NEURO-ENDOCRINE RELATIONSHIP.

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Introduction.

In recent years our views of the interaction between the nervous system and the ductless glands have been gradually more defined. In the present review, for descriptive reasons the subject has been classified as follows with reference to the main elements of the neuro-hormonal inter-relation :

(1) The influence of the nervous system on the pituitary itself and, through the pituitary, on the other ductless glands.

(2) The influence of the ductless glands and their secretions on the functions of the nervous system.

The factors concerned and the paths of their action can be summarized as follows :

(*a*) The reactions between the brain cortex and subordinate brain centres, *e.g.* the hypothalamus.

(*b*) The direct excitatory or inhibitory effect of the hypothalamus on the pituitary.

(*c*) The functional regulation of the subordinate ductless glands by the different trophic hormones produced in the pituitary anterior lobe.

(*d*) The action of the ductless glands and their hormones on the body.

(*e*) The centripetal nervous impulses from the periphery to the brain cortex.

(*f*) The nervous impulses from the periphery to the hypothalamus.

(*g*) The action of the ductless glands and their hormones on the different elements of the nervous system.

The variety of factors concerned shows the very complex character of the neurohormonal relation. Mental disturbances, emotions, affections may produce endocrine disturbances, and these, in turn, may affect cerebral functions. Pathological processes may very often result from such vicious circles. The necessity for considering these facts in the analysis of pathogenetic syndromes is obvious.

Nervous regulation is not indispensable for the functioning of the ductless glands, but it serves to maintain the hormonal balance in the body, and regulate certain cyclic hormone functions and the reactions of certain ductless glands to changes in the environment. The hormones regulate the orderly functioning of the nervous system. Thus not only is cortical activity influenced by the ductless glands as in disorders of the thyroid, but the autonomic system is even

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more directly influenced by the hormones. So far little is known of the relations between the hormones and the functions of the central nervous system, but recent investigations promise rapid progress in this all-important branch of neurophysiology.

There is evidence that the brain is a possible storage organ for certain hormones. In this connection may be cited the old experiments by Schittenhelm showing that iodine is stored in the tuber cinereum after thyroid administration. The recent experiments by Selye (1941) showing the possibility of inducing anaesthesia by administration of desoxycorticosterone and other steroid hormones are suggestive. It is possible that certain cell elements among the glia cells of the brain serve as storage organs for certain substances necessary for the brain function, e.g. hormones or even pre-hormones of lipoid character, which are partly released as soon as necessity arises, partly continually used by the cells. Series of ketosteroids from the brain have been isolated in the Burden Laboratories and will be described in due course.

The alleged secretory activity of neurons in the hypothalamus has been recently reviewed by Scharrer and Scharrer (1940). The cells in question are multinucleated, and have inclusions of colloid material and granules which are regarded as the product of the secretory activity of the cells themselves. Situated mainly in the nuclei supraopticus and paraventricularis, they are vascularized by an exceedingly dense capillary bed. The nerve cells are partly directly attached to the vessels lining them in a dense epithelium-like pattern. All the morphological investigations dealing with the so-called secretory cells of the hypothalamus are likely to remain inconclusive so long as the problem has not been studied by the methods usually applied in endocrine work. Since extirpation experiments cannot be carried out without damaging the total hypothalamus, the only really decisive method would be the preparation and biological investigation of extracts from large aggregates of hypothalamic nuclei.

The Influence of the Hypothalamus on the Ductless Glands and their Functions.

Le Gros Clark (1938) regards hypothalamus and pituitary as parts of a common functional mechanism. Not only do excitatory and inhibitory impulses to the pituitary from various parts of the central nervous system traverse the hypothalamus, but also stimuli arriving from the periphery.

The anatomical details of the nervous connection between pituitary and hypothalamus have been reviewed recently by Ingram (1939, 1940). The main component of the so-called hypothalamico-hypophysial tract is the supra-optical-hypophysial tract. Its fibres are accompanied by others coming from different sources, particularly from the tuber region and from the nucleus paraventricularis. According to Brooks and Gersh (1941) most of these nerve fibres end in the neurohypophysis, but many continue in the pars intermedia and the anterior lobe. In the latter these fibres are supplemented by a smaller number of unmyelinated fibres originating from the carotid plexus. Hair (1938) suggested that they reach the gland together with the entering vessels, partly directly, partly after having passed the posterior lobe. As these fibres

are not completely destroyed by cervical sympathectomy, they do not all originate from the ganglion cervicale superius, and it has been assumed that in cats some of them are coming from the glossopharyngeal nerve, and belong to the parasympathic system. These nerve fibres terminate as a pericellular network round the secretory cells of the anterior and posterior lobe (Hair, 1938; Brooks and Gersh, 1941). The secretory function of the latter is carried out by cells resembling the so-called pituicytes which survive, grow and expand in a network in tissue culture, whilst the nerve fibres degenerate (Griffiths, 1938).

