Part I.—General Review.

THE PHYSIOLOGICAL PATHOLOGY OF THE ANTERIOR PITUITARY.

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[In the physiology of the central nervous system, the hypothalamus has of recent years obtained a position of much enhanced importance. There is reason to believe that it has a determining influence on cortical function and evidence is not wanting that some psychotic conditions are associated with hypothalmic disturbance. It may well be that many forms of mental disorder are conditioned by a lesion of the hypothalamus. This close anatomical and physiological relationship between this area of the brain and the pituitary we think, therefore, cannot be over-emphasized. Dr. Max Reiss was asked by the Research Bureau to present a review of our present knowledge of the anterior pituitary, on which he is a recognized authority.]

IN the last ten years our views on the physiological significance of the pituitary have undergone many changes and our knowledge of this subject has greatly increased. Research is still in progress, and the position is still far from defined. It is, however, possible at the present stage to indicate the lines on which our investigations will proceed and the modifications necessary in the older interpretations.

The literature of the anterior pituitary function has grown so rapidly in the last few years that it is impossible to give a full account of it in the small compass of this review. The facts referred to here are only those which are most likely to interest psychiatrists and neurologists or could become interesting to them in the future. So much must necessarily be omitted from this account of the subject that in parts it may seem to be misleading unless it is realized that in this subject truth can only be approached by absolute completeness.

The results of investigations on the endocrinology of the hypophysis serve as a point of departure for nearly all the research work in modern endocrinology, inasmuch as both from the neurological and purely endocrinological point of view there is the closest relation between the pituitary and other internal secretory glands.

It was at one time thought that complete hypophysectomy proved fatal in a very short time. The pituitary was considered to be necessary to life; a conclusion which was based on faulty operative technique. It is now possible to extirpate the pituitary without damage to the surrounding tissue

and blood-vessels. Monkeys, dogs, rabbits, rats and mice survive after hypophysectomy for months and even years. The animals never show acute deficiency symptoms at death. The disturbances leading to death are of a chronic type. The improved operative technique allows of accurate differentiation of the deficiency symptoms from those due to injury. The particularly easy operative technique in the case of the rat has facilitated the study of deficiency symptoms in large numbers of animals. This method proved to be especially useful for the analysis of the endocrinology of the anterior lobe.

The production of a series of hormones has been definitely proved and their number alone shows that the three histologically differentiated cell types of the anterior lobe cannot be associated with specific types of hormone secretion. It must, however, be borne in mind that the crude tinctorial methods at the disposal of the histologist are probably insufficient for a functional cell differentiation. On the other hand, there is ample evidence that the type and amount of hormone secreted is determined by the needs of the body extraneous to the gland itself. Both during the process of development and in disease, the body calls for various types of hormones from the anterior pituitary and it seems to be easiest to assume that the various hormones may be produced from a single type of cell. This view is paralleled by the undoubted fact that in an organ like the liver, in which even fewer cell types can be demonstrated than in the pituitary, there is an even greater degree of functional differentiation. In the same liver-cell that stores glycogen, its synthesis and metabolism also take place, protein is converted into sugar, fat metabolism is carried on, urea, bile constituents and anti-anæmic principles are produced.

(*a*) The Physiotropic Function of the Anterior Pituitary.

The first deficiency symptoms noted were the cessation of growth after hypophysectomy of experimental animals and, in man, pituitary dwarfism from destruction of the anterior lobe. H. M. Evans (1) who, in 1921, gave the first exact demonstration of the growth-promoting properties of anterior lobe extracts, was able to produce gigantic rats, twice as long and heavy as the control animals of the same litter by a year's treatment with alkaline extracts. Putnam, Benedict and Teel (2) and Evans, Meyer and Simpson (1) were able to produce by administration of such extracts definite acromegalic changes in the skulls of dogs. The skulls of the treated animals were 5 cm. longer than those of the controls of the same litter. The skin was hypertrophied and folded in a manner reminiscent of human acromegaly. In young guinea-pigs changes were found after a short treatment in the long bones similar to those described (3) in acromegaly. After only four injections a stimulation of bone growth could be demonstrated by weighing the tibia and fibula (4). Various bodily organs attain a greater size under the influence of the growth hormone. Teeth (5) and hair (6) are thus affected. The rapid

growth of the tail and of the tail vertebræ in rats is particularly instructive (Freud and Levie (7)).

Not only normally growing tissues, but even pathological tissue is influenced by the growth hormone. Both implantation tumours and tar carcinoma grow much more slowly after hypophysectomy, and administration of growth hormone accelerates their development (8). The growth hormone administered to normal animals at the epoch when the natural growth process is coming to a standstill has a very marked effect (1). Hypophysectomized animals treated by the growth hormone grow faster than normal animals (9).

The standardization of the hormone is biological. Till recently this was done by measuring the growth after treatment of normal rats which had just ceased to grow further, or of hypophysectomized rats (9). Recently, however, it has become apparent that weight does not afford the best criterion of growth, and measurements of length have been substituted. A particularly good test is furnished by the measurement of the tail vertebræ of the rat (7) (Fig. 1). Recently it has been doubted whether the growth hormone is a unitary specific anterior lobe hormone, or whether the growth-promoting action depends on a number of substances in the anterior lobe not yet adequately defined. Bates, Riddle, Lahr and Schooley (10) support the latter view on the strength of their experiments on pigeons. It should, however, be noted that the growth of birds is in all probability subject to different laws from the growth of mammals. Quite recently Freud and Dingemanse (11) have prepared a pure growth hormone which possesses none of the other hormonic properties of the anterior lobe hormones.

Bodily growth is, however, a complex process which can only take place through the participation of a whole series of metabolic events. Of these we need only cite protein metabolism, since tissue growth is based on protein synthesis, and calcium metabolism, without the participation of which increase in bone measurements is not possible. Further, the effect of the growth hormone is dependent on the nature of the food. A sufficient quantity of the growth vitamin is essential (12). The hormone action appears to be direct, whilst that of the vitamin is subordinate. Hypophysectomized rats do not show the typical picture of avitaminosis, or at least only very late with a vitamin A free food. It is evident that since they are not growing they have no need of vitamin A.

The growth hormone, or the growth hormone complex, is the essential growth factor of the organism. When a thyroidectomized animal fails to grow there is reason to think that this is due to a non-production of the anterior lobe growth hormones, since if these be administered the thyroidectomized animal begins to grow; but, on the other hand, administration of thyroid to a hypophysectomized animal does not cause growth (13). In the anterior lobe of dwarf animals the gonadotropic hormone is present in normal quantity, whereas the growth hormone is absent. This last finding should be noted in

connection with the various forms of human pituitary dwarfism. Some pituitary dwarfs are fat, others emaciated, and the type of dwarfism apparently depends on whether or not the production of other anterior lobe hormones is involved together with that of the growth hormone. The category of pituitary dwarfism is an insufficient classification. In each case it is necessary to specify the presence and nature of hyper- or hyposecretion of other anterior lobe hormones. The same criticism must be adopted in the case of acromegaly. Rarely does any one case of acromegaly resemble another in all its symptoms. It is non-recognition of this fact that has led to such varying descriptions of acromegaly in text-books. When acromegaly occurs with hypothyroidism or myxœdema we have to do with a hypersecretion of growth hormone accompanied by a hyposecretion of thyrotropic hormones. Symptoms of hyperthyroidism in acromegaly indicate a hypersecretion of the thyrotropic hormone. The same considerations apply to such accompanying symptoms as disturbances of sexual function, obesity or cachexia. The designation acromegaly is not descriptive of other than the leading symptom of the complex. The growth hormone has proved to be of therapeutic value in man so long as epiphyseal fusion has not occurred (15).

