The experiments thus afford another example of the correlation between physiology and pharmacology. In this case it has been possible, by studying the actions of drugs, to gain some insight into the normal processes going on in the body.

Summary

The discovery that the chemoreceptors of the carotid and aortic bodies when stimulated by oxygen want or carbon dioxide excess induce increased breathing made it desirable to investigate their role with regard to the action of certain drugs.

It was found that cyanides stimulate respiration mainly via the chemoreceptors, but also, especially in later stages, directly on the centre, probably through formation of lactic acid.

Moderate doses of lobeline act exclusively on the chemoreceptors, but the point of attack is central to that of oxygen want or carbon dioxide excess.

An intravenous injection of adrenaline leads to decreased respiration or even apnoea; this is due to the sudden elimination of the "chemoreceptor drive."

The same holds true for acetylcholine after atropinization, though there are differences which can be explained from the fact that acetylcholine also stimulates the carotid and aortic bodies in a similar way to lobeline. Before atropinization the stimulating effect of acetylcholine is enhanced by the simultaneous lowering of the blood pressure, which leads to oxygen want.

Local application of eserine to the carotid bodies increases the respiratory response to oxygen deficiency and carbon dioxide accumulation; the sensitivity of the chemoreceptors to these stimuli as well as to lobeline is abolished by local treatment with atropine. These results indicate that acetylcholine is the chemical mediator within the carotid body.

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NEURAL CONTROL OF THE PITUITARY GLAND: II. THE ADENOHYPOPHYSIS

WITH SPECIAL REFERENCE TO THE SECRETION OF A.C.T.H.*

BY

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As described previously, only two endocrine glands—the adrenal medulla and neurohypophysis—have a secretomotor nerve supply and are dependent on this supply for normal function. The adenohypophysis (anterior pituitary gland), thyroid, adrenal cortex, ovaries, and testes lack a well-defined innervation. It has been known for many years, however, that these latter glands are influenced by nervous processes—the evidence for this statement has been reviewed (Harris, 1948a)—but the mechanism whereby such an influence is exerted was uncertain. The position would be clarified if it could be found how the adenohypophysis is brought under neural control; for the thyroid, adrenal cortex, and gonads would then be indirectly under similar control via the action of the anterior pituitary eutrophic hormones. Some such sequence of events as illustrated in Fig. 1 may be envisaged. Stimuli arising in the external environment, such as changes in exposure to light or temperature or exposure to a variety of conditions grouped under the heading "stress," are reflected by changes in activity in various parts of the central nervous system. These changes, and those arising from mental and psychological upsets, may affect the secretory activity of the adenohypophysis by means of structures in the hypothalamus and pituitary stalk.

FIG. 1.—Diagram to illustrate a possible mechanism whereby the activity of the anterior pituitary gland, thyroid, adrenal cortex, and gonads may be modified by changes in the external environment or in the central nervous system (psychological or emotional upsets). It seems likely that such changes may affect anterior pituitary secretion via the intermediation of the thyrotrophic, adrenocorticotrophic, and gonadotrophic hormones may thus affect also the activity of the thyroid gland, adrenal cortex, and gonads.

These changes, and those arising from mental and psychological upsets, may affect the secretory activity of the adenohypophysis by means of structures in the hypothalamus and pituitary stalk.

Anatomical Links Between the Central Nervous System and the Adenohypophysis

Nervous

Three nervous pathways have been described as passing from the central nervous system to the adenohypophysis; branches from the cervical sympathetic

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chain, the parasympathetic fibres of the greater superficial petrosal branch of the facial nerve, and the hypothalamo-hypophysial tract of the pituitary stalk. Section of these various pathways, however, is compatible with normal function of the adenohypophysis and does not necessarily prevent neural processes from affecting anterior pituitary function. Microscopical examination of the adenohypophysis also throws serious doubt on the functional significance of these possible nerves of supply, for most workers have found few, if any, nerve fibres present in the greater part of the anterior lobe of the pituitary gland.

Neurovascular

Many years ago Professor Fr. I. Rainer, of Bucharest, noticed prominent blood vessels running along the human pituitary stalk, and suggested that one of his pupils (later

FIG. 2.—Diagram of a sagittal section through the hypothalamus and pituitary gland to illustrate the hypophysial vascular system. Small twigs (T.) from the internal carotid arteries supply a vascular plexus situated between the pars tuberalis (P.T.) and the median eminence. From this plexus sinusoidal loops (L.), in large numbers, penetrate the tissue of the median eminence. The blood from these loops is drained by the large portal trunks (T.P.), which eventually break up into the sinusoids of the pars distalis (S.). The pars distalis also receives a systemic arterial supply (A.H.) from the internal carotid artery, and the infundibular process a similar supply (P.H.) from the same source. The venous drainage of the pituitary gland is by wide short veins into the surrounding venous sinuses (V.). O.T.=optic tract; III V.=third ventricle. (By kind permission of the Royal Society of Medicine.)