After hypophysectomy or lesions of the stalk, retrograde degenerative changes take place in the hypothalamic nuclei. White and Heinbecker (1939) reported definite changes in the supra-optic and paraventricular nuclei in dogs after hypophysectomy. Magoun and Ranson (1939) found a loss of about three-quarters of the cells of the supra-optic nucleus nine to twelve weeks after interruption of the stalk in monkeys. Rasmussen has recently carried out most extensive investigations on the subject (1940). According to this author, the cells in the supra-optic nucleus of normal rats number about 7,000. Ten days to three weeks after hypophysectomy or transection of the stalk a marked decrease of cells takes place, while the nucleus supra-opticus of a rat killed 154 days after operation contained only 1200 cells. The supra-optic nucleus of a rat hypophysectomized at the age of 77 days and killed 149 days afterwards contained less than 1,000 cells. The paraventricular nucleus, however, did not show an actual loss of cells in these experiments. While the normal supra-optic nucleus of a dog contains 35,000 to 41,000 cells on each side, six months after transection of the hypophysial stalk only 3–4,000 cells could be counted. In dog-pituitaries after transection of the stalk there is a certain amount of atrophy, though histologically the tissue appears to be normal. The supra-optic nucleus of man contains normally about 60,000 cells. Five months after cauterization of the hypophysial stalk of a 46-year-old man, who had suffered from hypertension, only 9,200 cells could be found in the right nucleus supra-opticus, and 8,700 in the left. The weight of the pituitary was only half the average, the anterior lobe being below the normal minimal size. About a quarter of it was fibrosed, and less than half the normal amount of parenchyma was present. The infundibular processus was about one-eighth of the average size; the pars intermedia, however, appeared to be normal. Some basophil invasion into the neural lobe could be traced (Rasmussen, 1940).

The part played by the hypothalamus in the physiological control of the pituitary function has been demonstrated by experiments, in which the effect of destruction of certain parts of the hypothalamus or transection of the stalk on the pituitary hormones was studied. Though no assay was made of the hormone content of the body fluids after such manipulations, the functional changes supply ample evidence for the physiological interdependence of the hypothalamus and pituitary. The technical difficulties involved in attempts to injure the hypothalamus without touching the pituitary, and vice-versa, make it necessary to exercise caution in judging the experimental evidence. Experiments in which lesions of the hypothalamus were made by means of the Horsley-Clarke instrument and hypophysectomy experiments on rats seem to

be the most reliable—the latter, because the operation method generally used for rats makes simultaneous hypothalamic lesions most unlikely.

It is not yet clear to what extent the growth hormone production of the pituitary anterior lobe depends on the hypothalamus. After transection of the stalk there was no impairment of growth either in rabbits (Brooks, 1938) or in male rats (Uotila, 1939). After inflicting lesions in different parts of the hypothalamus of rats by means of the Horsley-Clarke instrument, Hetherington and Ranson (1942) found some dwarfing in some of the animals.

There is ample evidence for the influence of the hypothalamus on the gonadotrophic function of the pituitary anterior lobe. Previous work (reviewed lately by Hartman, 1939) has shown that copulation in rabbits, which normally do not ovulate spontaneously, starts the process of ovulation, to be followed by luteinization and the formation of the pregravid uterus membrane. The whole process is conditioned by secretory impulses reaching the anterior lobe and giving rise to increased secretion of the gonadotrophic hormone; the response fails if the rabbit has first been hypophysectomized. Brooks (1940, review) claimed that following complete transection of the hypophysial stalk in the rabbit ovulation did not occur though the animals mated frequently. Histological examination of the hypophysis of these stalk-cut rabbits showed some changes in both eosinophil and basophil cells.

Brooks found also that the intravenous injection of copper salt which, according to Fevold, Hissaw and Greep (1936), produces ovulation in the rabbit, has no effect after transection of the stalk. Interruption of a possible alternative pathway in the greater superficial petrosal nerves does not disturb ovulation in rabbits (Vogt, 1942). In guinea-pigs, suppression of the oestrus cycle and genital atrophy have been observed by Dey (1942) after destruction of the median eminence or interruption of the connections with the hypothalamus. Dempsey (1939) published contradictory results.

Many results obtained after stalk transection in rats are still contradictory. Westman and Jacobsohn (1938) found genital atrophy after this operation, while Uotila (1940), Dempsey and Uotila (1940), Richter (1933) *et al.* report no changes. Richter, however, found the cycle prolonged. Uotila (1940) reported it to be normal after stalk-transection in rats, and unchanged after the rats had been put in a cold room. Normal control animals, when exposed to cold, showed prolonged dioestrus intervals and prolonged periods of cornification. Uotila suggests, therefore, that hypothalamico-hypophysial influence is only effective under certain environmental conditions. After lesions in the rostral part of the hypothalamic area of rats vaginal oestrus was persistent (Hetherington and Ranson, 1942), whilst animals with lesions in the under and caudal parts of the hypothalamus had normal oestrus cycles. Dey, Fisher, Berry and Ranson (1940) found after lesions of the anterior hypothalamus of female guinea-pigs disturbances of reproductive functions.

Brooks and Bard (1942) found in studies on monkeys that neither bilateral ablation of the stellate ganglia nor bilateral removal of the superior cervical ganglia, abdominal chains and coeliac ganglia abolished the rhythm of catamenia or the regular occurrence of signs of ovulation. In two immature monkeys transection of the hypophysial stalk with ablation of the lower

portion of the tuber cinereum prevented sexual maturation. Three mature monkeys which had had normal cycles showed complete absence of cycles following similar lesions. In four mature females practically complete section of the hypophysial stem was accomplished. These animals, after several months during which menstruation did not occur, began to ovulate and menstruate regularly, although the cycles were 36 to 42 days in duration.