(*b*) The Gonadotropic Function of the Anterior Lobe.

The gonadotropic function of the anterior pituitary is one of the best observed phenomena in the whole subject of endocrinology. The interrelation of gonads and anterior lobe has not, however, been fully investigated, and equally so the relationship of other glands of internal secretion to normal sexual function is still a matter of discussion. It appears to be certain that the ovarian production of the follicular hormone and the corpus luteum hormone depends on the secretion of two distinct anterior lobe hormones of which one excites the follicular development, acting on the egg-cell and granulata, whilst the other has only a luteinizing action on the theca cells. In addition to these factors Evans (16) considers that there is yet a third hormone, the so-called synergistic hormone, which has little or no gonadotropic action; combination of this substance with prolan causes a marked increase of its potency. The action of this specific synergistic factor is disputed. Fevold (17) considers that it is only a question of the relative amounts of the various hormones in the particular extracts acting on the follicles.

Prolan, which is obtained from the urine of pregnant women and from the placenta, has an action similar to the gonadotropic hormone, but it is not identical. Whilst it is possible to restore the sexual function of hypophysectomized animals with an extract of the anterior lobes, Evans (1) was unable to obtain this result with prolan. If hypophysectomized animals are treated with prolan some time after hypophysectomy, even large doses do not bring the infantile ovary to maturity, whilst administration of anterior lobe extracts

causes early maturity. The same conditions are found in hypophysectomized dogs (1). The degeneration of the ovaries of adult hypophysectomized rats cannot be inhibited by prolan administration. It is possible, however, to produce signs of prolonged vaginal œstrus by prolan, but not in infantile animals in which œstrus has not yet appeared (Collip (18)). In contradistinction to the effects of anterior lobe administration prolan never causes the formation of normal corpora lutea. The appearance of radial nuclear cells can be inhibited by prolan (Wade (19), Selye, Collip and Thomson (20)). Anterior lobe extracts which are either inactive or possess only very weak gonadotropic action have the power to activate prolan so that it is effective when administered to hypophysectomized animals in producing follicle ripening and luteinization (Evans, Collip and Leonard (22), De Jongh and Kober (23)). Prolan has no gonad-stimulating action in male birds, in contradistinction to the anterior lobe hormone. Whilst the weight of infantile rat ovaries varies directly with the amount of anterior pituitary extract administered, it is not notably influenced by the administration of prolan. The combined administration of anterior lobe extract and prolan to infantile animals has a maximum effect on the gonads when each component is separately just below the threshold value for eliciting a response (Evans (1)). It is still questionable whether prolan does not represent a degradation product of the anterior lobe hormone excreted in the urine (24). The site of formation of prolan in the body is as yet unknown. An increasing number of workers consider that it is formed in the placenta. The original idea that prolan consists of two functionally distinct substances has not been supported by recent work (28). Attempts to divide prolan into folliculin stimulating and luteinizing varieties (A and B prolans) have failed.

The action of the gonadotropic hormone on the testes has been much investigated. The follicular stimulating hormone has been shown to act only on the germinal epithelium and to stimulate spermatogenesis, whilst the luteinizing hormone stimulates the interstitial cells to growth and hormone production (Fevold (17)). This last action is also exerted by prolan. Evans (16) considers that the interstitial exciting fraction can be distinguished from the luteinizing fraction, but this is disputed by Fevold (17). Aschheim and Zondek (28) found large quantities of a follicle-stimulating substance in the urine of castrated women. This substance appears to be identical with the follicle-stimulating hormone of the anterior lobes.

There is as yet no international standardized preparation of the gonadotropic hormone, although there exist many tentative definitions of the unit action. The reactions used in the estimation of the gonadotropic substances are the following: production of corpora lutea in the ovaries of immature animals, opening of the vagina and causing the dehiscent stage in immature rats, growth of the pigeon testicle, growth of the comb in immature cocks. The sensitivity of these various reactions is very uneven, so that in the absence of

an agreed international standard the reports on the hormone value of preparations varies considerably. Most commercial preparations are standardized in rat units, that is in terms of the minimum dose that will exert a luteinizing action on the immature rat.

The discovery of the gonadotropic substances of the anterior lobe has thrown a new light on the pathogenesis of ovarian and testicular disturbance in human pathology. Menstrual disturbances of hormonic origin are not to be regarded as necessarily of primary ovarian origin; in every case the relation of the anterior lobe to the symptom complex must be investigated. The role played by the anterior pituitary may be very complex; over and under-secretion of the follicle or lutein hormone may be the cause of amenorrhœa, but here again the primary cause may be a disturbance of the secretion of the follicle- or lutein-stimulating hormones of the anterior lobe. For this again there are a series of causes of which some (the nervous hormonal relations) will be discussed later. In addition it must be borne in mind that conditions may exist in the ovary which will render it inexcitable to the gonadotropic hormones, although they may be produced in great quantity. The variability of the types of hormone disturbances in cases of gonadal dysfunction makes profound hormonic investigation of such cases very necessary.

Whilst for therapeutic purposes the physician may readily obtain all the prolan he needs, the anterior lobe gonadotropic substances are hardly as yet on the market. In view of the difference between prolan and the anterior lobe hormone it might be thought that the gonadotropic substance would be much more effective than prolan. Prolan has given good results in cases of menstrual disturbances in women in whom the disturbance is obviously secondary to diminished luteinization in the ovary. In developmental disorders of the testicle there are so far few observations on the action of the gonadotropic anterior lobe hormones. Juvenile cryptorchidism has been successfully treated with prolan. According to most writers descent of the testicle may be effected after a few weeks of prolan treatment; this is brought about by the growth of the scrotum under the influence of prolan, and consequent mechanical stress on the testicle.

(*c*) The Galactagogue Function of the Anterior Lobe.