Professor G. T. Popa) should examine them in detail. Popa made serial sections through the hypophysis, still in connexion with the diencephalon, and observed that the prominent vessels of the stalk were in reality portal vessels ending in capillaries at both ends, in the tuber cinereum above and in the hypophysis below. These observations remained unpublished until, at the suggestion of Professor G. Elliot-Smith, the anatomy of these structures was again investigated at University College, London. Popa and Fielding (1930, 1933) then made their first reports on the "hypothalamo-hypophysial portal vessels." They suggested that blood flowed from the pituitary gland up the vessels and was redistributed in the hypothalamus.

The main anatomical features of the vessels were confirmed by Wislocki and King (1936) and Wislocki (1937, 1938). According to these workers, however, the capillaries at the superior end of the portal vessels were situated in the median eminence of the tuber cinereum (then recognized as part of the glandular neurohypophysis and not hypothalamus proper). Therefore they denied the existence of a hypothalamo-hypophysial portal system, and renamed the vessels the hypophysial portal vessels on the grounds that the whole extent of the vessels was intrinsic to the hypophysis. One unfortunate consequence of this correction in terminology

was the general belief that the hypothalamo-hypophysial portal vessels had been "disproved." From the histological evidence Wislocki drew the conclusion that the direction of blood flow in these vessels was in a direction *towards* the pituitary gland. Green and Harris (1947) reinvestigated the region in a variety of mammals, and largely confirmed the findings of Wislocki. The vascular pattern of the adenohypophysis may be compared to that of the liver in that it has a systemic arterial supply (a small branch from the internal carotid artery), a portal supply (the hypophysial portal vessels), and a systemic venous drainage (short wide veins passing laterally to the surrounding venous sinuses) (see Fig. 2).

The pathway of the portal blood is as follows. Small twigs from the internal carotid arteries and posterior communicating arteries run to supply a rich vascular plexus in the pars tuberalis. From this plexus arises a multitude of wide capillary loops which penetrate into the tissue of the median eminence, where they come into intimate relationship with the nerve fibres of the hypothalamo-hypophysial tract. The blood from these loops is drained into the large portal trunks which pass down the pituitary stalk and redistribute the blood into the capillaries and sinusoids of the anterior pituitary gland. Green (1947, 1948, 1949) has made a thorough investigation of the portal vessels in many types of vertebrates, and finds a similar system of vessels in all forms examined, from amphibians to man. Microscopical examination of these vessels in living forms has established that the direction of blood flow is *from* the median eminence *to* the tuber cinereum. (Amphibians: Houssay, Biasotti, and Sammartino, 1935; Green, 1947. Mammals: Green and Harris, 1949.)

In view of the above anatomical facts it was suggested (Harris, 1944; Green and Harris, 1947) that the hypothalamus may influence the secretion of the adenohypophysis by means of a neurovascular link—for example, that hypothalamic nerve fibres end in close relation to the capillary loops in the median eminence, and, on excitation, liberate some chemotransmitter into these vessels, this substance being transported by the portal vessels to excite or inhibit the pars distalis of the gland.

Hypothalamic Control of Anterior Pituitary Function

To investigate the hypothesis that the hypothalamus regulates anterior pituitary secretion by a neurovascular mechanism an attempt was made to analyse some of the factors underlying gonadotrophic secretion. For this purpose the rabbit was chosen as the experimental animal. It is well known that in the rabbit the stimulus of coitus excites the adenohypophysis by means of a nervous reflex to secrete gonadotrophic (luteinizing) hormone, and that ovulation thereby occurs some ten hours after mating. On the supposition that one part of the path of the nervous reflex involved the hypothalamus, this structure and various parts of the pituitary gland were subjected to localized electrical stimulation in a number of unanaesthetized rabbits (Harris, 1948b).

The method used was that of remote control stimulation as described previously (Harris, 1951). It was found that stimulation of the tuber cinereum, particularly the posterior part, might be effective in causing a full ovulatory response after as short a stimulus as three minutes. Similar stimulation, however, applied direct to the pars distalis, pars intermedia, or infundibular stem of the pituitary gland for as long as seven

and a half hours produced no sign of activation of the ovaries. Assuming that the only tissues in this region which are sensitive to electrical stimulation are nerve fibres (and this would seem probable—cf. the results obtained by Cannon and Rosenblueth (1937), who studied the effect of electrical stimulation of the denervated adrenal medulla), then these results are explicable on the idea of neurovascular transmission (see Fig. 3).

