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Median eminence and its relation to the anterior pitiutary

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THE MEDIAN EMINENCE AND ITS RELATION TO THE ANTERIOR PITUITARY

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I. Introduction and General Comments

A. Endocrinology

The word "hormone" comes from the Greek meaning "I arouse to activity". Hormones are secreted by the various endocrine glands of the body into the bloodstream and are carried to their target tissue where each hormone carries out its specific effect on its particular target tissue. Hormones are known to be polypeptide in nature.

Endocrinology is defined as the study of these hormones or internal secretions[2] Endocrinology encompasses a study of the pituitary, thyroid, adrenals, gonads, pancreas, etc.

It has been said that the pituitary is the "master gland" of the endocrines, having a profound controlling influence over its subservient target glands as well as other tissues in the body. There is now important evidence which points out that the pituitary gland, including both its lobes, is not an autonomous physiologic unit. The "master gland" would seem to have its "master". This brings us into the realm of neuroendocrinology.

B. Neuroendocrinology

Neuroendocrinology is the study of the effect of the central nervous system upon the familiar hormonal secretions. This effect seems to be mediated through the pituitary. To use a specific example, the Scharrers in their recent book[2] state that although there may be a feedback between the adrenal and pituitary, it is not of primary interest. They suggest that the feedback system

includes the central nervous system where the influences of the hormones are brought together with the other afferent stimuli (neural impulses). To strengthen this premise these workers state that the adrenal steroids can modify central nervous system function as shown by electroencephalography. Finally, they point out that without the controlling influence of the brain, no ACTH is released by the pituitary.[3] The pituitary gland most certainly has a "neural master". The study of this "master" is neuroendocrinology. There is no mystery as to the identity of this "master of the pituitary gland", for it is the central nervous system with its stimuli playing upon it, be they neural, hormonal, or chemical.

The relation of the paraventricular and supraoptic areas to the posterior pituitary has been well demonstrated many times. Evidence concerning the central nervous system relationships of the adenohypophysis has been emerging in recent years. The median eminence is the connecting link between the anterior pituitary and central nervous system according to work being done in this area. A discussion of the median eminence follows.

II. The Median Eminence

A. Anatomy

1. Gross

A description of the gross relationships of the median eminence is in order. G.W. Harris has defined the median eminence as ".... that part of the tuber cinereum related to the pars tuberalis or the primary plexus".[4] This definition should become more clear as the anatomical discussion of the median

eminence continues. (See Figure 1)

The tuber cinereum, which is rostral to the mammillary bodies, is the elevated area to which is attached the infundibulum. A funnel-shaped extension of the third ventricle, the infundibulum, points inferiorly. Anterior to the tuber cinereum is the optic chiasm. The pituitary is inferior to the infundibulum.

An anterior and posterior lobe comprise the pituitary gland. The anterior lobe (adenohypophysis) is derived from the ectoderm of Rathke's Pouch, and the posterior lobe (neurohypophysis) is derived from neural ectoderm. The infundibular process, infundibular stem, and the median eminence of the tuber cinereum make up the posterior lobe of the pituitary. Comprising the adenohypophysis are the pars tuberalis, pars intermedia, and pars distalis. The median eminence and the infundibular stem make up the infundibular or neural stalk. Being designated the hypophysis are the infundibular stem and its surrounding pars tuberalis.[5] The above description can be outlined thus:[6]

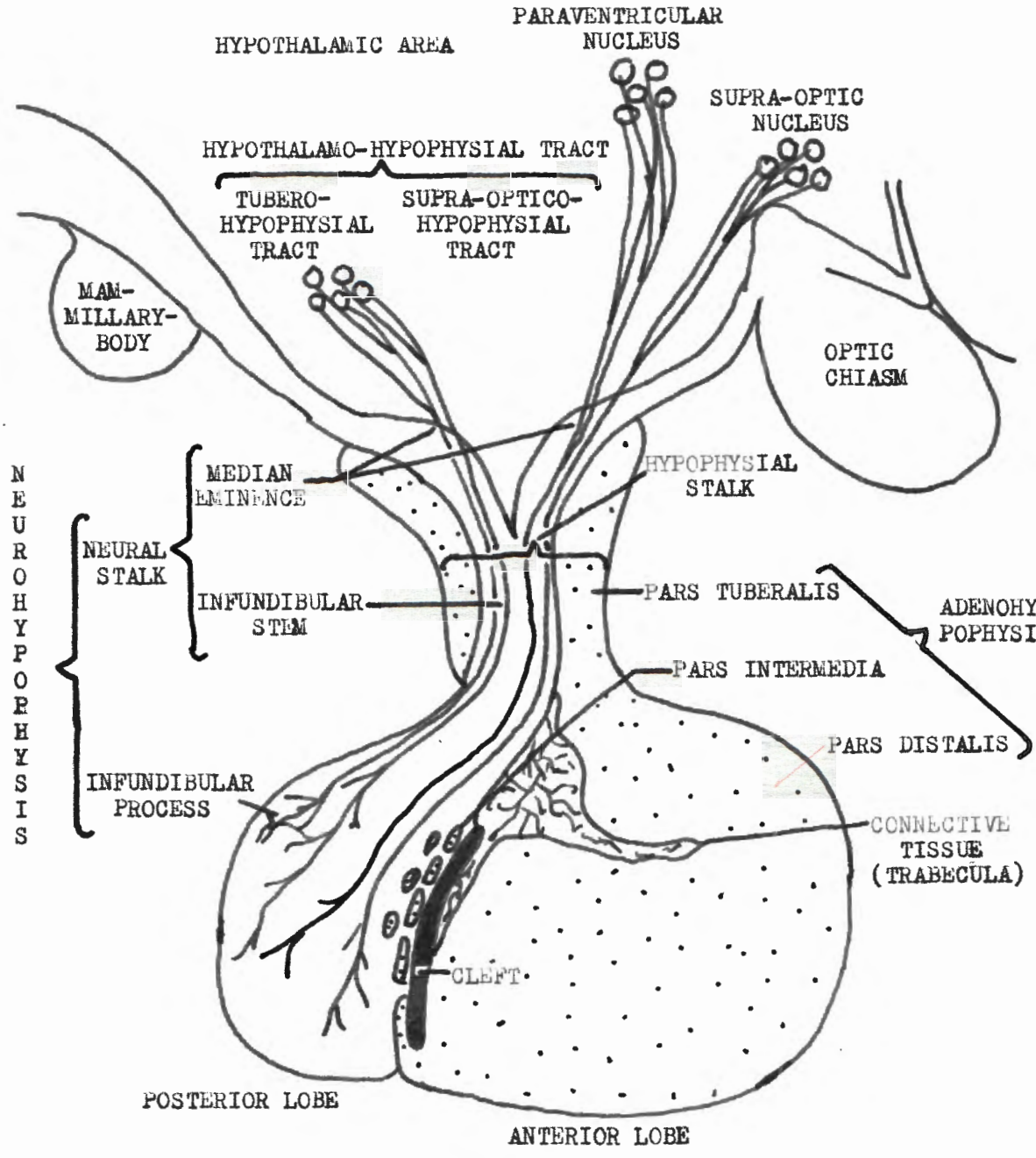
Neurohypophysis
- Median eminence of the tuber cinereum } = Infundibulum or neural stalk
- Infundibular stem
- Infundibular process (neural lobe)