Sexual precocity associated with hyperplastic abnormalities of the tuber cinereum has been reported by Bronstein, Luhan and Mavrelis (1942). Weinberger and Grant (1941) describe cases of precocious puberty in which the hypothalamic region was involved. Several authors claim that the Lawrence-Moon-Biedl syndrome is due to hypothalamic abnormalities (Rathwell and Burns, 1938; Marmor and Lambert, 1938). Dott (1938) suggested that lesions about the mammillary bodies cause pubertas praecox because they cut out inhibitions and leave the opposing natural stimulative neurohypophysial mechanisms to operate unimpeded.

The relation of the hypothalamus to sexual behaviour has been recently reviewed by Bard (1940).

The production of lactogenic hormone by the pituitary seems also in some degree to depend on the regulatory influence of the hypothalamus. The existence of a neurohypophysial influence in the production of lactogenic hormone is generally admitted. This is primarily based on the fact that, in the rat, sucking reflexly affects the release of lactogenic hormone from the pituitary (Turner, 1939). After transection of the stalk, this neurohormonal mechanism seems to be interrupted (Herold, 1939).

Up to the present a direct secretory innervation of the thyroid was taken for granted. This assumption has proved to be utterly unfounded, since work with thyrotrophic hormone has shown that thyroids, though transplanted, denervated or even kept *in vitro*, can be stimulated directly by thyrotrophic hormone. At present, it can only be assumed (White and Smithwick, 1942) that the very complex vasomotor nerves of the glands regulate the escape of hormone in the blood and, perhaps, govern its production by regulation of the oxygen supply.

The pituitary-thyroid regulation works autonomously. The dependence of this mechanism on the hypothalamic centres is manifest when responses are evoked to environmental changes. According to Uotila (1939) the thyroid remains histologically normal after transection of the stalk. After subtotal thyroidectomy, compensatory hypertrophy of the remaining fragments occurs to an equal degree in stalk-cut and normal animals (Uotila, 1940).

The stimulation of the thyroid occurring normally on exposure to cold is prevented by stalk transection (Uotila, 1940). The thyroid follicles of stalk-sectioned rats which had been exposed to cold for several days failed to hypertrophy.

The relation between the pituitary anterior lobe and the hypothalamus in the production of corticotrophic hormone has not yet been closely investigated. The only fact recorded so far (Uotila, 1940) is that, unlike the thyroid, the adrenal cortex of stalk-cut rats hypertrophies following exposure of the animals to cold.

There is still considerable confusion regarding the relation of the hypothalamus to fat metabolism and development of adiposity. It is partly due to the over-simplifying views of pathologists dealing with the so-called cerebral adiposity, partly to our rather limited knowledge of the hypophysial relation to fat metabolism (Reiss, review, 1939). In any case, it may be of use to base the pathophysiological analysis of stages of adiposity on the fact that there are hypo- and hyper-hypophysial forms of adiposity, and that destruction or stimulation of certain parts of the hypothalamus might cause either of them. Earlier literature is full of discrepancies. The only explanation for all these contradictory results—e.g. those of Smith, who produced adiposity by hypophysectomy and simultaneous impairment of the hypothalamus by chromic acid, of Camus and Roussy, Bailey and Bremer, and others, who described adiposity after tuber lesions, and of Ranson, Ingram and others, who could not find any adiposity after hypothalamic lesions of different kinds—seems to be the fact that the part played by the pituitary in fat metabolism was not known then, and the different lesions of the hypothalamus were not sufficiently localized. Bearing in mind these principles of pathophysiological analysis, one can easily expect the development of any symptom, adiposity, emaciation, no influence at all, adiposity combined with genital disturbances, adiposity without any genital disturbances, and so on, as the nature of the changes depends only on the circumscribed site of the lesion.

The introduction of the Horsley-Clarke instrument has eased the task considerably. In recently published experiments (Tepperman, Brobeck and Long, 1941; Hetherington and Ranson, 1942) distinct parts of the hypothalamus were damaged with the Horsley-Clarke instrument. Hetherington and Ranson found that obesity can be produced in rats by fairly symmetrical lesions which destroy bilaterally—

(1) Most of the ventromedial hypothalamic nuclei, together with some of the tissue immediately around them, especially on their lateral sides.

(2) The caudal ends of the ventromedial hypothalamic nuclei, the premammillary area, and a considerable part of the lateral hypothalamic areas adjacent to it.

(3) In the caudal hypothalamus the areas which lie dorsolateral to the mammillary body.

These pairs of lesions appear merely to represent interruptions at successive levels of paired systems (one on each side of the hypothalamus, and each one capable of acting more or less independently). Obesity is *not* produced in rats by lesions which destroy—

(1) The fornix bilaterally with small damage to surrounding tissue in the anterior hypothalamus.

(2) Large portions of the caudal halves of the anterior hypothalamic areas symmetrically.

(3) Most of the mammillary body.

(4) Most of one side of the hypothalamus.

(5) The midline structures in and close to the floor of the third ventricle, including the median eminence and the arcuate and suprachiasmatic nuclei.