It seems likely that stimulation of the tuber cinereum excites nerve fibres normally involved in the ovulatory reflex, and that the negative results of stimulating the pituitary stalk and gland are due to the stimulus being transmitted humorally in these structures. It may be argued that the mechanism of ovulation in the rabbit is specialized and that results obtained from its study are not of general application. However, in a few rabbits it was found that prolonged stimulation of the tuber cinereum by the same method resulted in a glycotrophic response—that is, a marked decrease in sensitivity to small doses of insulin (Harris, 1951, unpublished observations).

Another approach to the problem of control of gonadotrophic secretion involved sectioning the pituitary stalk. The results of stalk section on reproductive function, as reported in the literature, are very discordant. After performing this operation on the rat, Dempsey and Uotila (1940) and Dempsey and Searles (1943) found that some animals exhibited normal reproductive processes, Richter (1933) found that oestrous cycles were prolonged, while Westman and Jacobsohn (1938a, 1938b) and Brolin (1945) reported gonadal atrophy. Equally discordant results have been reported by workers who have studied the effects of stalk section on other pituitary functions. It is difficult to explain these varied results if the effects of pituitary stalk section are held to be due to sectioning the nerve fibres of the stalk, as these nerve fibres do not regenerate after they are cut. If normal anterior pituitary activity is dependent on the hypophyseal portal vessels, however, the discrepancies reported after stalk section might be due to variations in the degree of regeneration of these vessels.

Differences in the operative techniques used by different workers—such as the distance the two ends of the cut stalk are separated at operation—might account for variations in vascular regeneration. To investigate this possibility a temporal approach to the pituitary stalk region of the rat was devised and the stalk sectioned in a series of animals (Harris, 1950). The reproductive processes (oestrous cycles and pseudopregnancy response to sterile coitus) were observed in these animals, after which they were killed and their vascular systems perfused with an indian-ink solution. A study of serial sections through the hypothalamus, pituitary gland, and base of skull of these rats revealed (a) that regeneration of the hypophyseal portal vessels did occur in the majority of animals operated on in this way, and (b) that such regeneration could be correlated with the post-operative return of oestrous cycles and pseudopregnant responses to sterile coitus.

In a further series of animals it was demonstrated that the insertion of a foreign body (usually a small plate of paper) between the cut ends of the pituitary stalk would prevent regeneration of the portal blood vessels, and that in these rats the ovaries and reproductive tract underwent atrophy. It should be mentioned

that cutting the pituitary stalk inevitably disturbs the vascular supply of the gland, but in the above experiments there was no correlation between the amount of anterior pituitary tissue in the animal, or the richness of the vascular bed of this tissue, and the post-operative return of reproductive activity. It was concluded that the return of anterior pituitary function after stalk section is dependent on regeneration of the hypophyseal portal vessels across the site of section. The portal vessels of the monkey have been observed to regenerate in a similar manner (Harris and Johnson, 1950).

A striking feature of anterior pituitary tissue, reported by many workers, is the inability of such tissue to maintain normal function when transplanted to a distant site in the body of the hypophysectomized animal. Other endocrine glands, such as the thyroid, parathyroids, ovaries, testes, and adrenal cortex, may regain normal function after transplantation. One possible explanation of this difference is that the thyroid, gonads, and adrenal cortex depend on a supply of pituitary

FIG. 3.—Diagram of a sagittal section through the hypothalamus and pituitary gland of a rabbit. Electrical stimulation of the tuber cinereum is effective in causing release of gonadotrophic hormone from the pars distalis of the pituitary gland, whereas similar stimulation applied direct to the gland—to the infundibular stem (I.S.), pars intermedia (P.I.), pars distalis (P.D.), or zona tuberalis (Z.T.)—is ineffective.

eutrophic hormone, carried in the general systemic circulation, for their normal activity. Therefore transplantation does not remove them from the field of their normal stimulus. If, however, the anterior pituitary gland is dependent on a humoral excitant carried by the local circulation of the hypophyseal portal vessels, then transplantation to the spleen, anterior chamber of the eye, or other sites would remove it from its physiological stimulus.