Adenohypophysis
- Pars tuberalis
- Pars intermedia
- Pars distalis

Neural stalk and pars tuberalis = hypophysial stalk

2. Histology

It has been found that the median eminence of most mammals, including man, is differentiated into layers:[7]



DIVISIONS OF THE PITUITARY GLAND AND RELATIONSHIP TO HYPOTHALAMUS

Redrawn and modified from Ezrin, Calvin, The Pituitary Gland, Clinical Symposia, 15:73, 1963

figure 1

(1) An ependymal zone which underlies the third ventricle.

(2) An internal zone containing the hypothalamohypophysial tract (which contains the axons of the supraoptico- and paraventricular-hypophysial tracts).

(3) The external or palisade zone which is just beneath the pars tuberalis. Ramifying in this palisade layer are the primary capillary loops which are discussed below.

Benoit[8] has some excellent photomicrographs of the median eminence in the duck. He found the following layers: (See the drawing of Dr. Benoit's photomicrograph, Figure 2)

(1) Ependymal layer.

(2) Internal layer of the hypothalamo-hypophysial tract.

(3) Layer of fine fibers derived from layer #2.

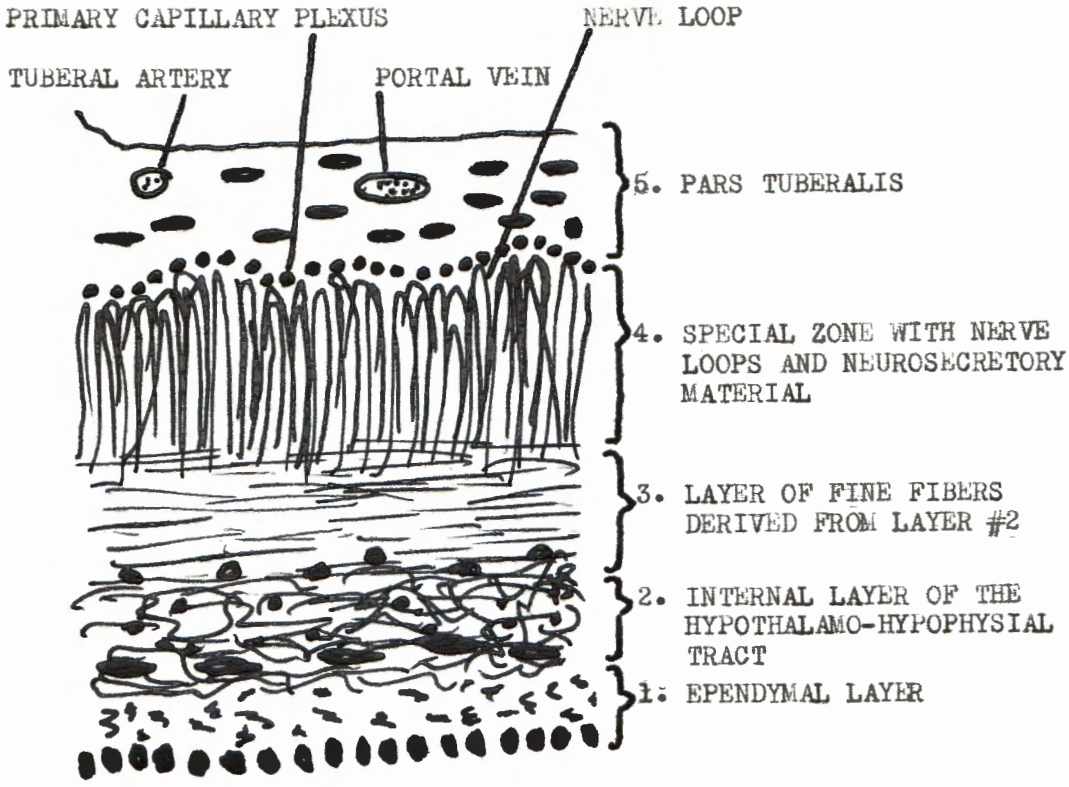
(4) Special zone with nerve loops and neurosecretory material.

(5) Pars tuberalis.

Note . Benoit mentions that layer #4 is a special zone with nerve loops and neurosecretory material. (See Figure 3 for an enlargement of this area). The neurosecretory material and primary capillary plexus are very important in the discussion of the median eminence. The median eminence in all vertebrates including the human fetus contains varying amounts of neurosecretory material.[9]

3. Vascular considerations

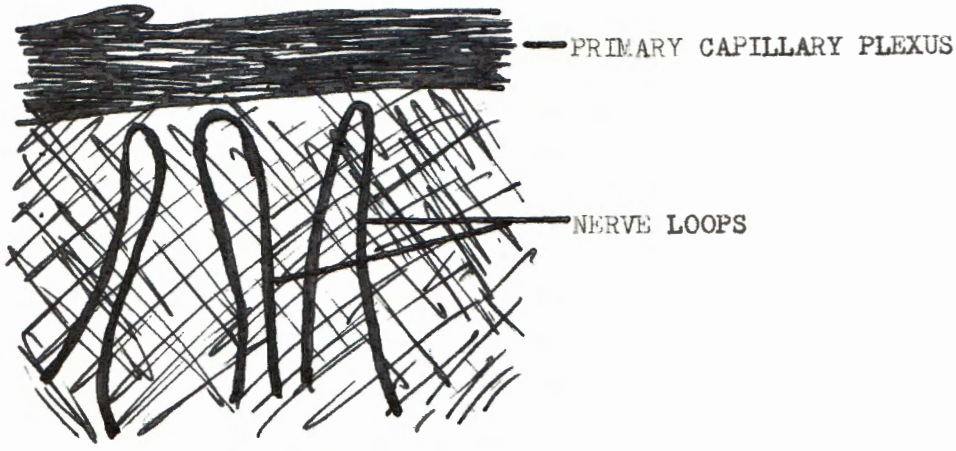
The blood supply of the pituitary gland[5] is derived from the left and right superior hypophysial arteries and from the left and right inferior hypophysial arteries. (See Figure 4) These supply the optic chiasm, hypothalamus, stalk, trabecula,