Mammary development is under the control of the ovarian hormones, but lactation itself is never caused by these hormones. The follicular hormone indeed inhibits the onset of lactation. If the mammary gland is caused to grow by follicular hormone, it is only when this is discontinued that lactation begins. Lactation is evoked by the action of the prolactin formed in the pituitary, and the secretion of prolactin is inhibited by the follicular hormone. Animals which suckle their young cease to do so after hypophysectomy (31). Long before these facts were known Stricker and Guter (32) succeeded in

inducing lactation or augmenting existing milk secretion in various experimental animals by the administration of anterior lobe extract. They showed, moreover, that only a mammary gland developed by the influence of the ovarian hormone can be brought to secrete milk by the anterior lobe hormone. Evans and Simpson (33) showed that rats treated by crude anterior lobe extracts show hypertrophy of the mammæ and eventually lactation. Riddle (35) has used the crop glands of pigeons as a test for the action of crude anterior lobe extracts. Under their influence the crop hypertrophies and the so-called crop milk is secreted. By these experiments on the pigeon Riddle was able to separate the lactogenic substance called by him prolactin from the anterior lobe extracts. Prolactin acts especially on the mucosa of the crop gland, which in the beginning appears as a very thin membrane weighing 140 to 300 mgrm. After administering prolactin for four to five days this membrane is thickened and folded, and its weight is increased to 2,000 to 4,000 mgrm. Prolactin inhibits ovulation in pigeons and has an inhibitory action on the hormone that stimulates the ovarian follicles. Broodiness is induced in hens and infantile rats (36) by prolactin administration.

These animal experiments help us to understand human lactation and its pathological deviations. Thus the sudden appearance of lactation occurs when the follicular hormone, increasing in the blood during pregnancy, suddenly disappears. The production of prolactin by the pituitary is now no longer inhibited by the follicular hormone. The inhibitory action of prolactin on the production and action of the gonadotropic hormone explains the absence of menstruation during lactation. Some forms of disturbance of menstruation are known in which amenorrhœa is present with galactorrhœa. The pituitary origin of such disturbances is evident without hormone analysis, the increased production of prolactin inhibiting the increased production and action of gonadotropic hormone.

(*d*) The Thyrotropic Function of the Anterior Lobe.

Adler (52) was able to show in 1914 that extirpation of the thyroid inhibits the metamorphosis of tadpoles, and Hoskins (53), Hogben (54) and Spaul (55) that anterior lobe extracts accelerate the tadpole metamorphosis. Aschner (56), Ascoli and Legnani (57), Smith (58), and numerous other observers described atrophy of the thyroid in mammals after extirpation of the anterior lobe. Loeb and Bassett (59) and Aron (60) showed in 1929 for the first time the stimulating action of the anterior lobe extract on the histological structure of the guinea-pig thyroid. Junkman and Schöller (61) isolated the thyrotropic hormone. The systematic chemical investigation of the anterior lobe extracts has achieved the isolation of the hormone, free from admixture with other pituitary hormones. One milligram of the pure extract is sufficient to cause thyroid hypertrophy in 40 to 50 guinea-pigs. After administration of the

thyrotropic hormone the thyroid increases in weight. The gland-cells hypertrophy and exhibit frequent mitosis, and there is increased vascularity. The colloid shows ever-increasing vacuolization and may ultimately disappear, so that the histological appearance of the thyroid resembles that of a case of Graves's disease. The Golgi apparatus of the thyroid gland-cells also hypertrophies (62). In hypophysectomized animals the normal appearance of the thyroid may be restored by thyrotropic hormone administration and even some degree of hyperthyroidism may be attained (63) (Fig. 2). The action of the hormone may even be demonstrated on the guinea-pig fœtus (64). The effective dose of the hormone varies in different animals ; in rats it is 200 to 2,000 times and in rabbits 10 times that of the guinea-pig (65). The sensitivity of animals to the thyrotropic hormone increases in the following sequence : mouse, rat, rabbit, cat, pigeon, guinea-pig (66). The young duck is particularly susceptible (67). Castrated rats react less than normal rats (68).

The action of the thyrotropic hormone is diminished by simultaneous administration of thyroid extract (69), or potassium iodide (70). The simultaneous administration of the follicular hormone inhibits the thyrotropic action (71).

The thyrotropic hormone acts directly on the thyroid. Extirpation of the cervical sympathetic does not affect its action (72). The growth of implanted thyroid grafts is stimulated by the hormone (73). An *in vitro* effect on the thyroid may be even observed (74). The oxygen consumption of thyroid tissue treated *in vitro* by the hormone is increased (75).

The internal secretion of the thyroid hormone is increased by the thyrotropic hormone, leading to the bodily symptoms of hyperthyroidism. The iodine content of the thyroid decreases (76) whilst thyroxin and organically bound iodine increase in the blood (77). Whilst experimental exophthalmos is only elicited with great difficulty by thyroxin administration, it can easily be produced by the thyrotropic hormone (78). The hormone differs in yet other ways from thyroxin ; it does not give rise to the degenerative changes in the viscera of rats and mice that follow excessive thyroxin treatment (79). The cardiac frequency increases more rapidly with the hormone than with thyroxin administration (80). The effect on tissue metabolism of thyrotropic hormone resembles that of thyroxin (81). In the Reid Hunt acetonitrile experiment on mice thyrotropic hormone raises the resistance to the poison in the same way as thyroxin (82).

An international standardization of thyrotropic hormone was established in 1938 by the standardization committee of the League of Nations. Rowlands and Parkes (83), Junkmann and Loeser (84) have established a mathematical expression for the relation of the hormone activity to the weight of guinea-pigs' thyroid. These weight methods are sufficient routine tests (see also the method on the thyroid of young chickens (86)), and are from the practical point of view more applicable than the histological examination as it has been worked

out by Junkmann and Schöller (61) and Heye and Laqueur (85). Only the histological response of hypophysectomized animals is absolutely specific, and using the histological method the alleged presence of the hormone in the ovaries, adrenal medulla and pancreas claimed to exist by Sturm and Schöning (87) may be disproved.

The discovery of the thyrotropic hormone and of its functions has thrown a new light on the pathogenesis of thyroid hyper- and hypo-function. The following questions at once suggest themselves:

1. Can hypothyroidism follow under-production of thyrotropic hormone?

2. Can hypothyroidism be attributed to a diminished sensitivity of the thyroid to thyrotropic hormone produced in normal quantity?

3. Can hyperthyroidism follow over-production of thyrotropic hormone which again may be due to defective regulation owing to the existence of a diencephalic lesion?

4. Can hyperthyroidism result from increased thyroid sensitivity to thyrotropic hormone produced in normal quantity?

Certain forms of thyroid disorder are obviously conditioned by the pituitary, such as the hyperthyroidism in acromegaly and the hypothyroidism found in cases of tumours of the hypophysis and in pituitary cachexia. In some cases of myxœdema thyrotropic hormone will raise the basal metabolism rate, but in others it is ineffective (88). The reaction of the patient to thyrotropic hormone is the crucial test in differentiating between primary myxœdema and that secondary to pituitary dysfunction and is obviously of the greatest importance in deciding therapeutic measures.

(*e*) The Corticotropic Function of the Anterior Lobe.