In collaboration with Dr. Dora Jacobsohn, of the University of Lund (Harris and Jacobsohn, 1951), it was decided to hypophysectomize a series of rats and to graft anterior pituitary tissue into the subarachnoid space under the tuber cinereum. In this way it was possible to check the completeness of hypophysectomy (after death) by examination of serial sections through the empty hypophyseal capsule, but yet to place the grafted tissue near the median eminence and the cut hypophyseal portal vessels so that regeneration of the vessels into the grafted tissue might occur. Control experiments were performed in the same way, except that the grafts were placed in the subarachnoid space under the temporal lobe of the brain. It was seen that

the grafts placed under the tuber cinereum became revascularized by the portal vessels of the median eminence, and in the majority of these cases normal anterior pituitary function was regained by the grafted host. Normal function was demonstrated by regular oestrous cycles, pregnancy, and milk secretion, the weights of the ovaries and adrenal glands being within the normal range, and a normal histological picture for the ovaries, thyroid, and adrenal cortex.

Microscopical examination showed that the control animals with "temporal lobe grafts" had as much viable anterior pituitary tissue, which was as well vascularized, as in the animals that had the graft placed under the median eminence. In the control group, however, the graft was not vascularized by the portal vessels. In these animals, also, there were no oestrous cycles, and the ovaries, thyroid, and adrenal glands were atrophic. It would seem that anterior pituitary grafts that become revascularized by the hypophyseal portal vessels may regain normal activity, but grafts vascularized only by systemic vessels show very reduced functional activity, if any at all. It is of interest that anterior pituitary tissue taken from male rats and placed under the tuber cinereum of female rats would support normal oestrous cycles and pregnancy, and that tissue taken from newborn rats would support adult reproductive functions within a few weeks of grafting—that is, long before the donor rats would have reached puberty.

Strong evidence, then, supports the view that the normal stimulus to anterior pituitary activity is derived from the hypothalamus via the hypophyseal portal blood supply, and that changes in activity of the gland (in response to external stimuli such as coitus) are mediated through these structures. A similarity could be drawn between the hypothalamus/hypothalamo-hypophyseal tract/neurohypophysis on the one hand and the hypothalamus/hypophyseal portal vessels/adenohypophysis on the other. In both cases the activity of the gland ceases or is seriously impaired if separated from the hypothalamus, and probably in both cases the hypothalamus is involved in the adjustments of secretory activity necessary to integrate pituitary function with the requirements of the organism as a whole.

There is little evidence regarding the details of the mechanism by which the hypophyseal portal vessels affect activity of the adenohypophysis. On the grounds that a sympatholytic drug (dibenzamine) blocks the ovulatory reflex in the rabbit, and other evidence, Markee, Sawyer, and Hollinshead (1948) and Sawyer, Markee, and Townsend (1949) suggest that the portal vessels transmit an adrenergic substance which stimulates the release of the luteinizing hormone from the anterior pituitary gland. Evidence of a similar nature has been adduced also for the rat (Sawyer, Everett, and Markee, 1949; Everett, Sawyer, and Markee, 1949; Everett and Sawyer, 1949).

One question that follows from the above argument is whether each of the six "hormones" secreted by the anterior pituitary gland requires the supposition of a separate humorally transmitted excitatory substance. Although it is possible, by chemical extraction, to separate six "hormones" from anterior pituitary tissue, very little data are available to show how the substances enter the blood stream. It is possible that they reach the blood as six separate substances, but it is also possible that two or more are linked together as different fractions of a larger molecule.

Control of the Secretion of the Adrenocorticotrophic Hormone

In view of the important advances being made in the field of clinical medicine regarding the treatment of a variety of conditions with the adrenocorticotrophic hormone (A.C.T.H.), the investigation of the factors underlying the normal secretion of this hormone have received much attention in the laboratory. There are two sides to this problem. First, the means by which a steady secretion of A.C.T.H. is maintained in the normal animal under optimum conditions; and, secondly, the mechanisms employed in producing increased secretion under conditions of stress. The same factors may be involved in both cases, but it is possible that stress stimuli may activate one or more additional mechanisms.

A.C.T.H. maintains the structure and function of the adrenal cortex. Since accurate assays of the blood level of A.C.T.H. cannot yet be made, the rate of secretion of this hormone has to be measured indirectly. The criteria which have been most used in the investigation of the factors controlling A.C.T.H. release are (1) the effects of A.C.T.H. on the size, weight, and histology of the adrenal cortex, and on the cholesterol and ascorbic acid content of the adrenal cortex; and (2) the effect of an increased secretion of the adrenal cortex as shown by a fall in blood lymphocytes or eosinophils (see Fig. 4). The validity of these methods, and others, has been discussed by Sayers (1950) in a detailed review.

At the present time three views, not necessarily incompatible, have been put forward concerning the regulation of A.C.T.H. release: (1) A.C.T.H. secretion is regulated by the systemic blood level of adrenaline; (2) A.C.T.H. secretion is regulated by the systemic blood level of the adrenal cortical hormones; (3) A.C.T.H. secretion is controlled by the hypothalamus acting through the hypophyseal portal vessels. These three views will be discussed in turn.