TRANSVERSE SECTION OF THE DUCK MEDIAN EMINENCE

(magnification approximately 300)

figure 2

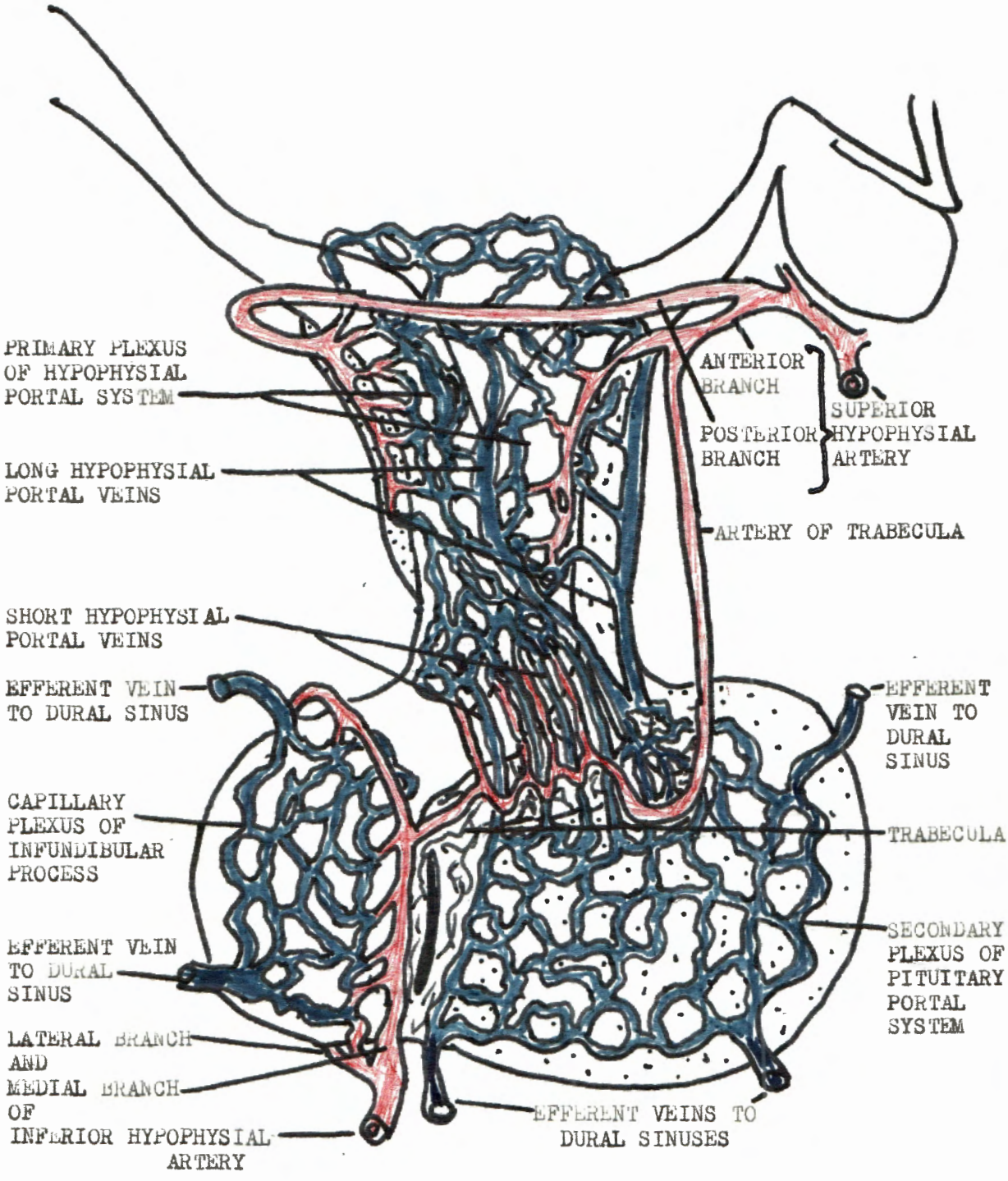


NERVE LOOPS IN THE "SPECIAL ZONE" OF THE DUCK MEDIAN EMINENCE

(see layer #4 above)

Drawn and modified from photomicrographs in Benoit, J. Hypothalamo-hypophysial Control of the Sexual Activity in Birds, General and Comparative Endocrinology, Supp. 1:254, 1962

figure 3



BLOOD SUPPLY OF THE PITUITARY

Redrawn and modified from Egrin, Calvin, The Pituitary Gland, Clinical Symposia, 15:73, 1963

figure 4

and posterior lobe of the pituitary. Note that the adenohypophysis does not receive an arterial blood supply.

The blood supply of the adenohypophysis is via the hypophysial portal veins. (See Figure 4) These portal veins are the long hypophysial portal veins which arise from capillaries originating in the median eminence and upper stalk. Arising in the lower stalk are the short hypophysial portal veins, which also supply the adenohypophysis.

The superior hypophysial artery and a small part of the inferior hypophysial artery in the pars tuberalis form an extensive vascular plexus from which arise many, many capillary tufts or loops which penetrate into the median eminence and come into intimate relation with certain nerve tracts to be discussed below. (See Figures 2 and 3) It is these capillary tufts which are called the primary capillary plexus of the hypophysial portal vessels. The drainage of blood from this plexus of capillaries is down the portal veins and into the sinusoids of the pars distalis.[10]

In man, the primary capillary plexus is found in the median eminence and extends well into the neural stalk. Also, it forms a tufted pattern and there is more connective tissue in the walls of these tufts.[11] The loops of the primary capillary plexus in man form spike-like structures of complexity.[12]

Adams, et al[13] suggest there is a selective distribution of portal blood. With complete transection of the pituitary stalk there is bilateral infarction in the pars distalis. They have found that with only a partial transection of the pituitary stalk the infarction is smaller, unilateral, and

on the same side as the lesion. It was their conclusion from this information that there are circumscribed areas in the pars distalis supplied by groups of portal vessels.

Worthington[14] has found the arterioles supplying the primary capillary plexus to be quite contractile. He reports none of this in the hypophysial portal vessels. Furthermore he has found that each artery supplying the primary capillary plexus has a definite area of distribution[15] Developing this further, Adams et al[15], mention that it is well known that the various types of cells of the pars distalis have a tendency to be grouped in certain areas of it. They suggest that the arteries supplying the primary capillary plexus can individually contract thus varying the blood flow to a certain region of the primary capillary plexus and in turn varying the blood flow to a certain area in the pars distalis containing one particular group of cells. Perhaps certain hypothalamic nuclei send their axons to specific areas in the primary capillary plexus thereby being linked with a certain cell type in the pars distalis.

Wislocki and King[16], using dye injection, found that the tuber cinereum was unstained except for the median eminence, i.e., no blood-brain barrier in the median eminence. (They concluded that the median eminence was a part of the infundibulum and not the tuber cinereum.) This would allow for perfusion in this area.