The authors found further that the obesity might or might not be accom-

panied by disturbances of the sex glands, and that apparently no significant correlation exists between the occurrence of adiposity and diabetes insipidus, the lesions which cause these stages being apparently fundamentally different. Other recent papers confirm that the obese condition due to hypothalamic lesions may occur associated with or without sexual disturbances, dwarfism or diabetes insipidus (Gagel, 1941; Brooks, Lambert and Bard, 1942). The results of Hetherington and Ranson make it clear that adiposity can also occur after destruction of hypothalamic nuclei which do not send any fibres to the hypothalamo-hypophysial tract. On this basis it becomes understandable why stalk transection is not bound to produce obesity and why, on the other hand, hypophysectomy closely following appropriate hypothalamic lesions does not prevent the appearance of typical obesity. The latter fact, moreover, proves the existence of a purely hypothalamic obesity which develops independently from the pituitary anterior lobe, and may or may not be based on a direct hypothalamic influence, on disturbed functions of the adrenal cortex, the gonads or other factors.

The relation of the hypothalamus to carbohydrate metabolism has been recently reviewed by Long (1940). As it is known that the carbohydrate metabolism is disturbed after hypophysectomy, and that the pituitary produces several hormones (thyreotrophic, corticotrophic, diabetogenic, and so on) which influence the carbohydrate metabolism, the existence of a regulatory influence of the hypothalamus may be postulated, though no direct evidence is as yet available. Previously published results on insulin hypersensitivity after hypothalamic lesions have not been confirmed by Brobeck, Magoun and Ranson (1939) in their recent investigations. In experiments carried out on large series of cats and monkeys these authors found insulin hypersensitivity only very rarely.

There is conclusive proof for the existence of the hypothalamic control of the posterior pituitary lobe. The extensive earlier literature on neurohormonal control of water balance has been reviewed by Fisher, Ingram and Ranson (1938). Interruption of the supraoptico-hypophysial tract is always followed by diabetes insipidus. The supraoptic nuclei atrophy, the posterior pituitary lobe becomes atrophic, and the pituicytes disappear. No antidiuretic, pressor or oxytocic substance is left in the posterior lobe. In a recent paper Heinbecker and White (1941) found after stalk transection diabetes insipidus in 150 dogs, and claim that diuresis was moderated if as little as 5 per cent. fibres were left intact, while failure to interrupt 15 per cent. of the fibres innervating the cells of the posterior lobe would prevent the development of polyuria entirely. These experiments may offer an explanation for earlier contradictory results. The authors showed further that the anterior lobe may not be necessary for the development and maintenance of a permanent state of diabetes insipidus. Even after its complete removal no interference with thirst and polyuria was noted. Polyuria only ceased in some operated animals in which infections in the region of the hypothalamus had occurred. Keller found recently (1942) that complete isolation of the pituitary from the hypothalamus by removal of the ventral tuberal portion of the hypothalamus failed to produce diabetes insipidus; nor did uncomplicated total hypophysectomy in dogs

result in polyuria. Only total hypophysectomy combined with drastic infringements upon the hypothalamus was followed by continuous diabetes insipidus. The author assumes the existence of an extrahypophyseal antidiuretic elaborating mechanism. Hetherington and Ranson (1942) saw diabetes insipidus in rats after lesions in the rostral portion of the hypothalamus in the neighbourhood of the optic chiasma by means of the Horsley-Clarke instrument. Hickey, Hare and Hare (1941) found (in rats) diabetes insipidus after stalk transection. No antidiuretic substance could be found in the pituitaries of these rats.

Influence of the Higher Centres.

The level and type of activity of the anterior pituitary lobe and therefore, in a secondary way, of subordinate glands can be modified by influences reaching the organism through sense organs and traversing parts linked with the highest forms of mental and neural activity.

The nervous stimulation of the pituitary is particularly evident under different conditions of light, temperature and seasonal changes. Ferrets that were exposed daily during November and December for some hours to intensive illumination developed oestrus. This result was absent in hypophysectomized animals (Hill and Parkes, 1933). Clark, McKeown and Zuckerman (1939) made at the beginning of the non-breeding season lesions at various levels in the visual pathways of the brains of female ferrets. Afterwards the animals were exposed to 6½ hours of bright illumination at the end of each day so as to find out whether in this way oestrus could be produced in the anoestrus period. If the optic nerves of the ferrets had been divided the animals either never developed oestrus, or did so much later than the controls. The normal response to visual stimulation did occur, however, in the absence of the anterior corpora quadrigemina when all retinal impulses to the dorsal nucleus of the lateral geniculate body and the visual cortex were completely interrupted. It was suggested that the visual response depends on impulses passing either to the ventral nucleus of the lateral geniculate body, or to the subthalamus by way of the accessory optic tracts. The timing of ovarian function, follicular maturation and ovulation can be reversed in nocturnal animals, e.g. mice (Snell, Fekete, Hummel and Law, 1940). It is well known that increase of egg-laying in fowls through the winter can be induced by prolonged lighting time. Young drakes that were daily exposed to intense light developed precocious sexual maturity, and hypophysectomy inhibited this effect. The anterior lobe of such illuminated animals contained an excess of gonadotrophic hormone. If the animals were blindfolded the stimulating action of light was absent (Bissonnete, review, 1938). Blinding flashes of light stimulate the output of antidiuretic substance from the pituitary of frogs (Boyd and Young, 1940). This reaction did not take place if the eyes had been removed, the reflexes lost under anaesthesia or the brain destroyed by pithing. Pithing of the spinal cord, on the other hand, does not affect the reaction to optical stimuli. Transcerebral diathermy increased the production of antidiuretic substance in dogs (Michez, 1938).