1. Systemic Blood Level of Adrenaline

In 1944 Vogt found that an intravenous infusion of adrenaline causes an immediate and large increase in the rate of secretion of the adrenal cortex. At first it was considered likely that adrenaline exerted a direct effect on the cells of the adrenal cortex, but the findings of Long and Fry (1945) that depletion in adrenal cholesterol and ascorbic acid follow injection of adrenaline in the normal but not in the hypophysectomized animal threw doubt on this interpretation.

FIG. 4.—The structure, weight, and cholesterol and ascorbic acid content of the adrenal cortex bear an immediate relationship to the blood level of A.C.T.H., whereas the lymphocyte and eosinophil counts are related to the blood level of the adrenal cortical hormones, which in turn reflects the level of A.C.T.H.

It seems clear that the major influence of adrenaline in exciting the adrenal cortical secretion is mediated in some way through the pituitary gland, though the question of whether adrenaline exerts any action directly on the adrenal cortex is unsettled (Pickford and Vogt, 1951).

Long (1947) stated that stimulation of the autonomic system with the concomitant release of adrenaline, which occurs under a variety of conditions, appears to be a major factor in the activation of A.C.T.H. secretion from the anterior pituitary gland. This view might be expressed diagrammatically as in Fig. 5. The data on which this view is based are given by Gershberg, Fry, Brobeck, and Long (1950), and McDermott, Fry, Brobeck, and Long (1950a).

FIG. 5.—Diagram illustrating the views of Long and his colleagues. Stimulation of the autonomic system with concomitant release of adrenaline, which occurs under a variety of conditions of stress, is believed to be a major factor in the activation of A.C.T.H. secretion from the anterior pituitary gland. A = the hypothalamic level. B = the spinal level.

Infusions of small doses of adrenaline which appear to be within the physiological range produce a fall in the level of adrenal ascorbic acid in the normal but not in the hypophysectomized rat. Conditions of stress, which have been known for many years to be associated with increased activity of the autonomic system and adrenaline liberation, cause a fall in the adrenal content of cholesterol and ascorbic acid in the normal but not in the hypophysectomized rat.

In order to see if there is a causal relationship between adrenaline and A.C.T.H. liberation in response to stress, Long and his colleagues have investigated the effect of stress after demedullation of the adrenal glands, and after interrupting the neural pathway responsible for adrenaline secretion at the hypothalamic (A, Fig. 5) or spinal (B, Fig. 5) level. They found that adrenal-demodulated rats no longer responded to mild stress stimuli (stimulation of an afferent nerve trunk for 15 minutes), but such rats still showed a marked response to more severe stress (fasting plus exposure to cold for four hours, haemorrhage, or laparotomy). Rats with the spinal cord sectioned at the level of the third thoracic vertebra behaved in a similar way, in that a mild pain stimulus (injection of hypertonic saline beneath the skin of the scalp) no longer resulted in A.C.T.H. release, but more severe stress (cold) produced a marked response. Also, rats with diencephalic lesions still reacted to laparotomy by releasing A.C.T.H., as shown by an eosinopenic response.

A study of the time relations of these responses showed that the rats in which adrenaline release was prevented had a longer latency in the secretion of A.C.T.H. to stress. Normal animals responded to stress by a marked release of A.C.T.H. within one hour of the

stress, and the response was maximal at the fourth hour. The animals in which adrenaline secretion was prevented showed no response at one hour but a normal response at the fourth hour after stress. For this reason Long and his colleagues suggested that a double mechanism underlies the secretion of A.C.T.H. following stress: (a) a quick autonomic mechanism depending on reflex secretion of adrenaline which activates the anterior pituitary; and (b) a slower metabolic mechanism which is not dependent on adrenaline secretion and which is therefore not abolished by adrenal demedullation or denervation.

In an attempt to localize the site of action of adrenaline in producing A.C.T.H. release McDermott, Fry, Brobeck, and Long (1950b) transplanted anterior pituitary tissue to the anterior chamber of the eye in hypophysectomized rats. Definite eosinopenic responses occurred in these animals following subcutaneous injection of adrenaline or injection of adrenaline into the eye containing the graft (but not into the normal eye). The conclusion drawn from these experiments is that adrenaline may cause A.C.T.H. secretion by a direct action on anterior pituitary cells. It is perhaps significant that the pituitary transplants of these animals did not prevent partial adrenal atrophy or complete atrophy of the testes and did not maintain body growth.