4. Neural Considerations

Green[17], along with the majority of workers, has found

no innervation of the pars distalis. It has been suggested that the confusion here has been due to misleading reticular fibers interpreted as nerves[18]. Neither parasympathetics nor sympathetics appear to play a significant part in the neural control of the pituitary[19].

In amphibians, Green[20] describes nerve fibers running from the diencephalon into the infundibulum, passing through the median eminence and into the pars nervosa. Nerve fibers branching from this hypothalamo-hypophysial tract into the median eminence seem coarser than the fibers of the neural lobe. Amphibia have a primary capillary plexus analogous to that in mammals.

Okamato and Ihara[21], from thir studies of mammals, birds, and amphibians, give us this picture: The loops of the primary capillary plexus are surrounded by Grevig's islets which are structures of reticular fibers. Neurosecretory fibers were found to branch off from the hypothalamo-hypophysial tract, and, after a varying course depending on the animal species, end at or near the walls of the primary capillary in the median eminence. A considerable accumulation of neurosecretory material was seen by the authors along the loops of the primary capillary plexus.

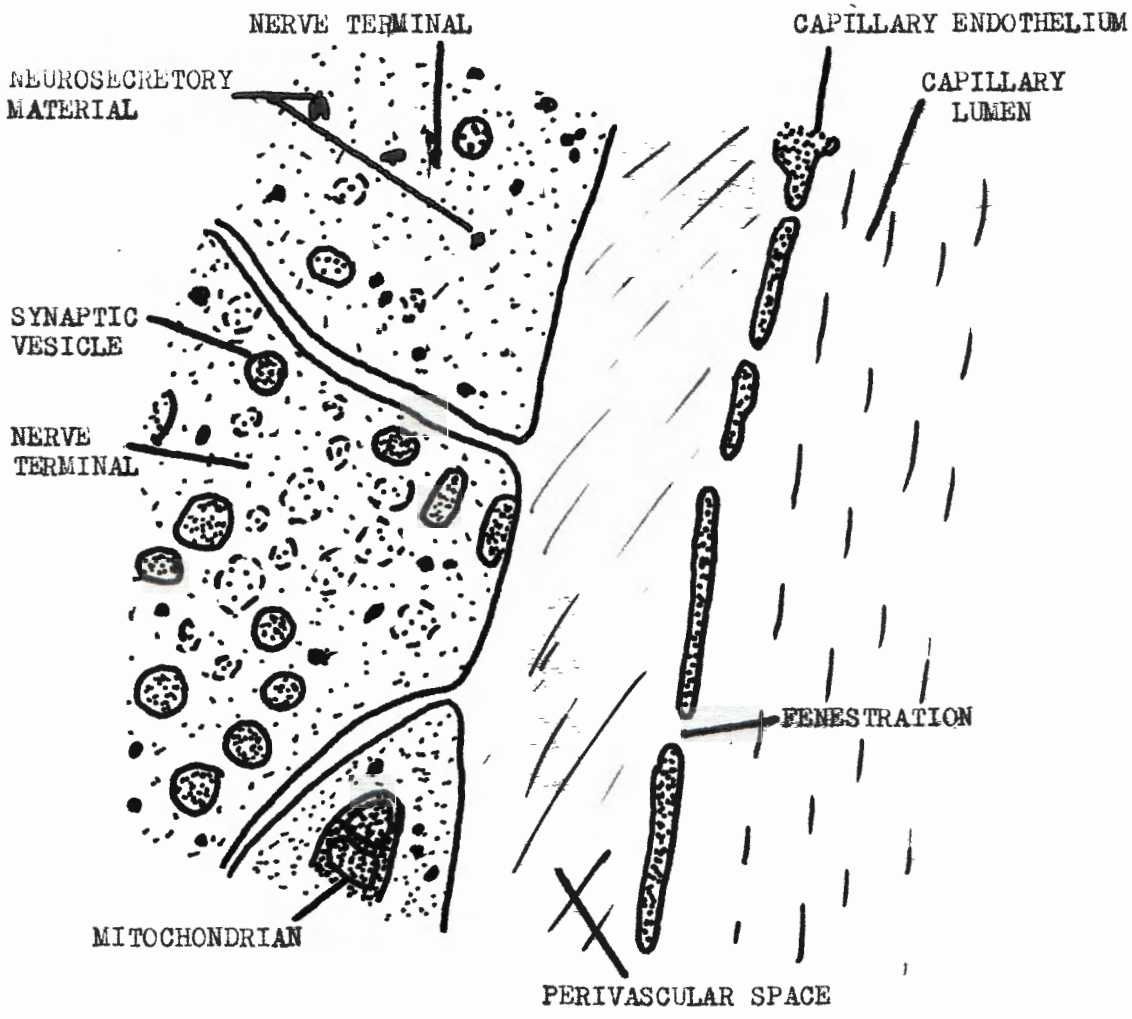
Rinne has made a study of this neurosecretory material using special stains[22a]. With aldehyde-fuchsin he found A.F.-stained neurosecretory material around the primary capillary plexus in the median eminence in both dorsal and ventral walls.

It was most profuse in the external layer of the ventral wall of the median eminence. Recall that this external layer contains the primary capillary loops. A.F.-stained transverse nerve fibers (on the section) were found running toward the primary capillary plexus in this region. Neurosecretory material was also found around the portal vessels in the area of the median eminence's dorsal wall and the pars tuberalis. He found evidence suggesting that this neurosecretory material also arrived in this area via nerve fibers.

The neurosecretory material discussed above had similar histochemical and histological properties as that in the hypothalamus and infundibular process. He concluded that it was protein in nature. Experimentation suggested that the neurosecretory material found around the primary capillary plexus and portal vessels and that in the hypothalamus and infundibular process were functionally linked. At this point, it would seem likely that the neurosecretory material found in the median eminence and neighboring regions is from nerve fibers of the hypothalamo-hypophysial tract with their nuclei being located in the hypothalamus.

5. Electron Microscopy

The closeness of the nerve fibers in the median eminence to the capillaries of the primary plexus of the hypophysial portal system[22b] has been stressed by recent electron photomicrographs. (See figure 5). The nerve terminals containing synaptic vesicles and neurosecretory substance are shown. The capillary walls are fenestrated and are surrounded by a



ELECTRON PHOTOMICROGRAPH OF THE MEDIAN EMINENCE OF THE RAT
(X 91,500)

Drawn and modified from an electron photomicrograph in Harris, G. W. A Summary of Recent Research on Brain-Thyroid Relationships in Cameron, M. P. and O'Conner, Maeve, eds., Brain-Thyroid Relationships, Boston, Little, Brown and Company, 1964, figure 1(a).

figure 5

perivascular space. The perivascular space is continuous with spaces between the nerve terminals. The implication here is obvious: neurosecretory material escaping from the nerve terminals could enter the perivascular space and thus enter the primary capillary plexus via fenestrations in the capillary endothelium.