The adrenal cortex atrophies after hypophysectomy (90). Administration of crude anterior lobe extracts has been found to cause adrenal hypertrophy in rats (91), rabbits and dogs (92). Collip (93) succeeded in separating from the crude anterior lobe extract a substance that is principally corticotropic. After hypophysectomy the adrenals show a rapid disappearance of the cortex, whilst the medulla is unaffected. The cortical atrophy is often preceded by the appearance of small hæmorrhages (94). Cutuly (95) undertook some quantitative experiments on albino rats, estimating the adrenal cortex by the silhouette method of Donaldson (96). He showed that the weights of the adrenals of hypophysectomized male rats diminish after 30 days by 63% and the female adrenals by 70%, and this diminution in weight is due to atrophy of the cortex. The reaction of the lipoids of the adrenal cortex is of special importance. Seven days after hypophysectomy in the rat, a lipoid-free sudanophobe zone develops in the adrenal cortex starting from the zona glomerulosa, spreading

over the zona fasciculata to the zona reticularis. The diffuse granular lipoid distribution of the normal cortex becomes coarsely granular after hypophysectomy (Reiss (97)). Administration of the corticotropic hormone to the hypophysectomized animal causes an increase in the weight of the adrenals after a short tonic. The cortex deepens and exhibits active mitosis, the lipoid becomes again finely granular and is distributed throughout the sudanophobe zone (93 and 97) (Fig. 3). Atwell succeeded in producing similar reactions in hypophysectomized tadpoles (98). Many observers find that the corticotropic hormone leads to increase of the adrenal cortex in normal animals, although a strictly objective demonstration of the action of the hormone can only be carried out with hypophysectomized animals (Collip (99)). Reiss (97) found no direct relation between the amount of the hormone administered and the increase in weight of the adrenals. Therefore a method for standardization has been described which is based upon the disappearance of the sudanophobic zone following the administration of corticotropic hormone (Fig. 3).

The corticotropic hormone of the anterior lobe undoubtedly exercises a very profound influence on normal life processes and the reaction to pathological states. It has long been known to pathological anatomists that the most diverse lesions and diseased conditions affect the suprarenals. Very soon after the development of a pathological process well-marked changes may occur in the adrenal cortex which are heralded by lipoid disappearance and vacuolar degeneration (100). Again, following acute disease a secondary hypofunction may be often noted in the adrenal cortex. Death in acute infectious diseases is often characterized by a symptom-complex suggesting the loss of function of the adrenal cortex. During convalescence typical Addisonism symptoms may appear for a time and may even lead to severe complications. Many of the symptoms observed in avitaminosis, particularly pellagra and beri-beri (pigmentation and gastro-intestinal disturbances), may be ascribed to hypofunction of the adrenal cortex.

Adrenalectomized animals show a diminished resistance to infections and to bacterial toxins. Administration of the hormone of the adrenal cortex increases resistance (101). Adrenalectomized animals are hypersensitive to morphine and histamine. Administration of cortin to such animals again raises the resistance, and this has been proposed as a method for the quantitative estimation of cortin (102, 103). Similar results are obtained on administration of corticotropic hormone from the anterior lobe to hypophysectomized animals also hypersensitive to histamine (104). In this connection Perla (105) investigated the very important relations of the anterior lobe to resistance of the body to various noxæ. The relation of the reticulo-endothelium to the resistance to infection that is a function of the adrenal cortex and the anterior lobe is indicated by the fact that when the reticulo-endothelium is blocked certain responses to injection of cortin (such as the diminution of blood cholesterol (106)), do not occur. Further, that when animals have

been treated by corticotropic hormone the absorption capacity of the reticulo-endothelial system for lithium carmine is markedly increased (107). When the reticulo-endothelial system of rabbits is treated by Congo red injections, it is found that the disappearance of the dye from the blood is accelerated by treatment with anterior lobe extracts (108). The defensive response to various noxæ causes adrenal hypertrophy, as exemplified in the adrenal response of the rat to chronic suppuration (97). Selye (109) has studied the effect on the organism of various noxæ and finds the following characteristic morphological changes: Involution of the thymus and other lymphatic organs, hypertrophy of the adrenal cortex and loss of chromaffin of the adrenal medulla, œdema in various tissues, multiple ulcers and hæmorrhage in the alimentary tract, and polynuclear leucocytosis with a relative leucopenia. He designates the whole complex as the "alarm reaction". After hypophysectomy the hypertrophy of the adrenal cortex does not take place, whence it may be assumed that such hypertrophy is conditioned by hypersecretion of the corticotropic hormone.

(*f*) The Metabolic Function of the Anterior Lobes.

The relation of the anterior lobe to metabolism has elicited so great a mass of work that a summary is difficult. Much of this work has been done with crude extracts that throw no light on the existence of a specific endocrine action. There are two ways of investigating the relation of the pituitary to metabolism. The first is the investigation of metabolism after hypophysectomy and the reaction of the metabolism of such hypophysectomized animals; and furthermore the application of well known and purified hormones of the pituitary gland by which these alterations of the metabolism may be normalized. The second method is to test the effect on the metabolism of normal animals of administration of a series of anterior lobe preparations. The different effects found in these experiments have mostly been attributed to the existence of hormones in the extracts with a specific action on the metabolism; a series of hormones of the anterior lobe has so been described and called by different names the existence of which in most cases has still to be proved.

O_2 consumption and basal metabolism.—It is generally agreed that there is a fall of the basal metabolic rate after hypophysectomy. This fall is generally explained by the depression of gonadal function, growth and temperature regulation, and of a number of endocrine glands owing to the elimination of their specific hormones. This is certainly the case with the thyroid, the most important factor in basal metabolism. The same factors are at work in patients suffering from pituitary cachexia (Simmond's disease). Cases of chiasmal glioma and cranio-pharyngioma compressing the pituitary will show a similar depression of basal metabolism (110). The action of the specific

hormones of the anterior lobe on metabolism is as follows. The growth hormone depresses the basal metabolism, the depression following an injection by some days (111). The metabolism of rats made gigantic by growth hormone administration is depressed (112). The gonadotropic hormone has no action on metabolism (113); even when administered to immature animals the gonadotropic hormone does not affect metabolism (114). Small and doubtful decreases in metabolism have been recorded in the human being (115).

The thyrotropic hormone causes a rise of metabolism within a few hours of injection ; its action in the normal animal is, of course, indistinguishable from that of the thyroid hormone. In the thyroidectomized animals it is without effect (114, 116). In man, after an injection of from 600 to 1,000 units, the basal metabolism rate may be raised by 40% (88, 89). In cases of hypothyroidism the rise may reach higher percentages of the normal. The rise of metabolic rate caused by the thyrotropic hormone in hypophysectomized animals is greater than in normal animals (117). Thyroxin has likewise a more pronounced action on the metabolism of hypophysectionized rats than on normal animals and may even prove rapidly fatal (118). The greater susceptibility of the guinea-pig than the rat to thyroxin has been thought to be due to lesser development of the accessory adrenal cortex in the guinea-pig (118). Administration of sodium iodide diminishes the effect of the thyrotropic hormone (119). Riddle (120) found that the effect of thyrotropic hormone administered to pigeons depended on the temperature. Injections at 30° increased metabolism ; at 15° they often lowered it. Prolactin increases the metabolism of pigeons. Riddle (120) considers that prolactin acts as an adjuvant to thyrotropic hormone in its action on metabolism.