The general view, upheld by Long and his colleagues, that adrenaline secretion is part of a physiological mechanism underlying A.C.T.H. release in response to stress, is open to question. The completely sympathectomized animal may resist many forms of stress almost as well as do intact animals (see discussion by Sayers, 1950). Hume and Wittenstein (1950) found that electrical stimulation of the hypothalamus of dogs resulted in an eosinopenia that was not altered by total sympathectomy, and Colfer, de Groot, and Harris (1950) observed that the lymphopenic response which followed a mild pain stimulus in rabbits did not differ from the response obtained with the adrenal glands denervated.

Recently Fortier (1950) showed that audiogenic stimulation (sound) of normal rats produces a rapid and intense discharge of A.C.T.H. The response to this sensory stimulus was not affected by removal of the adrenal medulla. Vogt (1951) also found that mild stress stimuli (emotional in type) still produce a fall in adrenal ascorbic acid after adrenal demedullation. This fall was not so large as in normal rats, but, contrary to the results of Long and his co-workers, did occur within the course of one hour. Vogt concludes: "... The secretion from the adrenal medulla is an important but not the only cause for the adrenocortical response to emotion." Sayers (1950) suggested the possibility that adrenaline may act by promoting the tissue utilization of adrenal cortical hormones, thus lowering the blood level of these substances and producing increased A.C.T.H. output.

2. Systemic Blood Level of Adrenal Cortical Hormones

The view that A.C.T.H. secretion from the anterior pituitary gland is regulated by the blood level of the adrenal cortical hormones has been described in detail by Sayers (1950), and reference should be made to this work for a detailed discussion. The evidence in support of Sayers's view may be summarized as follows. Chronic administration of adrenal cortical extracts or desoxycorticosterone (deoxycortone B.P.) acetate to normal animals results in adrenal atrophy, presumably by causing decreased secretion of A.C.T.H. from the animal's

own pituitary gland. Deoxycortone acetate will prevent the adrenal hypertrophy that normally follows the application of a variety of non-specific damaging agents.

In acute experiments Sayers and Sayers (1947) showed that the drop in adrenal ascorbic acid which normally follows the application of cold or heat, or the injection of typhoid toxin, adrenaline, or histamine, can be prevented by the pretreatment of the animal with adrenal cortical extract or crystalline cortical steroids. Since the effect of injected A.C.T.H. is not modified by administration of adrenal cortical extracts they believe that the cortical substances act by inhibiting the release of A.C.T.H. from the pituitary gland. A quantitative relationship has also been found to exist between the dose of cortical steroid administered and the degree of inhibition of A.C.T.H. release in response to stress

FIG. 6.—Diagram illustrating the view of Sayers that the secretion of A.C.T.H. by the anterior pituitary gland is regulated by the blood level of adrenal cortical hormones. Stress is thought to act direct on the tissues, increasing the tissue utilization of the adrenal cortical hormones, so that the level of these substances in the blood supplying the pituitary gland is lowered, thereby increasing the output of A.C.T.H.

mainly by variations in activity of the peripheral tissues (see Fig. 6).

It is difficult, however, to believe that the blood level of adrenal cortical hormones is the only factor which regulates the secretion of A.C.T.H. For example, blood from the aorta eventually supplies both the peripheral tissues and the pituitary gland. Therefore under conditions of prolonged stress the peripheral tissues could not receive an increased supply of adrenal cortical hormones, for the pituitary gland would also receive the same increased supply, which would in turn reduce the output of A.C.T.H. and so of adrenal cortical hormones.

Cheng, Sayers, Goodman, and Swinyard (1949) found that hypophysectomized rats bearing intraocular or intrasplenic grafts of anterior pituitary tissue responded to histamine stress (intravenous injection of small doses of histamine) with a fall in the level of adrenal ascorbic acid. The results were interpreted to mean that neural or vascular connexions between the hypothalamus and anterior pituitary are not essential for the immediate discharge of A.C.T.H. in acute stress. However, the physiological significance of these results is open to doubt, for the adrenal glands of the rats bearing pituitary grafts were as atrophic in most cases as in the hypophysectomized control animals without grafts. It would

appear that the natural stimulus of the animal's own need for increased A.C.T.H. secretion was insufficient to increase the activity of the graft (an activity which *could* be increased, as shown by the effects of histamine).

It is felt that the evidence is conclusive that the blood level of the adrenal cortical hormones influences the rate of secretion of A.C.T.H., though the manner in which this occurs is obscure. It is doubtful whether this is a direct action on the cells of the adenohypophysis.

3. Hypothalamic Control

In view of the strong evidence that the hypothalamus plays a prominent part in controlling the secretion of the gonadotrophic hormones, an investigation was undertaken to see whether a similar mechanism regulated the output of A.C.T.H.