In the human there is abundant evidence that psychic emotions which are accompanied by activities of the highest centres can influence even to a pathological degree the pituitary function. The influence takes the form of inhibition

or depression. A commonplace observation is, in women, the frequent occurrence of amenorrhoea after fright or psychic shock, and, in men, the appearance of certain preclimacteric symptoms due to mental overstrain. Women suffering from personality disorders always show both, quantitatively and qualitatively, variations in their menstrual function. Reviewing 150 patients Allen (1935) found that a depressive mood, psychical depletion and motor underactivity are conducive to amenorrhoea, irrespective of whether or not the patient is delusional or hallucinated. An expansive, elated or ecstatic mood with good physical condition and motor overactivity predisposes to a profuse and prolonged menstrual period. The only explanation for changes of this kind is suggested by the fact that certain cortical centres are able to stimulate or inhibit the production of follicle stimulating and luteinizing hormone in the pituitary anterior lobe, through the mediation of the hypothalamus. It is probable that the production of all the other trophic hormones of the pituitary anterior lobe can be equally influenced by psychic emotions. This is particularly the case in anorexia nervosa, where amenorrhoea (lack of gonadotrophic hormone), atrophy of thyroid (lack of thyrotrophic hormone), emaciation and asthenia (lack of cortin and corticotrophic hormone) are combined. Reiss (1943) described a case of anorexia nervosa in which particular attention was drawn to the disturbed function of the pituitary. The patient, weighing at the start of the investigation 3 st. 12 lb., excreted in 24 hours 6 mgm. of the 17-ketosteroids and no traceable gonadotrophic or corticotrophic hormone. After change of environment, a full general diet and some psychotherapy the patient started gaining weight; ketosteroid as well as gonadotrophic and corticotrophic hormone excretion in the urine went up to a normal level; the patient seemed cured and was released from hospital. But in the following 3–5 months the patient continued putting on weight up to over 12 st., the ketosteroid excretion went up to 20 mgm. in 24 hours, and the fat distribution and general appearance of the patient suggested adiposity of the type seen in Cushing's syndrome. This case shows how pituitary anterior lobe function, once disordered by a nervous stimulus, can swing from one extreme to the opposite. Apart from this, the case would appear to justify the assumption that the so-called anorexia nervosa may exist as a cerebral form of pituitary cachexia. This pathophysiological conception of the anorexia nervosa syndrome may be paralleled by the distinction between cerebral and pituitary adiposity, and amenorrhoea due to cerebral damage and to hypopituitarism. Thus the syndrome of anorexia would, as in the case of pituitary cachexia, be due to the inability of the organism to metabolize food owing to the impaired production of the necessary anterior lobe hormones. It does not therefore seem to be necessary to go back to such fantastic interpretations of anorexia as that "one has a baby by eating," advanced by Waller, Kaufman and Deutsch (1940).

It has, of course, to be borne in mind that chronic inanition in rat experiments results in a generalized hypoplasia of the endocrine organs, which has been termed by Mulinos and Pomeranz (1940) "pseudo-hypophysectomy," because of the resemblance between the effects of inanition and those of hypophysectomy; see also Vollmer (1943). The patho-physiological analysis of

anorexia nervosa seems to some extent complicated by the existence of a vicious circle, the primary cerebro-hypophysially conditioned anorexia producing by chronic inanition a further deterioration of the pituitary function. It is obvious that the interaction between cerebrum, pituitary and subordinate glands may nearly always proceed in a vicious circle. Primary psychic disturbances, affections or shocks may produce a disturbance in a gonadal function, and the gonadal affection may, in turn, affect cerebral activities. Such a circle of events may form the start of a pathological process, bound to grow worse and worse. This is, most probably, also the case in certain stages of schizophrenia.

Hemphill, MacLeod and Reiss (1942) saw a considerable increase in 17-ketosteroid output frequently follow electric convulsion therapy and prefrontal leucotomy. The greatest changes were seen where the original levels were low. It was assumed that the increased 17-ketosteroid output represents hyperactivity of the adrenal cortex due to increased production of corticotrophic hormone, since injection of corticotrophic hormone in cases of hypoadrenalism produced a similar increase in 17-ketosteroid excretion. It has been suggested that interference with nervous pathways between the frontal lobe and the hypothalamus may influence the pituitary to produce the same result.

One frequently observes the restoration of normal endocrinological appearance and function accompanying the cure of a severe psychosis. Such results are not infrequently seen to follow closely after prefrontal leucotomy. This would seem to indicate that interference with connections to the higher centres which alleviated an abnormal psychic condition, at the same time allowed the pituitary to resume its normal function.

The Influence of the Ductless Glands on the Brain Function.

In spite of the facts accumulated on the influence of normal and pathological endocrine function and hormones on brain function, the mechanism and precise physiological processes are barely understood. It is evident that where endocrine interferences produce alterations in brain function, they do so by primarily effecting a disturbance of brain metabolism with subsequent development of patho-physiological activity. So little is known about normal brain metabolism that the changes it may undergo under hormonal influence can be surmised. With the limited means of investigation at our disposal a general idea of the subject can best be obtained by considering the known data on the following: the influence exerted by the endocrines on brain metabolism, on cerebral circulation, on the reaction of the brain to stimuli and changes in the environment of the organism, on pattern of behaviour and on the relationship of glandular disturbances to mental and physical illness and the therapeutic effects of hormones.

These last two aspects, which are of a clinical rather than experimental interest, have been treated in another chapter by R. E. Hemphill.