O'Donovan and Collip (121) have recently found a substance in the anterior lobe extract which is thermostable at pH 10, and causes an increase of metabolism of 30% three hours after injection into a rabbit. Its action is independent of the presence of the pituitary, thyroid or adrenals (122). Reiss (123) has noted an increase of metabolism on injection of corticotropic hormone into normal animals which is not obtained in hypophysectomized animals.

The oxygen consumption of liver and kidney slices is diminished in the hypophysectomized animal (124). The thyrotropic hormone increases the metabolism of tissue slices by virtue of the increased thyroid secretion. It achieves a greater and more rapid result than can be obtained by isolated thyroxin or thyroid injection, and it must be assumed that the hormone activates in the thyroid a much more potent substance than has yet been obtained artificially (81).

The ovary of virgin animals shows an increase in aerobic and anaerobic glycolysis and in oxygen consumption very soon after injection of gonadotropic hormone (125).

Carbohydrate metabolism.—It has long been known that carbohydrate tolerance is increased in pituitary dwarfs and that they are hypersensitive to

insulin (126). Dogs, after loss of the anterior lobe, show a lowering of the blood-sugar level, and in a hunger state they may even develop hypoglycæmic convulsions. These animals are hypersensitive to insulin (127). In the hypophysectomized monkey this hypersensitivity is extreme and insulin shock can readily be produced (128). Removal of the posterior lobe alone does not increase insulin sensitivity (129).

Hypophysectomized rats, when starved, lose most of their muscle and liver glycogen (130), and this is due, on the one hand, to diminished glycogenesis, and, on the other, to more efficient sugar utilization. It is further thought that such animals cannot form sugar from fat (131). Russell (132) and Bennet (133) consider that there is a glycostatic factor acting directly on the tissues that tends to keep muscle and liver glycogen at a constant level. Corey and Britton (134) consider that the principal glyco-stabilizing role is played by the adrenal cortex (134). Hypophysectomized animals metabolize ingested glucose at double the normal rate and seem unable to store it. The influence of corticotropic hormone on such animals is to normalize the sugar metabolism and storage, and even to lead to fat formation (123).

Houssay (135) and his co-workers showed that in hypophysectomized dogs destruction of the pancreas does not lead to diabetes (135). There are two possible explanations: one, that a substance is absent in the hypophysectomized animals that regulates normal glycogen storage, and the other that there is a diabetogenic anti-insulin in the pituitary and in its absence diabetic symptoms cannot develop. Houssay (136) found that when crude extract of the anterior lobe was administered to such animals diabetic symptoms appeared. Normal dogs injected with these extracts for several days showed rise of blood sugar, glycosuria, ketonæmia and ketonuria. Also Evans (1) had noted that diabetic symptoms appeared in animals treated by his alkaline growth-producing hormones. In the experiments of Houssay, injection of anterior lobe extract caused the diabetic symptoms to persist for only such time as the injections continued. Young (139), using enormous daily doses of anterior lobe extract (up to 25 grm. of fresh gland daily) in dogs, was able to produce a permanently diabetic condition, remaining even after stopping the injections. The animals showed glycosuria, hyperglycæmia, polydipsia, polyuria and in some cases ketonuria. The excretion of ketones was considerably lower under carbohydrate diet than after feeding high amounts of protein. Glucose given *per os* was almost completely excreted with the urine and the sugar tolerance curve showed a diabetic character. The respiratory quotient was abnormally low and was not raised by the administration of glucose. About 60 units of insulin had to be injected into these dogs in order to get the urine free of glucose and ketones. The effect of the crude extracts was attributed to the presence of a glycotropic factor which remained in the crude extracts after removing the gonadotropic, thyrotropic and lactagogic hormones. The purified extract also increases the glycogen content in liver and muscle under various

experimental conditions (139). Investigating the pancreas tissue histologically hyalinization of the Langerhans cells was found in one case. Kater (140) was able to confirm some of Young's findings. There is a difference between Young's "permanent-diabetic" and pancreatectomized dogs. The former survive indefinitely without administration of insulin, their body weight does not decrease and the glycogen depots are not exhausted. Furthermore, in normal starved tropic factor and the insulin resistance is lowered. As to the effect of the "glycotropic factor" on glycogen, we have to take into consideration the "glycostatic factor", Russell (132) and the effect of adrenal cortex (141) or corticotropic hormone (142) on the storage of carbohydrates. But these facts need not be discussed here. Thus Képinov (143) showed that while transfusion of the blood of a diabetic dog into a normal animal causes a rise of blood sugar, this does not take place if the pituitary of the diabetic dog has been removed. Blood from some diabetics diminishes the sensitivity to insulin (144).

These facts might enable us to differentiate between the classic forms of diabetes mellitus and forms of diabetes of pituitary or cerebro-pituitary origin.

It remains to be seen whether the increased excretion of ketones after administration of crude extracts has to be attributed to a special hormone (145) or whether the ketonuria and ketonæmia are due to far-reaching changes in the carbohydrate metabolism.

The alleged existence of a pancreaticotropic hormone (147) seems very doubtful, and it is difficult to see how it could be compatible with the undoubted fact that hypophysectomy causes an increased sugar metabolism. It is possible that the results claimed for the pancreaticotropic hormone are to be ascribed to contamination with thyrotropic hormone which, as Zunz and LaBarre (148) showed, depresses the blood sugar, acting, according to these authors by increasing the secretion of insulin. The so-called "Kohlehydratstoffwechselhormon" is supposed to diminish the glycogen content of the liver. As this is no specific effect, the "Kohlehydratstoffwechselhormon" can be explained by the presence of thyrotropic hormone in the extracts in these experiments.

Fat metabolism.—The existence of both pituitary adiposity and pituitary cachexia shows the intimate relation of the pituitary to fat metabolism. Rats show a 60% diminution of body fat two to three weeks after complete hypophysectomy. If the animals are allowed to survive for six or more weeks after the operation, the initial fat loss is reversed by a return to normal, and even a slight increase of the body fat. The acute loss of fat after hypophysectomy can be inhibited by corticotropic hormone, which may even cause an increase of fat in the normal rat. This fat loss and subsequent recovery after hypophysectomy would therefore appear to be primarily conditioned by hypofunction and subsequent stimulation of the adrenal cortex (142). Cortin administration causes an increase of body fat and an acute loss

of fat follows adrenalectomy. Animals thus mutilated cannot be fattened by fatty diet (150). Administration of alkaline anterior lobe extract causes fatty deposition in the liver (157) which is absent if the adrenals previously have been extirpated (152).