B. Physiology

1. General Comments

In his excellent review of neuroendocrinology, Reichlin[7], states , ".... the activity of most of the endocrine glands is under the influence of the central nervous system and .... certain functions of the nervous system in turn are affected by endocrine substances". This has already been alluded to. The particulars involved in Reichlin's statement are postulated thus: "Neurohumoral substances arising from nerve endings in the median eminence of the hypothalamus enter capillaries of the primary plexus of the hypophysial-portal circulation, whence they are carried by the portal veins of the hypophysial stalk into the sinusoids of the anterior pituitary gland".

Recall that the blood in the portal vessels flows to the sinusoids of the adenohypophysis. Thus, most of the blood reaching the anterior pituitary has first perfused the primary capillary plexus where direct contact with neural tissue is made[7].

The Scharrers, in their book, would seem to agree. They also mention the fact that neurohumoral substances are hypothalamic in origin[23]. Brodish and Long have suggested a different

route for the neurohumoral substances, it being the systemic circulation[24]. Earlier work by Hume and Wittenstein supports this route[25]. Most workers agree with a route via the portal circulation. Campbell, et al[26], have some results which are against a route via the systemic circulation. Median eminence extracts infused into the anterior pituitaries of female rabbits of 47 of 75 animals was performed. Using high intravenous doses of the same extract, 5 of 21 ovulated. Certainly blood from the median eminence carried by the portal vessels would have a higher, more physiologic, dose of neurohumor than that in the systemic circulation.

Benoit[8] has found that the nerve loops in layer #4 of the median eminence of the duck contain neurosecretory material. This is also seen in layers #2 and #3. He emphasizes the fact that the nerve loops are in contact with the primary plexus of the hypophysial portal system. Benoit suggests that this material originates in the neurons of the anterior hypothalamic nuclei.

Two interesting pieces of evidence are cited by Benoit in his article. Firstly, passage of neurosecretory material into the hypophysial portal veins of the chicken has been noted[27]. Secondly, neurosecretory substance has been reported to pass into sinusoids and cells of the pars distalis[28].

In his studies of the avian median eminence hormones, Hirano[29], has found that the amount of neurosecretory material in the median eminence is closely related to the neurohypophysial hormonal activity of the median eminence. This and the previously

cited evidence suggest that the neurosecretory material is in fact neurohormone which has the anterior pituitary cells as its target tissue.

Again, to briefly review the model that has been developed here: neurosecretory material from the hypothalamic nuclei enter the hypothalamo-hypophysial tract and to go to the nerve loops in the median eminence. Here the substance passes into the capillaries of the primary plexus. The neurosecretory material is then carried by the hypophysial portal system to the pars distalis. These neurosecretions are then felt to influence the anterior pituitary parenchymal cells.

Some of the evidence supporting this hypothesized central position of the median eminence between the central nervous system and the anterior pituitary will now be presented and discussed. Lesions in the frontal part of the median eminence and somewhat anterior to it result in findings similar to those after hypophysial stalk section[30]. Here it seems that important nerve fibers to the median eminence have been interrupted making it impossible for the neurosecretory substance to reach the pituitary.

When rat pituitaries are transplanted to the kidney, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and corticotrophin (ACTH), all decrease in measureable amounts while luteotrophic hormone (LTH) rises[31]. (This rise in LTH is to be explained later.) The pituitary here has been removed from its important portal blood supply containing influencing neurohumors, and the pars

distalis thus cannot manufacture or at least release the hormones studied with the exception of one.

If blood flow through the hypophysial portal vessels is prevented following section of the hypophysial stalk in rabbits[7], the following occur which go along with the data just preceeding: atrophy of the gonads, failure of ovulation, depressed adrenal function, and thyroid inhibition. This is also true of the human being- recall hypopituitarism. From this evidence, the conclusion is that the pars distalis and median eminence must be in and have their proper anatomical relationships for normal pituitary function.

2. The Specific Hormones:

a. Somatotrophic hormone-releasing factor (SRF)

In 1960, Reichlin[32], produced various lesions in the rat central nervous system and found that massive lesions which involved the anterior half of the median eminence were most effective in stunting growth. The more severe degrees of growth reduction were found when the anterior half of the median eminence, the arcuate nuclei and the supraopticohypophysial tract as it crosses through the median eminence were involved. There was no significant change in growth when the following were involved: anterior commissure, fornix, preoptic area, mammothalamic tract, and the supraoptic, paraventricular, suprachiasmatic, posterior, dorsal, anterior, ventromedial, and mamillary nuclei. Thus, the supraoptico-hypophysial tract and median eminence appear to be of importance where an SRF is involved. We might hypothesize that

SRF is found in either or both of these structures.

When the hypophysis is transplanted, the somatotrophic hormone (STH)-producing cells of the adenohypophysis disappear. If a rat is given prolonged injections of posterior pituitary preparations containing antidiuretic hormone (ADH), there is an enlargement of the tibia cartilage. Oxytocin does not produce similar results. If a posterior pituitary preparation containing ADH is given to a hypophysectomized rat, there is no change in the epiphyseal cartilages. It can be concluded from these findings of Del Vecchio, et al[33], that there was no STH contamination of the posterior pituitary extract because it did not induce growth in hypophysectomized animals. Something in the ADH preparation caused the STH to be released.

Deuken and Meites[34] have added rat hypothalamic extracts to rat pituitary culture which resulted in increased production of somatotrophin in the culture. The evidence for the existence of SRF (s) is there. In a private communication to those authors, Martini, Mueller, and Pecile have demonstrated this in vivo in rate by single carotid injections. Deuken and Meites have confirmed it.

b. Corticotrophin-releasing factor (CRF)

There is no important feedback between the adrenals and pituitary. However, the feedback for the control of the adrenal cortex probably includes the central nervous system. Indeed, adrenal steroids can influence the central nervous system as shown by electroencephalograms. That the CNS is involved in this

feedback system is borne out by the fact that in anencephali in which there is an adenohypophysis present, the adrenals are smaller than normal. Without the influence of the brain, the pituitary does not release ACTH, therefore[35].

Are there regions in the brain which contain a corticotrophin-releasing factor? Brizee and Eik-Nes[36] found that a one milligram intracarotid injection of a saline extract of supraoptic nucleus and median eminence tissue produced significant increases of 17-hydroxycorticosteroids in dogs. This was similarly attempted with the same amounts of lateral hypothalamic nucleus, mammillary body, optic tract, paraventricular nucleus, and posterior sigmoid cerebral cortex without the same results.

These authors go on to note that vasopressin will promote ACTH secretion and that the supraoptic nucleus and median eminence contain vasopressin-like material. Recall from above that posterior pituitary ADH extract chronically administered to rats produces growth. Perhaps these extracts contain SRF & CRF as impurities or perhaps vasopressin is a weak CRF and SRF.