In preliminary experiments (Colfer, de Groot, and Harris, 1950) it was shown that rabbits behave as other animals, in that emotional stress stimuli (restraint or subcutaneous faradism) evoke a lymphopenia. Hypophysectomy abolished this response to stress, though injection of A.C.T.H. was still followed by a lymphopenia in the hypophysectomized animal. There was then available for investigation a reaction which could be indicated: emotional stress → anterior pituitary gland → adrenal cortex → lymphopenia. To see whether A.C.T.H. secretion could be evoked by hypothalamic stimulation, de Groot and Harris (1950) used the remote-control technique, with the primary coil enlarged to surround the cage containing the animal. Thus the animal was not subjected to concurrent emotional stress during the periods of stimulation. It was found that stimulation of the posterior region of the tuber cinereum or mammillary body resulted in a lymphopenia that was similar in time relations and magnitude to that following an emotional stress stimulus or intravenous injection of an appropriate dose of A.C.T.H. Stimulation of other regions in the hypothalamus (including the supraoptico-hypophysial tract) and pituitary gland (pars and zona tuberalis, pars distalis, pars intermedia, and infundibular stem) did not elicit the response.

Results which are in the main similar to these have been obtained by Hume and Wittenstein (1950) by stimulating the hypothalamus of the unanaesthetized dog. The effect of electrolytic lesions placed in the hypothalamus or pituitary gland was also studied (de Groot and Harris, 1950). It was found that in two rabbits in which the zona tuberalis (the part of the anterior pituitary gland of the rabbit traversed by the hypophysial portal vessels) was destroyed, and in other animals in which the posterior part of the tuber cinereum or mammillary body was damaged, the lymphopenic response to stress was diminished or abolished. It was concluded that the secretion of A.C.T.H. which follows an emotional stress stimulus in the rabbit is regulated by the hypothalamus acting via the hypophysial portal vessels.

Results which lend strong support to this view come from the experiments of Harris and Jacobsohn (1951) on pituitary grafts in hypophysectomized rats. As mentioned above, it was found that if anterior pituitary tissue was placed under the tuber cinereum of the hypothalamus in hypophysectomized rats the graft became revascularized by the hypophysial portal vessels, and normal function was regained in the majority of animals. The adrenal glands of these animals were within the normal range as regards weight and structure.

In control animals in which similar grafts were placed elsewhere in the subarachnoid space, although the grafts were viable and richly vascularized (but not by the hypophyseal portal system), the adrenal glands underwent marked atrophy. It is felt that these results are highly significant with regard to the mechanism of A.C.T.H. secretion under non-stress conditions. The adrenal atrophy reported by Cheng *et al.* (1949), McDermott *et al.* (1950b), and many other previous workers in hypophysectomized rats bearing pituitary grafts in the anterior chamber of the eye and other sites stand in marked contrast to the above results.

Conclusions Regarding Control of A.C.T.H. Secretion

The evidence derived from studies of pituitary transplants and grafts shows that the basic steady output of A.C.T.H. by the anterior pituitary gland is largely dependent on this gland's anatomical relationship with the hypothalamus. The same data also show that the structures connecting the hypothalamus and adeno-hypophysis which are of importance in maintaining normal A.C.T.H. liberation are the hypophyseal portal vessels. It is likely that under optimum conditions the blood level of adrenal cortical hormones exerts a fine control of A.C.T.H. output. It is felt probable, however, that this control is mediated via the hypothalamus, since the adrenal atrophy (and presumably decreased level of the adrenal cortical hormones in the blood) is not effective in maintaining A.C.T.H. output in rats that have had

FIG. 7.—Diagrammatic representation of a possible mechanism of control of A.C.T.H. secretion. Under optimal, quiescent conditions it is believed that the basal output of A.C.T.H. is under hypothalamic control mediated by the hypophyseal portal vessels of the pituitary stalk. According to the type of stress, this basal output may be increased either by (a) an effect on the blood level of adrenal cortical hormones and adrenaline, or (b) an effect mediated via the hypothalamus and pituitary stalk. On the data available it is thought likely that the blood level of adrenal cortical hormones and adrenaline affect anterior pituitary activity via the hypothalamus, and not by an action directly on anterior pituitary cells.

the anterior pituitary gland transplanted to a site remote from the hypothalamus. These views are expressed diagrammatically in Fig. 7. Analogy might be drawn to the respiratory mechanism, where the act of respiration is basically dependent on the nervous system but modified by the carbon dioxide content of the blood supply to the respiratory centre.