Pituitary cachexia (Simmond's disease), occurring from gross lesions affecting the anterior lobe or its destruction by embolism or abscess formation, is thus explicable by the results of experimental hypophysectomy. The fact that after a time the hypophysectomized animal again begins to put on fat may be attributed to the secondary diminution of basal metabolism following the late consecutive degeneration of the thyroid and gonads. Such a secondary fat increase in hypophysectomized animals is paralleled in the Fröhlich pituitary dystrophy with its gonadal atrophy. In rats partially hypophysectomized Reiss (142) found shortly after operation a marked increase of the fat content of the body and a hypertrophy of the suprarenals. It would appear that the adiposity is the response to hypersecretion of the corticotropic hormone. Instances of such hypersecretion adiposity occur in human pathology in greater or less degree, depending on the amount of pituitary disturbance. The adiposity in Cushing's syndrome represents an extreme case of pituitary hypersecretion of corticotropic hormone. Reiss found in two cases of Cushing's syndrome evidence of an increase of corticotropic hormone in the blood. Anderson, Haymaker and Joseph found an increase of cortin in the blood and urine of three cases of Cushing's syndrome (153). Corticotropic hormone diminishes the neutral fat content of dog's blood and depresses the lipæmic curve following oil injection (142). This reduction of lipæmia may possibly be an expression of increased tissue-fat fixation. Raab (154) claimed to have isolated a separate hormone from anterior lobe extracts which depresses lipæmia. This body, which he calls lipoitrin, is in all probability identical with corticotropic hormone.

It has long been known that administration of the impure gonadotropic substance from the anterior lobes and the urine of pregnancy causes hypercholesterinæmia (155). Recently it has been shown that in the urine it is the luteinizing and not the follicular factor that causes the hypercholesterinæmia (156). The reaction can only be obtained from the urine of pregnancy (157). Administration of thyrotropic hormone causes a diminution of serum cholesterol in rats and dogs. After ablation of the thyroid and pituitary the depression of serum cholesterol thyrotropic hormone can no longer be produced (158).

Protein metabolism.—It is obvious that in conditions in which there is an increased or decreased production of thyrotropic hormone there will be a corresponding increase or decrease of nitrogen metabolism. After hypophysectomy rats lose 19% of their total nitrogen (159). Administration of growth hormone may cause as much as a 50% diminution of nitrogen excretion. The urea and ammonia excretion are chiefly affected, while creatine excretion remains normal (160). Lee and Schaffer (161) determined the nitrogen balance in

20 hypophysectomized rats and found that when treated with growth hormone the rats excreted 25% less nitrogen. The residual nitrogen of the blood (162) and the free arginine (163) are diminished by administration of growth hormone. An obvious explanation of these results is that protein synthesis takes place. Hypophysectomized dogs excrete the same amount of nitrogen as normal controls after a protein meal, but the rate of excretion is slowed. Such animals fasting excrete about a third less than normal (164). Nitrogen excretion during nitrogen starvation is more markedly diminished in hypophysectomized animals (165). Intraperitoneal injection of glycocoll increases the basal metabolism of hypophysectomized rats less than that of normal rats (166). In acromegaly the de-aminizing power of the liver appears to be impaired, and a similar impairment occurs on administration of anterior lobe extracts (167). Hypophysectomized dogs excrete more allantoin and less purine bodies than normal.

Water metabolism.—Our knowledge of the relation of the anterior lobe to water metabolism is very incomplete. Thyrotropic hormone, as might be expected from its stimulating action on the thyroid, has a diuretic action (168). There does not appear to be any clear evidence of an anterior lobe diuretic hormone other than the thyrotropic hormone. Richter (169) has shown that diabetes insipidus following hypophysectomy in white rats lasts only ten days; if, however, only the posterior lobe be removed the diabetes insipidus is permanent. Pencharz (170) obtained similar results. Keller (171) performed total hypophysectomy fifty days after the establishment of an operative lesion in the hypothalamus of a dog which had caused marked diabetes insipidus. As a result the diabetes disappeared immediately, but returned when anterior lobe extracts were injected. Thyroid extract also had the same effect. These experiments have led to a re-interpretation of the pathology of diabetes insipidus. It would appear that destruction of the posterior lobe is only effectual in causing this condition in the presence of a diuretic hormone from the anterior lobe, and that this is in all probability identical with the thyrotropic hormone.

Calcium metabolism.—The relation of the anterior lobe to calcium metabolism is an obvious factor in the stimulation of bone growth by the growth hormone. Other evidence of the relationship is afforded by the incomplete calcification of the teeth after hypophysectomy, and the signs of bone lesions in Cushing's syndrome which point to a negative calcium balance. In acromegaly (172), and in Cushing's syndrome (173) parathyroid hypertrophy has been observed. Degenerative changes in the parathyroids have been observed after hypophysectomy (174 and 175). Anselmino, Herold and Hoffmann (176) and Hertz and Kranes (177) observed hypertrophy of the parathyroids after injection of anterior lobe extract in normal animals (178). The blood calcium is increased by anterior lobe extract injection, but this does not occur after extirpation of the parathyroids (175, 178). It is as yet undecided whether the parathyroid effect is dependent on the thyrotropic hormone or on some other

hormone, possibly the growth hormone. If hypophysectomized rats are fed on a calcium-poor diet they show a negative calcium balance, which becomes positive on administration of growth hormone (179).

The Secretion and Structure of the Anterior Lobe in Physiological and Pathological Experimental Conditions.

Growth hormone.—The growth hormone is present in the fœtal hypophysis (180). It is absent in hereditary dwarfism in mice (14).

Gonadotropic hormones.—The structural change of pregnancy persists even after birth or removal of the fœtus so long as an active corpus luteum is present in the ovary. It disappears with the onset of œstrus (184). The castration cell-structure in the anterior lobe depends on the absence of the secretion of the germinal epithelium and may be abolished by injection of extract of germinal epithelium. It is a matter of indifference whether follicular or testicular hormone be administered to castrates of either sex (185, 186, 187 and 188). More testicular than follicular hormone is necessary. Administration of large amounts of follicular hormone causes great increase in size of the female anterior lobe with histological changes in the chief cells, characterized by swelling of the cell body with ill-defined margins and nuclei poor in chromatin with frequent mitosis (189). Treatment lasting several months may lead to adenoma with extensive loss of chromophil cells, multiple hæmorrhages and colloid degeneration. The animals become cachectic and growth is inhibited. The size of the pituitary may increase fourfold (190, 191). An increase in size of the hypophysis may result after 12 days' treatment with excessive doses of progesterone (192). Similar increase of the anterior lobe may result from continual administration of prolan (193, 194). The increase, which is accompanied by an increase of the basophil cells with loss of granules, is not obtained when prolan is injected in castrated rats (195). The de-granulating effect on the cells of the follicle-stimulating hormone from menopausal or castration urine on the anterior lobe is well marked (196). Changes similar to those due to castration are found in the anterior lobe of rats with cryptorchidism, and these changes may be abolished by the administration of prolan (197). Estimations of the metabolic activity of the isolated rat pituitary show maximum activity during the pre-œstrus period, minimum in the di-œstrus period. The pituitary of the castrated rat shows the same diminished metabolism as that in the di-œstrus conditions. Anaerobic glycolysis is also higher in the pre-œstrus than in the di-œstrus state (198). Folliculin *in vitro* or injected previous to ablation of the anterior lobe causes a greater increase of glycolysis than can be achieved by thyroxin injection (199). Tissue cultures of the anterior lobes of pregnant and non-pregnant animals showed no difference in hormone production (200). During œstrus the hypophysis increases in size but