Thyroid.

It is reasonable to suppose that the psychic phenomena and increased

nervous activity of hyperthyroidism and the retardation of these processes in hypothyroidism result from a profound disturbance of brain metabolism. There are, however, only very few facts published on the matter. Cohen and Gerard (1937) treated rats for 16–19 days with thyroid powder and measured the respiratory activity of minced brain. The oxygen uptake was about 20 per cent. higher than normal, and was still further increased by adding glycogen, glycerophosphate, lactate or succinate. Apparently the various enzyme systems are more concentrated in the hyperthyreotic brain. MacLeod and Reiss (1940) investigated brain slices of normal and hypophysectomized rats after treatment with thyreotrophic hormone. In the hypophysectomized rats the O_2 consumption of the brain was increased 5–8 days after the commencement of treatment. The brain O_2 consumption of the normal rats was also increased, but much less markedly. This difference is due to the very characteristically increased thyroxine sensitivity of hypophysectomized animals (Reiss and Fischer-Popper, 1936). Oxygen uptake of brainbrei of thyroid-treated rats was increased, particularly if vitamin B_1 was given simultaneously. Addition *in vitro* of thyroglobulin but not of thyroxin increased the O_2 consumption (Rossiter, 1940). Spirtes (1941) found no significant changes in thyroid-fed guinea-pigs.

Ross and Schwab (1939) found that the cortical alpha rate as obtained by the electroencephalogram is low in myxoedema and returns to normal with the administration of thyroid. There is a good correlation between the alpha rate and the state of metabolism.

The effect of thyroxin on the social behaviour of hens has been studied by Allee, Collias and Beeman (1940).

In a recent review Lerman (1942) thus summarizes the action of the thyroid hormone on the nervous system: "The action of the thyroid on the nervous system is best observed in states of excess or of scarcity of the hormone. In the former case the person has emotional instability, increased irritability and sometimes gross disturbance in cerebration. In the latter case the person lives at a low emotional level, reacts sluggishly and cerebrates slowly; the memory is poor, and there is diminished sensory acuity. The effect of the thyroid on the vegetative nervous system is manifested by increase in vasomotor activity, peristaltic activity and activity of the sweat glands in thyroid intoxication and by the reverse of these phenomena in thyroid deprivation."

It has, of course, to be borne in mind that because of the well known antagonism of the thyroid to gonads and adrenal cortex, a primary disturbance of the first can cause secondary reactions of the latter.

Parathyroids.

No further investigations of the increased neuromuscular excitability dependent on hypocalcaemia have been carried out recently. Symmetrical calcification of brain tissue associated with parathyroid insufficiency has occasionally been found (Eaten and Haines, 1939). Albright (1942) saw the same condition in one case in which no symptoms referable to the central nervous system had been observed, and in another case in which there had been epileptic seizures.

Considering the scarcity of biologically active parathyroid hormone, the therapeutic introduction of dihydrotachysterol during recent years has meant considerable progress in parathyroid therapy (Albright, 1939, and others).

Hyperparathyroidism gives rise to nerve and muscle reactions of a reverse nature to those of tetany. Just as hypocalcaemia causes increased neuromuscular excitability, so hypercalcaemia leads, according to Albright (1942), to decreased excitability. In patients with very high serum calcium there are certain symptoms, apparently due to the high serum calcium *per se*. The patients feel tired, lose weight and are constipated. According to Werner (1942) the excitability of peripheral nerves to electrical stimulation is greatly diminished.

Parathyroidectomized rats manifested increased appetite for foods with high calcium content and decreased appetite for such with high phosphorus content (Bodansky and Duff, 1941). Richter, Honeyman and Hunter (1940) investigated behaviour and mood cycles in parathyroid deficiency (in rats). In conditions where the maintenance of the normal blood calcium level is endangered, as in pregnancy and lactation, a very marked self-regulation develops. Pregnant and lactating rats, for instance, exhibit a craving for calcium (Richter, 1938). The curious, often observed phenomenon that growing and slightly rachitic children eat ashes may be similarly conditioned.

Thymus.

Although there is as yet little precise knowledge about the internal secretion of the thymus, the opinion that it exerts an influence on sexual behaviour is widely held. Bruner and Cunningham (1939) claim that sexual activity in female rats may be inhibited by injecting them with thymocrescin.

Pancreas.

There is no evidence that sugar combustion in the brain is disturbed in diabetic animals (Baker, Fazekas and Himwich, 1938). Sugar utilization and oxidation of brain are diminished in insulin-hypoglycaemic animals (Himwich *et al.*, 1937). Gellhorn *et al.* (1938) claimed that decreased oxidation produced by insulin is greater in brain than in other tissues. The immediate neurophysiological effect of insulin shock, metrazol epilepsy, continuous narcosis and therapeutic nitrogen inhalations has been attributed to cerebral anoxia (Gellhorn, 1938; Quastel, 1939; Himwich *et al.*, 1939/40). This point of view was opposed by Fraser and Reitman (1939).

