenal activation in response to stress. (Figure 6).

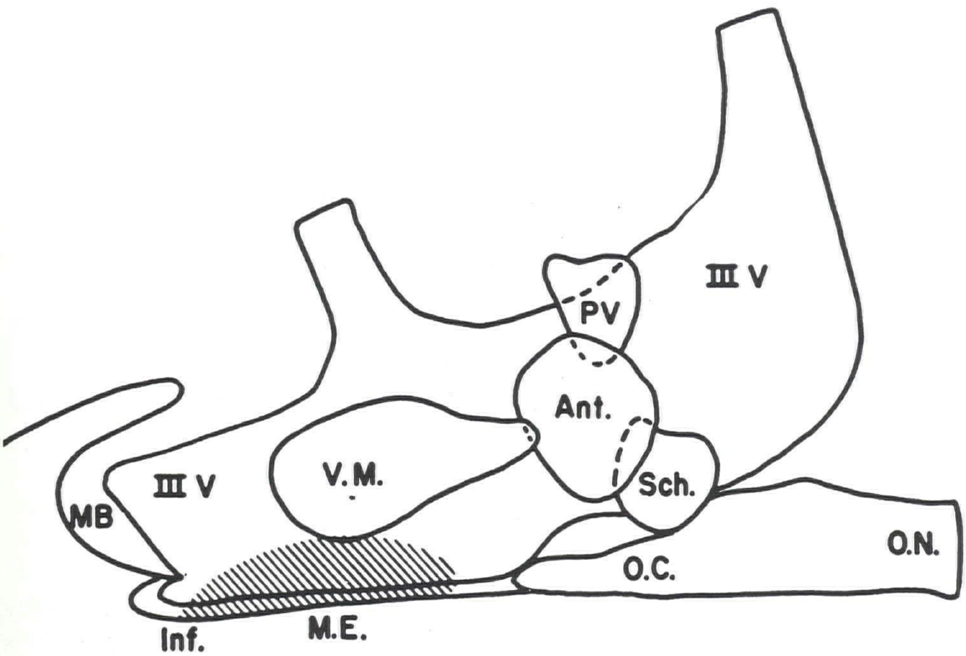

Figure 6

The Hypothalamus of a rat. The hatched section is the primary area controlling corticotropin secretion. (Greer[6])

THYROTROPIC SECRETION OF THE ANTERIOR PITUITARY.

Chronic propylthiouracil treatment in the rat will cause thyroid hypertrophy as well as a tenfold increase in the ability of the gland to concentrate inorganic iodide. By observing the results of hypothalamic lesions Greer found that the area essential for the normal growth response of the thyroid to antithyroid drugs seems to lie in the midline between the paraventricular nucleus and median eminence. Destruction of this area did not alter the ability of the thyroid gland to concentrate inorganic iodine. Lesions responsible for interfering with thyroid iodine metabolism seemed located somewhat posteriorly to those which inhibit the thyroid growth response. The greatest depression of thyroidal iodine metabolism resulted from lesions which prevent goiterogenesis, however. (Figure 7).

In transplanting pituitaries to heterotrophic sites, it was noted that the iodine metabolic factor is relatively unimparied, although the thyroid growth is considerably suppressed. It is therefore believed that the thyrotrophic hormone can be divided into two factors: One, the growth factor; two, the metabolic factor.

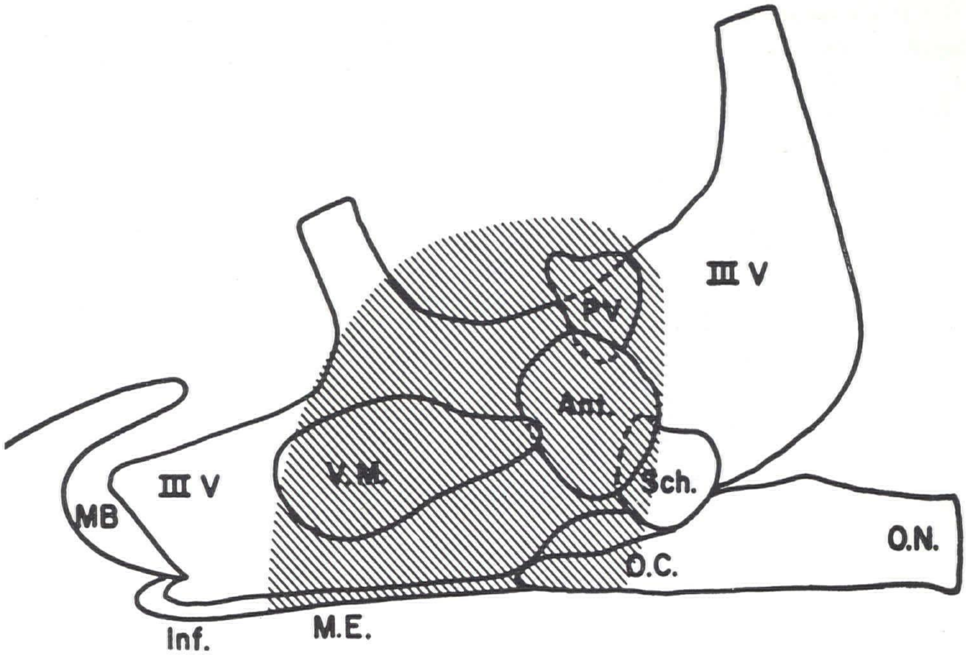

Figure 7

Hypothalamus of a rat. Hatched section is the primary area controlling thyrotropin secretion. (Greer[6])

In summary, evidence has been presented to show that the hypothalamus greatly influences the liberation of hormones from the adenohypophysis. This influence is not mediated through direct neural connections but indirectly through the hypophysial portal vessels.

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