diminishes in di-œstrus (201). The œstrus changes in rats, dogs and pigs affect chiefly the eosinophil cells. These cells are packed with granules which again diminish during the lutein phase. The number of eosin cells diminishes while that of the chief cells increases (202). In the infantile human anterior lobe only follicle-stimulating hormone is found. The glands of adults contain both follicle-stimulating and luteinizing hormone, and both hormones are equally present in male and female glands. During pregnancy the follicle-stimulating hormone is present during the first three months, and from that time till parturition both hormones are absent. During the period of lactation the follicle-stimulating hormone returns before the lutein hormone (208). The absence of the gonadotropic hormones from the anterior lobe during pregnancy (209) gives support to the view that prolan is derived from the placenta; a view strengthened by the fact that prolan is readily produced by implantation of chorionic villi in the infantile rabbit (210 and 211). The anterior lobe of castrated animals contains more gonadotropic hormone than in normal controls (212). The increase in both male and female castrates can be inhibited by the injection of folliculin (213), and the gonadotropic content of normal pituitaries can be reduced by folliculin (214). The human anterior lobe has more gonadotropic hormone per unit weight than that of the ox or pig (28). Horses have eight times the amount of that in sheep, and these latter twenty times that of oxen (220).

Using the method of parabiosis and castrating one animal it is possible, by observing the effect on the gonads of the partner, to prove that the anterior lobe of the castrated animal produces an excess of gonadotropic hormone (222). Parabiosis of castrated adult rats with infantile rats causes hypertrophy of testicles, vesiculæ seminales and prostrate of the latter or of the corresponding organs in the female infantile partner (223). This increase of gonadotropic hormone can be inhibited if sexual hormone be administered to the castrated animal (224). Parabiosis with castrated males gives rise to more potent gonadotropic secretion than when castrated females are used (225). This is constant with the greater amount of gonadotropic hormone found in the male anterior lobe. If female rats are united in parabiosis with castrated males, permanent œstrus is induced. If hypophysectomy is performed on the female there is no effect on the œstrus, but this becomes again normally cyclic if the male is hypophysectomized (226). The blood of castrated rats has more gonadotropic hormone than that of normal rats (227). The same is true of castrated women, in whom the hormone is also found in increased quantity in the urine (228). After the menopause the gonadotropic hormone is found to be increased in the blood and urine of women (28, 228 and 229). The unconcentrated urine at this stage will give the Aschheim-Zondek test I (230). This test is also positive in male castrates. The excretion of gonadotropic hormone in men between 70–84 is very irregular in occurrence; in some it is increased, and not in others (231). It is absent in carcinoma. An adult man

excretes 8–20 mouse units in 24 hours. In men between 50–90 the increase of gonadotropic hormone excretion is less common than in women of the same ages (232). The effect of pregnancy on the secretion is too well known to justify further study here (28). The lumbar and ventricular cerebro-spinal fluid is normally free from gonadotropic hormone. It has, however, been found in cases of encephalitis and cerebral tumour (233). Substantial amounts of the hormone are found in the tuber cinereum (234) and the hypothalamus (235).

Prolactin.—During lactation in the rat the anterior lobe shows the typical changes of pregnancy, and this condition cannot be terminated by castration. It is apparently due to a stimulation produced by the mammary gland and not to the corpus luteum. If the young are removed the condition subsides (236). The content of the lactation hormone in the anterior lobe increases immediately after parturition (237) and can be increased by prolan injections. It diminishes after castration (238). In both male and female it is increased by œstrin administration (239). It is increased with diets poor in vitamin B (240). In the urine of nursing mothers it has been found in considerable quantity (241). Using the pigeon-crop test it has been demonstrated in the blood of nursing mothers and of women suffering from cystic disease of the breast (243).

The thyrotropic hormone.—The changes in the anterior lobe after thyroidectomy resemble those due to castration except that the castration cells are more sharply defined and their plasma less coarsely granulated than the thyroidectomy cells. Whilst in the anterior lobe of castrates there are numerous eosinophil cells, these are almost entirely absent after thyroidectomy (244.) In thyroidectomy there is a two- to fourfold increase of basophil cells. The cells are vacuolated. In spontaneous myxœdema fibrosis of the anterior lobe is observed (245). The administration of thyroxin inhibits these changes in the pituitary (244). Continual administration of thyrotropic hormone to normal rats may cause degenerative changes and an increase of the "castration" cells of the pituitary (246). In the rabbit, particularly the doe, thyroidectomy gives rise to an increased secretion of thyrotropic hormone (247). If material from the basophil (internal) zone of the pituitary is implanted in tadpoles, an increase in the rapidity of development and hypertrophy of the thyroid is obtained, whilst material from the eosinophil zone only accelerates development (249). The compensatory hypertrophy of one-half of the thyroid on ablation of the other half is apparently due to increased thyrotropic hormone secretion, as the reaction is absent after hypophysectomy (252). The hypertrophy of the thyroid observed after castration of guinea-pigs may similarly be shown to depend on the thyrotropic hormone (253). The blood of castrated birds contains an increased amount of thyrotropic hormone (254). Aron (257) found in hyperthyroid cases a diminution of the thyrotropic hormone in the blood. Bodart and Fellinger (258) found it diminished in the serum of three cases of hyperthyroid, and increased in nine. The serum content was increased

in hyperthryoidism. Dogs showed diminished serum thyrotropic hormone after prolonged thyroid feeding and increased amounts after thyroidectomy (259). Thyrotropic hormone has been detected in the cerebro-spinal fluid and diencephalon (260).

Corticotropic hormone.—After injection of large doses of cortin there is a reduction of basophil and an increase of eosinophil cells in the anterior lobes. The basophil cells show degenerative changes (261). In hypophysectomized rats the compensation of the remaining adrenal after unilateral adrenalectomy is absent (262 and 263). The effect of incomplete hypophysectomy is to cause the resulting compensatory anterior lobe tissue to secrete an increased amount of corticotropic hormone. The compensatory hypertrophy of the adrenals is increased. The adrenals of such animals are heavier than those of controls (263). The effect of such partial anterior lobe destruction on fat metabolism has already been dealt with. Histological changes in the regenerating anterior lobe of the pituitary, see Fig. 4 (142).

The following might finally explain the correlations between anterior pituitary gland and subordinated endocrine organs. If for some reason the organism needs an increased amount of—for instance—sexual hormone, a higher amount of gonadotropic hormone is produced which is able to mobilize more sexual hormone from the gonads. But after administering sexual hormone equivalent to the increased demand no increased production of gonadotropic hormone will be found. If, on the other hand, too much of the sexual hormone is present in the blood—for instance, after injection of high doses of sexual hormone—the normal production of gonadotropic hormone will be stopped.

The production of anterior lobe hormone depends on the actual demand of the body periphery for subordinate hormones.

The Influence of the Nervous System on the Functions of the Anterior Lobes.