Insulin shock treatment is dealt with in another part of this volume. With regard to insulin treatment only two points may be treated here on general lines because they are responsible for numerous misconceptions. The points in question are insulin hypersensitivity and insulin resistance. Both these stages depend primarily on the sugar storage in the body, and on the blood-sugar level. When the sugar stores are depleted, by, say, exhaustive work, hypoglycaemia is reached much sooner than under normal conditions. If, on the other hand, the sugar stores are continuously enriched, partly by feeding, partly by increased sugar fixation, insulin resistance may develop. After hypophysectomy, sugar oxidation is increased and the carbohydrate stores are

very much diminished. Similar conditions prevail after adrenalectomy; therefore insulin hypersensitivity develops. The opposite phase is seen after treatment with the so-called glycotropic principle or adrenal cortex hormone and other procedures which fix sugar storage.

The diet selection of diabetic animals is of particular psychological interest (Richter and Schmidt, 1941). Diabetic rats manifested a marked appetite for fats and hardly any for carbohydrates; some ate large amounts of casein. All had an increased appetite for yeast. As long as the animals lived on this self-selected diet diabetic symptoms did not appear and they gained weight at practically the normal rate. When they returned to the normal diet, characteristic signs of diabetes were immediately observed.

Adrenal Cortex.

Considerable progress has been made in recent years in the isolation of about twenty crystalline adrenal cortex hormones and in the elucidation of the physiology of the adrenal cortex. Like the sex hormones, adrenal cortex hormones are all of steroid character and probably exert a far-reaching influence on brain function. Of that effect nothing definite is as yet known. Corticosterone and the so-called substance E are responsible for the adrenal cortical influence in the regulation of body temperature (Kendall, 1940).

The relationship of the adrenals to essential hypertension has been investigated by Raab (1941). Determination of the blood content of the adrenal hormonal compound, epinephrine and cortical steroids (adreno-cortical compounds), were carried out by the method of Shaw. A normal range was established, which did not vary much in normal controls. After muscular exercise the levels were only slightly increased. In essential hypertension they were also within normal range, but rose considerably after muscular exercise. Raab regards this as the decisive factor in the development of arteriosclerosis, and consequent ischaemia of the vasomotor centres.

The adrenals are involved in one of the most important self-regulatory mechanisms of the body, a disturbance of which produces salt hunger. It is well known that after removal of the adrenal gland sodium excretion increases excessively, causing profound changes in the body chemistry, with the appearance of grave symptoms and finally death. This catastrophe can be averted by adding large amounts of sodium chloride to the diet. Given access to sodium chloride, adrenalectomized animals ingest sufficiently large amounts to survive and to remain free from symptoms of insufficiency (Richter, 1942). Richter reports instances of this self-regulation in human beings. A boy, aged 3½, had, for over two years, eaten enormous amounts of salt. When restricted to a normal diet under observation he died within seven days, and it was found that a tumour in his adrenals had completely destroyed all cortex tissues. A 34-year-old sufferer from Addison's disease filled half of his glass of tomato juice with salt, so that, for him, the juice became a vehicle for the salt. He took salt also with grape fruit, oranges and lemons. Salt hunger seems to be a definite pathognomonic symptom of underfunction of the adrenal cortex and is, also in the experience of the author, of help in diagnosis. It has

occasionally been observed in persons suffering from Simmonds' disease who added excessive salt to the little food they ate.

Adrenalectomized rats failed to differentiate between sodium chloride solution and water, and died as quickly as adrenalectomized rats without access to salt after section of the taste nerves (Richter, 1942). Clark and Clausen (1943) found that the increased salt intake after adrenalectomy returned again to the pre-adrenalectomy level after administration of desoxycorticosterone. Intake of protein, carbohydrate, fat and yeast remains unaffected by adrenalectomy.

The adreno-genital syndrome has been reviewed by Young (1937), Broster *et al.* (1938), Haymaker and Anderson (1938), Cahill (1938), and Wintersteiner (1942). The patho-physiological analysis of this syndrome and of the accompanying homosexual stages has made some progress since it has been known that the adrenal cortex can produce androgens and oestrogens, and that the androgen secretion can be increased by the corticotrophic hormone of the pituitary anterior lobe (Hemphill, MacLeod and Reiss, 1942). At least two androgens are produced by the adrenal cortex, the 17-ketosteroid, dehydroandrosterone, and the unsaturated triketone, adrenosterone. It is possible that at some stage of the body development the production of these hormones is increased as a result of environmental changes or some adequate internal stimulus, e.g. scarlet fever, which may affect the adrenal cortex. The author has seen different degrees of hirsutism, menstrual disturbances and adiposity in patients who had once suffered from scarlet fever, which may have been due to adrenal disturbances. Haymaker and Anderson (1938) believe the principal difference between Cushing's syndrome and the adreno-genital syndrome to be the overproduction in Cushing's disease of the cortical hormone with its action in maintaining the electrolytes and carbohydrate metabolism, and the overproduction of sex hormones in the adreno-genital syndrome.

The role played by the adrenals in psychosis is dealt with by Hemphill in this volume.

Gonads.

The cerebral circulation is apparently increased by sex hormones. Steinach (1936) showed that the blood content in the brain of castrated rats can be increased by administration of oestrone, using a not quantitative vital staining method. Reiss and Golla (1940) measured the blood content of the brain and found it considerably diminished after castration. After treatment with sex hormones the brain blood content of normal and castrated animals increased. There was no difference between the actions of oestrone and testosterone.

Dusser de Barenne and Gibbs (1943) have reviewed variations in the electroencephalogram during the menstrual cycle. Gibbs and Reid (1943) have found variations during pregnancy.

The role of the sex hormones in psychiatry has been reviewed by Reiss (1940). The following additional facts may be noted.