McCann and Haberland[37] have added to our knowledge somewhat in this regard. From their studies they have concluded that only 10-20% of the ACTH-releasing activity is accounted for by vasopressin when the extract is from the stalk-median eminence area. They found CRF in relatively small amounts in posterior lobe (pars nervosa) extracts. Therefore, there is a differential location of CRF and vasopressin in portions of the neurohypophysis. These authors suggest that the greater amount of CRF in the median eminence coincides with the vascular link of the median eminence

with the pars distalis via the hypophysial portal vessels. However, they did conclude from their studies that vasopressin and CRF both release ACTH , but CRF is the principal factor of the two.

Guillemin[38] has re-evaluated acetylcholine, adrenalin, noradrenalin, and histamine with respect to their possible activation of pituitary ACTH activity by stress. None of these was found to be essential in the link between the hypothalamus and adenohypophysis in activation by stress.

A CRF was shown to be present in the peripheral blood in hypophysectomized rats by Brodish and Long[24]. It was not found in blood from normal animals. The authors also found that the adrenal glands were not necessary for its production. This agent was not detectable if there was a high steroid level in the blood. These workers found one millimeter in diameter lesions placed one to two millimeters behind the optic chiasm at the base of the hypothalamus resulted in no detection of the factor. This would place the lesion in the region of the median eminence and the nerve fibers running to it.

It has been found that lesions of the median eminence depress the adrenocortical response to stressful stimuli[39]. This was demonstrated by measuring eosinophils, lymphocytes, adrenal ascorbic acid, ACTH levels, various glucocorticoids, and Porter-Silber chromogens.

From the above studies, it can be concluded that the median eminence has an important position in the link between the hypothalamus and adenohypophysis with reference to ACTH funtion and that it contains a substance(s) which cause(s) the release of ACTH, by one mechanism or another.

Anterior pituitary tissue cultures lend support to this last statement. Guillemin and Rosenberg[40] found that ACTH activity disappeared in dog and rat anterior pituitaries grown alone. This activity was made to reappear with the addition of hypothalamus or median eminence explants. Control hypothalamus or cultures or anterior pituitary grown with explants of brain cortex, liver, and spleen had no ACTH activity.

Other studies show that the median eminence and related structures may not be the only site of ACTH-releasing hormones. A corticotrophin-releasing factor has been claimed to have been found in human cerebrospinal fluid.[41] Injected into the carotid artery of trained dogs, it caused a rise in plasma 17-hydroxycorticosteroids.

Porter and Rumsfield have studied hypophysial portal plasma for CRF. They have purified and partially characterized a fraction with ACTH-releasing activity.[42]

c. Thyrotrophin-releasing factor (TRF)

Studies relating to a TRF have been more confusing and the search for a TRF has been more difficult. It might be well to start with the studies of Knigge and Bierman.[43] They found that when the hamster was exposed to cold, thyroidal I^{131} release was greatly accelerated during the first twelve hours. If the animals were treated with reserpine or had median eminence lesions one day prior to exposure or had had chronic lesions (3 to 6 weeks) the accelerated release of thyroidal I^{131} was prevented. However, these did not interfere with normal hormone delivery.

In hypophysectomized hamsters, thyroid-stimulating hormone((TSH) can restore uptake to normal as is well known. When Knigge and Bierman discontinued TSH to hypophysectomized animals and exposed them to cold, I^{131} release from the thyroid was not accelerated. When they took pituitary tissue and transplanted it into the cheek pouches of hypophysectomized hamsters, release and uptake of I^{131} were temporarily restored. However, cold exposure did not accelerate I^{131} release in these pituitary-grafted, hypophysectomized animals.

The conclusions from the above experiments are: (a) A central nervous system stimulus sets off the pituitary-thyroid system in an accelerated response from cold exposure. (b) This depends upon the normal anatomical and proper connections of the pituitary.

Note that it was mentioned above that median eminence lesions prevented an accelerated response by the thyroid. Shibusawa, et al[44], found in lesions from the rostrum of the median eminence to the frontal area of the hypothalamus that thyroid and pituitary weight decreased, thyroid function was slightly depressed, and if methylthiouracil was given there was no goiterogenic response. Only if lesions involved the median eminence was there depression. Greer, in similar experiments had the same general results using propylthiouracil[45].

An interesting side-light might be mentioned here. Ford and Gross[46], upon intravenous injection of I^{131} labelled T_3 and thyroxin into normal rabbits, found these chemicals to be

concentrated in the brain gray matter, especially in the region of the paraventricular nucleus and median eminence. However, it was more heavily concentrated in the hypophysial lobes. T_3 concentration was greater than thyroxin in all.

Shibusawa and Nishi[44] claim to have isolated a thyrothrophin-releasing factor. It was extracted from the hypothalamus. When lesions rostral to the median eminence and in the frontal area of the hypothalamus were produced, pituitary weight and thyroid function decreased. Administration of their extract reversed this. Reichlin, et al, using Dr. Shibusawa's extract could not reproduce these experiments.[47]

Guillemin[48] has reported finding TSH-releasing activity in acid extracts of sheep hypothalamus. It was not active hypophysectomized animals, thus ruling out the possibility of significant TSH contamination of his extract.

From his observations, Reichlin concludes that the median eminence contains a thyrotropin-releasing factor. It is not thyroid-stimulating hormone[49].

From above, it was seen that there appears to be some thyroid activity possible without direct CNS influence. Brown-Grant, Harris, and Reichlin studied thyroid function in stalk-sectioned rabbits[50]. They found that pituitary disconnected from the hypothalamus has some autonomous TSH secretion. It could still be inhibited by an elevated thyroid hormone in the blood and also by stress of physical trauma. Evidently, at least from this data, the CNS modifies the release of TSH from the pituitary.

d. Gonadotrophin-releasing factors (GRF)

When female rats have been hypophysectomized, normal gonadotrophic activity is restored only if pituitary grafts are placed near the median eminence. Grafts elsewhere have been unsuccessful[51]. With stimulation of the median eminence electrically, gonadotrophin is released, but this is not so with electrical stimulation of the adenohypophysis itself[52]. Release of the gonadotrophic hormones, then, certainly does seem to be under CNS control, the median eminence playing an important role.

Campbele, et al[26]; found that infusion of median eminence extract into the anterior pituitaries of rabbits produced ovulation in 47 of 75 and only 3 of 73 controls ovulated. High intravenous doses of the same median eminence extract caused ovulation in 5 of 21. This is more direct evidence for a gonadotrophin releasing factor(s) from the median eminence.

In a similar experiment by Nikitovitch-Winer[53] using "pentobarbitol blocked" proestrus rats, extracts of rat and bovine median eminence were used. Results were similar. Intra-adenohypophysial infusion of the extract produced ovulation in 24 of 34 while only one control of 28 ovulated. Again, it was found that intravenous doses had to be quite high to produce ovulation. The author concluded that the median eminence contains a substance(s) which can release ovulating hormone from the pituitary.