There is no doubt that the normal functioning of the anterior lobe is governed by the nervous system, and that the anterior lobe is not only a regulator of the functions of the peripheral organs of internal secretion, but acts as a mediator between them and the nervous system. A recapitulation of some facts may make this relationship clear. Rabbits do not ovulate spontaneously. Copulation starts the process of ovulation, to be followed by luteinization and the formation of the pre-gravid uterine mucous membrane. This process is started as a reflex stimulation of the cervix, and sterile coitus with a vasectomized buck brings about precisely the same series of gonadal changes (264). In the case of the rat, pseudo-pregnancy changes may be induced by stimulation of the cervix with a glass rod (265). It has been found that the whole process is conditioned by secretory impulses reaching the anterior lobe and giving

rise to increased secretion of the gonadotropic hormone, because the response fails if the rabbit is first hypophysectomized (264 and 266), or the blood-vessels of the pituitary are blocked. Immediately after copulation the gonadotropic hormone in the doe's blood is increased. If the rabbit is only hypophysectomized an hour after copulation, that is when a sufficient secretion of gonadotropic hormone has taken place, ovulation and luteinization proceed normally (266).

Another factor that conditions the production of sexual hormone is illumination. Ferrets that were exposed daily during November and December for some hours to intense illumination developed œstrus. This result was absent in hypophysectomized animals (267). 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 gonadotropic hormone over normal controls. If the animals were blindfolded the stimulating action of light was absent (269).

In the case of thyrotropic hormone there is evidence of a regularity of intervention of the nervous system. Thus the thyrotropic hormone secreted by the anterior lobe has a direct action on the thyroid, but there is good evidence that the thyroid hormone is stored in the diencephalon and there stimulates the anterior lobe to secrete thyrotropic hormone (270). It has long been known that cold causes hypersecretion of the thyroid. Thus the thyroid of rats kept in the cold has an appearance of hyperthyroidism quite as intense as that which could be produced by thyrotropic hormone administration. In warm surroundings, on the other hand, there is an increase of colloid and the thyroid shows signs of inactivity. These changes appear to depend on the secretion of the thyrotropic hormone. The hormone content of the anterior lobe of animals kept in warm surroundings is negligible compared with that of animals from normal or cold cages (271). There is a marked increase of thyrotropic hormone in the blood of animals kept in the cold (see Fig. 5). There seems to be no doubt that the temperature stimulation is in the first place conveyed by the nervous systems to the anterior lobe.

The nerve supply of the pituitary has been studied by Greving (272), Pines (273), Roussy and Mosinger (274), Fischer, Ingram, Hare and Ranson (275) and Rasmussen (276). Nerve tracts exist in the pars nervosa which convey secretory impulses to the anterior lobe exciting gonadotropic hormone production. Westmann and Jacobsohn (277) interrupted the stalk immediately after coitus and showed that ovulation is inhibited. After section of the stalk the ovaries atrophy and show the same appearance as after hypophysectomy, although the anterior lobe itself shows no degenerative changes. Cahane and Cahane (278) produced isolated atrophy of the gonads by lesions of the diencephalon. Marshall and Verney (279) produced pseudo-pregnancy in the rabbit by electrical stimulation of the head. Harris (280) excited the hypothalamic region in the vicinity of the tuber cinereum and the posterior nuclei and obtained

ovulation and follicular hæmorrhages in the rabbits' ovary. In disagreement with Westmann he found degenerative changes in the anterior lobe after section of the pituitary stalk. He claims to have demonstrated paths for nervous conduction from the hypothalamus through the stalk to the anterior and posterior pituitary lobes.

The precise nervous paths from the genital zone to the pituitary have not yet been fully investigated and many of the factors, such as the role played by the superior cervical ganglion are yet in doubt (281). At any rate such facts as are at present well established allow us to formulate the pituitary

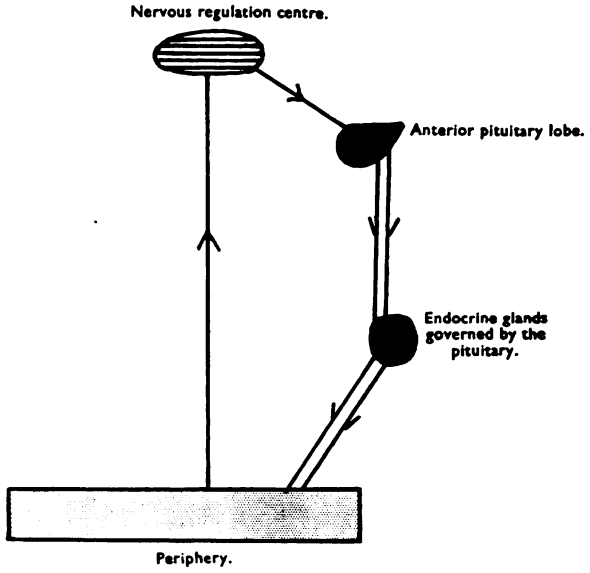

FIG. 6.

relationships in the subjoined diagram of the nervous humoral mechanisms (Fig. 6). The diagram needs no explanation other than the facts already given as to the relationship of the hormone requirements of the peripheral mechanisms and the central nervous regulation of the anterior lobe production of hormones. Its value should be in the attempt to systematize the possible disturbances implicit in a pathological account of a lesion of the anterior lobe or of a related endocrine system. Some examples may be given.

The presence of a gonadal centre in the nervous system governing the anterior lobe secretion would account for the sexual precocity sometimes met with after encephalitis and early senility due to central arterio-sclerosis. The influence of mental states on menstruation can be explained by the assumption of a nervous centre governing gonadal functions in relation with the cerebrum from which excitatory and inhibiting impulses proceed to the anterior lobe.

The nervous control of the anterior lobe indicates the mechanism of cerebral conditioned adiposity, which so closely resembles that due to lesions of the pituitary. Following disturbances of the central organ or an interruption of conduct between central nervous system and anterior lobe of the pituitary, functional changes will be found by which a hyposecretory adiposity may be caused. Conversely, mental symptoms often accompany hypersecretory adiposity, such as that of Cushing's syndrome ; such pathological relations are made more intelligible by the assumption of an increased production of corticotropic hormone by the anterior lobe, which receives secretory impulses from the hypothalamic nervous centre governing fat metabolism.

Anterior lobe secretion and morbid states.—In this account of the function of the anterior lobe the data are furnished for an understanding of the symptomatology of morbid states conditioned by pathological processes affecting the pituitary. It is, of course, necessary to distinguish between the disturbances due to primary lesions of the anterior lobe and those secondary to lesions of the governing nervous centres. Further, a revision of the present classification of anterior lobe syndromes is necessary in the light of what we now know of the effects of hyper- and hyposecretion of its hormones. Hormone analysis can at present only be formulated by a complete series of events in the case of the gonads, but rapid progress is being made in the investigation of other hormone systems. An exact early systematic analysis of pituitary disturbances in terms of hypo- and hypersecretion of hormones is a necessary step in the formulation of a rational therapy. In the present state of our knowledge the use of hormone therapy without a careful preliminary hormone analysis is often dangerous.

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