In an excellent review by Stone (1939) all behaviour patterns connected with sexual and reproductive function have been described. Recent experi-

ments are, without exception, in agreement with the previous reports. Testosterone propionate administered to female canaries suppressed the female functions and behaviour, and initiated male traits: singing, courting of untreated females, peck-dominance (Shoemaker, 1939). Leonard (1939) noticed male singing in some females after as little as two days' treatment with 5 mgm. testosterone daily.

Female mating behaviour in rats after administration of testosterone propionate (Beach, 1941) is still unexplained, and may be due to degeneration of the testicles or simultaneous stimulation of the adrenal cortex. Salmon and Geist (1943) reported increase of libido in women after treatment with different testosterone preparations. This testosterone action was explained by increased susceptibility to psycho-sexual stimulation, increased sensitivity of the external genitalia and greater intensity of sexual gratification. It was suggested on the basis of these observations that endogenous androgens in the normal mature woman may act as the physiological sensitizer of both the psychic and somatic components of the sexual mechanism.

The therapeutic results achieved by testosterone in cases of enuresis in children (Schlutz and Anderson, 1943) may, if confirmed, throw new light on the pathogenic analysis of this behaviour.

Pituitary.

After hypophysectomy there is no significant decrease of oxygen consumption by brain slices, although liver slices of the same animal show this effect. There is an increase in anaerobic glycolysis of about 25 per cent. (MacLeod and Reiss, 1940).

It is obvious that hypophysectomy or administration of the different pituitary glandulotrophic hormones produced by the pituitary can give rise to most of the conditions detailed. Apart from these static modifications, the presence or absence of these organotrophic pituitary hormones may lead to highly complicated variations of behaviour. These observations are to some extent consonant with claims made to have demonstrated an infection of the pituitary fossa from the sphenoidal sinus as a causal factor in some psychoses (Graves and Pickworth, 1941).

Rats show, after hypophysectomy, an increased drive for nest-building. According to Richter (1942) their thermoregulation is disturbed and they make, therefore, an effort to conserve their normal body temperature by building large thick nests. He compares this activity with the behaviour of rats which, after removal of the posterior lobe, have lost their physiological means of maintaining a constant water balance and compensate by drinking large amounts of water.

Riddle *et al.* (1942) recently studied endocrine conditions of maternal behaviour on the results of several thousands of tests. They found that among the pituitary anterior lobe hormones prolactin is the most effective in producing maternal behaviour, but follicle-stimulating hormone terminates it, even when well established. The authors found further the very interesting fact that every kind of treatment which exerts an antigonad action can, to a certain extent,

produce maternal behaviour. Hypophysectomy alone precipitates maternal behaviour in approximately 50 per cent. of otherwise intact rats; progesterone, desoxycorticosterone and testosterone have a similar effect to prolactin.

Chadwick (1940) investigated the water drive of *Triturus*, and found that pituitary anterior lobe extracts which contained growth hormone caused normal and hypophysectomized efts to enter water within five days after commencement of the injections.

Masculinization has been observed in newborn female rats after treatment with gonadotrophic pituitary extract (Bradbury and Gaensbauer, 1939; Greene and Burrill, 1939). It is assumed that this extraordinary reaction, which, of course, disappears after a few weeks, is due to the occurrence of early luteinization, since androgenic properties of progesterone are known (Greene and Burrill, 1939, and others). The results of these animal experiments may supply a new approach to the pathophysiological analysis of certain forms of homosexuality. Further progress in the investigation of the interrelationship of oestrone, progesterone, pregnandiol and testosterone in the body fluids may point to causes of homsexual aberration which, at present, are treated on psychological lines only.

Hemphill, Reiss and Taylor (1943) found in schizophrenics a disturbance of the testicle structure similar, in certain aspects, to the degenerative features of testicles in hypophysectomized rats. The earlier observations of Mott are thus in some degree confirmed.

The blood content of the rat brain, which is considerably decreased after hypophysectomy, increases after administration of gonadotrophic hormones in young animals, and is higher during oestrus than in the anoestrus phase (Reiss and Golla, 1940). According to Gillespie (1940), it is conceivable that alteration in the mental state of a depression corresponding with the phases of a menstrual cycle may be connected with a state of cerebral circulation.

Increased appetite and the pathological syndrome of overeating and greediness are possibly connected with changes of the pituitary anterior lobe function. After treatment of emaciated involutional melancholics with corticotrophic hormone return of an ever increasing desire for food was the first effect to be seen (Hemphill and Reiss, 1942). The loss of appetite in morbus Simmonds could be explained as an instance of self-regulatory behaviour. Hypophysectomized animals eat less because the lack of growth hormone is responsible for the absence of the specific dynamic action of proteins (Reiss, 1940), and lack of corticotrophic and, consequently, of adrenalcortical hormone is responsible for the disturbance of the fat metabolism. Excessive ingestion of food would lead to the appearance of toxic symptoms in hypophysectomized animals. Patients suffering from the Cushing's syndrome, on the other hand, have very often an increased appetite. An inhibiting centre is most probably in the frontal lobe. Appetite is increased after prefrontal leucotomy. After destruction of the tips of the frontal brain poles rats may eat almost incessantly (Richter and Hawkes, 1939; Beach, 1941). Also after lesions in the thalamus rats or monkeys eat excessively and become obese (Hetherington, 1941).

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