Working at this from another angle, Benoit[8], found that if

the hypophysial portal vessels are sectioned in birds, there is testicular atrophy and abolishment of the photosexual reflex. To throw in some controversy here, the Scharrers state that the pituitary does not need a functional connection to the hypothalamus for the maintaining of the male reproductive tract[61].

There is good evidence for each of the three gonadotropins. Igarashi and McCann injected the crude acid extract of rat median eminence intravenously into ovarectomized, estrogen and progesterone-blocked rats.[54] This caused a significant elevation of follicle stimulating hormone (FSH) in the plasma of these animals. Cerebral cortical extract used in similar animals caused no significant elevation in FSH plasma levels. The experiment was also performed on hypophysectomized rats without a rise in plasma FSH. Since administering the median eminence extract did not elevate plasma FSH in hypophysectomized rats while it did so in rats with intact pituitaries suggests the extract contained a substance capable of acting on the intact pituitaries to release FSH.

Guillemin[48] has found luteinizing hormone-releasing activity in median eminence and hypothalamic extracts. He also noted that these extracts were able to cause ovulation and corpus luteum formation in animals with hypothalamic lesions which had prevented these. More recently, Ramirez and McCann have found beef stalk-median eminence acid extracts caused an elevation of plasma LH in estrogen and progesterone-pretreated ovarectomized rats. This could not be accounted for by contamination of the extract by LH[55].

CNS control of LTH appears to be done in a different way than for the other pituitary hormones. For, when pituitary gland is in a tissue culture alone, it secretes large amounts of prolactin. However, if hypothalamic tissue incubates in this pituitary tissue culture, LTH secretion is depressed. Thus we have a prolactin-inhibiting factor (PIF) rather than a prolactin-releasing factor[48].

C. Biochemistry

Some chemical properties of the above discussed releasing factors are: a) soluble in dilute acid buffers b) more resistant to boiling than pituitary hormones c) affected by proteolytic enzymes d) relatively stable e) probably polypeptide[7]:

Deuben and Meites[34] have reported an extract of the hypothalamus with somatotrophin-releasing factor (SRF) activity. It was found in either acid or boiled extract of hypothalamic tissue.

At present, the most is known about CRF. Saffran, et al[56] separated CRF by paper chromatography and found it to be separate from vasopressin. CRF activity has to do with two types of compound, alpha CRF and beta CRF. Alpha CRF is similar to alpha melanocyte stimulating hormone (MSH), but has low ACTH-releasing activity when compared to beta CRF. Two types of alpha CRF have now been found: $alpha_1$ and $alpha_2$. Beta CRF is closely related to vasopressin. It has no melanophoric activity nor ACTH activity. Beta CRF's amino acid sequence as yet has not been determined. At present it would appear that beta CRF is the true releaser of ACTH. Almost all the ACTH-releasing activity in the median eminence is due to CRF.[7, 48]

Eik-Nes, et al[41] have partially isolated what they term a

"corticotrophin-influencing factor" (CIF) from human spinal fluid. They found it to be protein or polypeptide with an isoelectric point of 5.4.

Chemical data on TRF are scant. Guillemin states that alpha and beta MSH have been proposed as being involved here, but the evidence is not convincing. He and his workers have found TRF activity in acid extracts of sheep hypothalamus[48].

Acid extracts of stalk-median eminence tissue apparently contain FSH and LH-releasing factors. Igarashi, et al have concluded from studies that FSH and LH release were caused by small molecules dissimilar from vasopressin and oxytocin, but of the approximate molecular size[54]. Guillemin has reported that LRF has been partially purified. He concludes it is most likely a small polypeptide[48]. There is little information here in regard to PIF, but it is known to be present in hypothalamic tissue by studies using pituitary and hypothalamus tissue culture[48]. PIF has also been found in median eminence tissue[7].

Reighlin[7] has suggested that instead of being called "releasing factors" or "inhibiting factor" they might be termed "influencing factors". He reasons that there is a similarity between CRF and ACTH and that possibly "certain of these releaser substances serve as tropic-hormone precursors".

III. The Median Eminence in Relation to the Central Nervous System

An analogy between the median eminence and the pars nervosa has been drawn by Reichlin[7]. Nerves end in relation to blood vessels in each, there is an extracellular space in both, and

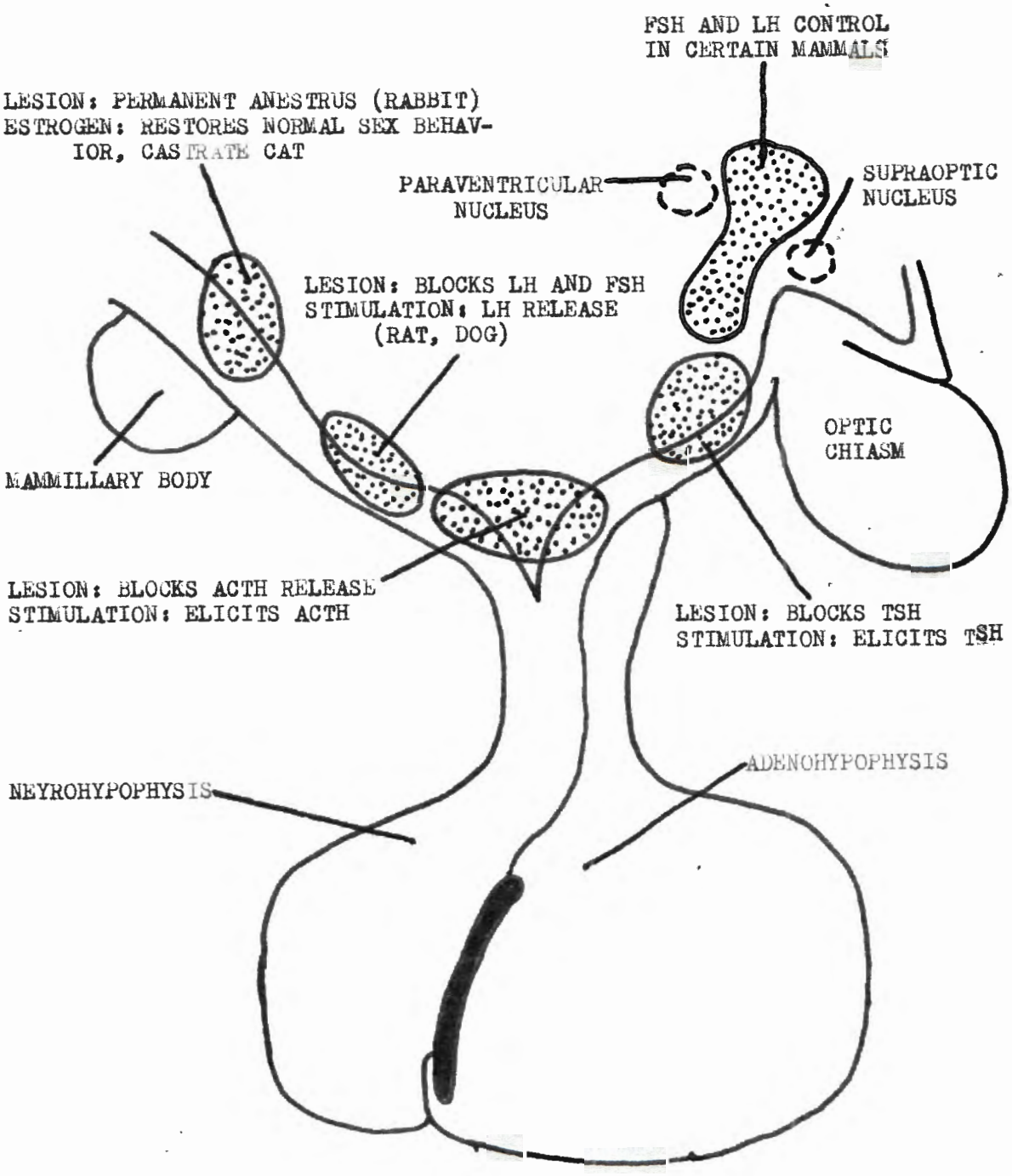
neurosecretory material is found at the nerve endings. In both cases this neurosecretory material appears to come from the hypothalamus.