The factors involved in the increased secretion of A.C.T.H. in response to stress stimuli probably vary according to the type of stress. The work of Fortier (1951, personal communication) is of much interest in this respect. Fortier exposed groups of normal rats, and hypophysectomized rats with anterior pituitary transplants in the eye, to varied types of stress stimuli: (a) systemic (adrenaline, cold, histamine); (b) emotional

(immobilization); and (c) sensory (sound) stimuli. It was found that adrenaline, cold, and histamine brought about a definite eosinopenia in both normal and grafted animals, but that sound and immobilization induced a marked fall of the eosinophils in the intact but none in the grafted animals. Fortier suggests that these results indicate a dual regulation of A.C.T.H. release—one purely humoral in response to systemic stress stimuli, and the other probably neuro-humoral mediated by the hypothalamo-hypophyseal neurovascular pathway, and coming into play under the influence of nervous or emotional stimuli. These two mechanisms might be indicated by *a* and *b* in Fig. 7.

The views expressed above regarding the factors regulating A.C.T.H. secretion are similar to those regarding control of gonadotrophic secretion. There can be little doubt that the normal output of gonadotrophin and the maintenance of oestrous cycles and other reproductive processes is dependent on hypothalamic control of the anterior pituitary gland acting via the portal blood vessels. The evidence indicates that the secretion of the gonads reacts back on to the hypothalamus (Everett and Sawyer, 1949; Harris, 1950), and that emotional and environmental stimuli modify gonadotrophin secretion by an action mediated through the hypothalamus. A point of interest in this connexion is that barbiturate drugs, which are known to have a selective action upon the hypothalamus (Masserman, 1937), also appear to block, at least partially, the release of A.C.T.H. (Sayers and Sayers, 1948; Hume and Wittenstein, 1950) and of the luteinizing hormone (Everett and Sawyer, 1950).

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COMPARATIVE ACTION OF E.C.T. AND OF PITUITARY ANTERIOR LOBE HORMONES ON THYROID FUNCTION

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In a previous paper (Reiss, Hemphill, Maggs, *et al.*, 1951) thyroid function in psychoneurotic and psychotic patients has been evaluated by radioactive tracer technique. The present communication deals with the effects of electric convulsion therapy (E.C.T.) on thyroid compared with that of thyrotrophic, adrenocorticotrophic, and sex hormones.

FIG. 1.—Thyroid indices of male patients before and after E.C.T.

Method.—The radioactive tracer method used in all these investigations has been described already (Reiss *et al.*, 1949; Haigh and Reiss, 1950; Reiss *et al.*, 1951). Thyroid function, estimated in this way, is remarkably stable in normal subjects and in untreated stationary psychiatric illness. Table I shows representative results.

TABLE I

Subject No.	Age	Thyroid Investigations		
		First I_t	Interval Between Both Investigations (Days)	Repeat I_t
1	30	14.5	28	16.8
2	33	10.7	21	10.2
3	28	8.0	34	7.4
4	23	6.3	32	6.7
5	28	4.3	356	5.7
6	55	3.3	36	3.4
7	45	0.88	185	0.89
8	30	0.67	354	0.55

In several normal subjects investigated regularly during the past three years thyroid activity did not vary by more than $\pm 10\%$.

The patients investigated belonged to the usual psychiatric material of out-patient clinics and psychiatric hospitals. However, the majority were cases of depression, normally submitted for E.C.T. In these the expectation of recovery with E.C.T. is high. There were also some other cases, complicated by constitutional and reactive factors, in which the prognosis was uncertain.

Results

Figs. 1 and 2 show the levels of thyroid function in male and female patients before, after completion of, and sometimes during electric shock treatment. The extent and trend of the changes after E.C.T. varied, but were most marked when thyroid function was initially high, which in these cases was always reduced. If the thyroid function was initially subnormal the level rose invariably to normal. Where the level of thyroid function was initially normal it sometimes changed, but only within the normal range. In no case that recovered in which the tracer index had been normal before treatment did the I_t value depart from the normal range with impairment of thyroid function. In some cases the thyroid function did not alter significantly and thus there did not seem to be a ready correlation between the effect of E.C.T. on the thyroid and the therapeutic result. In some cases in which the condition of the patient was unaltered or became worse, occasionally a thyroid function, originally in normal range, became reduced to subnormal; in other similar cases the thyroid function did not alter.

Investigations were made in another series of patients in which only the slope of the iodine uptake was measured, as the urine collection could not be completed. The changes of the slope of uptake K were in agreement with the I_t changes shown in Figs. 1 and 2, and wherever the slope was initially outside normal it was found to be within the normal range after successful E.C.T.

For comparison, Fig. 3 shows changes of thyroid activity after treatment with different hormones in patients suffering from varying psychiatric disorders. The second measurement