Where are the perikaryons of the nerve fibers which end in the median eminence? The consensus of opinion is that these nerves are from nuclear groups in the tuberal portion of the hypothalamus[7]. (See Figure 6 for proposed locations of these nuclear groups.)

Important neural connections of the median eminence region include the rhinencephalon, cerebral cortex, thalamus, and reticular-activating systems[7]. It must be remembered that afferants to the hypothalamus are from the oldest parts of the cortex and from the basal ganglia. The limbic system comprizes some of this[57]. The Scharrers also stress thepart played by the limbic system in the function of the anterior pituitary. Mason, et al[58] have studied the effects of the limbic system in pituitary-adrenal function by electrical stimulation of the amygdaloid complex in the rheusus monkey. It caused increased 17 hydroxycorticosteroid levels. Bilateral amygdalectomy bore this out. Next evidence for the importance of the hypothalamus in anterior pituitary control will be discussed.

That the hypothalamus contains an SRF has already been discussed. Deuben and Meites have shown growth hormone releasing activity in hypothalamic extracts in anterior pituitary culture[34]. This has also been demonstrated in vivo (private communication to these authors by Martini, Mueller, and Pecile).

It has been well shown that there is hypothalamic CRF



CURRENT VIEWS ABOUT THE LOCALIZATION, WITHIN THE HYPOTHALAMUS, OF ENDOCRINE REGULATING AREAS

Lesions' locations from a composite diagram in Tepperman, J. Metabolic and Endocrine Physiology: An Introductory Text, Chicago, Yearbook Publishers, 1963. Cited by: Reichlin, Seymour. Neuroendocrinology, New Eng. J. Med., 269:1182-1191, 1246-1250, 1296-1303, 1963.

Outline of hypothalamic and pituitary area from a drawing in Ezrin, Calvin, The Pituitary Gland, Clinical Symposia 15:71-98, 1963.

figure 6

activity[40, 24, 36]. However, hypothalamic activation may not be the only force determining ACTH secretion rate[7]. Guillemin and Rosenberg found thataddition of posterior hypothalamic explants to tissue cultures of dog and rat pituitaries caused ACTH activity to reappear. This posterior tissue alone had no ACTH activity[63]. The work of Slusher and Roberts supports the importance of the posterior hypothalamus in ACTH response[64]. TRF activity has been found in hypothalamic extract which is not active in hypophysectomized animals[48]. In the case of TSH, the hypothalamic function seems to be one of maintaining the normal rate of secretion and to modify this in reponse to stimuli acting through the CNS[50]. In the discussion ofphysiologic aspects of TRF it was mentioned that there seems to be some autonomous thyroid activity possible without CNS influence.

Since FSH-releasing activity has been found in median eminence extracts[54], we can assume its origin to be in the hypothalamus. Luteinizing hormone-releasing activity has been found in hypothalamic extracts[48] by Guillemin. The influence of the hypothalamus in relation to LTH seems to be one of inhibition[7, 48], or a prolactin-inhibiting factor (PIF). Pituitary gland culture secretes prolactin, but the addition of hypothalamus inhibits this. Hypothalamic lesions have their effect on the menstrual cycle[64]. Electrical stimulation of the posterior median eminence and the basal tuberal region of the hypothalamus or medial amygdala also has an effect in this regard[62]. Halasz and Flerko found that normal PAS-positive

basophilic cells of anterior pituitary grafts appeared only in grafts within a narrow area of the hypothalamus[63]. It extended from the paraventricular nuclei to the optic chiasm and posteriorly to the mammillary region.

IV. Summary

The author has attempted to stress the idea that the "releasing factor" material is produced within the hypothalamus. This material, which appears as neurosecretory material when found in axons, travels down efferent nerves from the hypothalamus and enters vascular tracts leading to the pars distalis. The location of the transferance of the material from a neural to a vascular tract is at the median eminence. Nerve fibers from the hypothalamus come into close contact with the primary capillary plexus here, facilitating the movement of the neurosecretory material across the perivascular space and into the capillaries. From these capillaries the substances travel down the hypophysial portal vessels into the sinusoids of the pars distalis of the adenohypophysis. Their effect is exerted on the parenchymal cells.

The various "releasing factors" for which there is evidence have been discussed. They appear to be polypeptide in nature, being relatively small molecules. In some cases they have been isolated and partially characterized.

Some of the material presented is admittedly controversial. Some of the concepts will change as new evidence appears. However, the importance of the median eminence has been well demonstrated experimentally, and this importance is likely to receive wider acclaim in the future, and moreso the concept with which it is involved.

V. Conclusions

1. The central nervous system through humoral and neural stimuli exerts an effect on the hypothalamus.

2. Through central nervous system and probably neural influence the hypothalamus produces polypeptide substances in some of its nuclei which reach the median eminence area via their axons in nerve tracts. The axons come into close contact with the primary capillary plexus of the hypophysial portal system.

3. The median eminence area is the region of transfer of the "releasing factors" from the axons of the hypothalamic nuclei across a perivascular space and into the capillaries of the primary plexus.

4. From the primary capillary plexus in the median eminence, the material enters the hypophysial portal vessels and flows to the sinusoids of the pars distalis upon whose parenchymal cells it exerts its effect.

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