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THE ANTERIOR PITUITARY HORMONES AND THEIR MODUS OPERANDI

by

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1936
FIG. I  Diagram showing the relations of the human hypophysis in median sagittal section; Dura - Pia - Arachnoid.

FIG. II  Diagram of the transverse section of the human hypophysis; Dura - Pia - Arachnoid.
The object of this thesis is to discuss the hormones of anterior pituitary from the standpoint of their history, their present recognized functions, and to emphasize the modern concepts as to the modus operandi of these trophic substances. In writing this paper I have attempted to cite the earlier fundamental works and the more recent recognized articles so as to present the topic as offered up until 1936.

As to its gross morphology and relations, "the hypophysis is a small body weighing in the adult males and nulliparae about 65 centigrams. It is oval in shape, being about one centimeter long, one to one and one half centimeters broad, and one half to one centimeter thick. During pregnancy it increases greatly in size, chiefly in lateral and vertical directions. Addison and Adams (3) have shown that the weight of hypophysis is greater in females than in males, this holding true only for women having borne children - the enlargement being limited primarily to anterior lobe. Rasmussen has shown a definite increase in weight of gland proportional to the height of the individual - and also a decrease in weight of the gland with age. The general relations of the hypophysis to the structures at the base of the skull, are illustrated in Figs. 1 and 2. It is attached above the hypothalmus by the infundibular stalk and is lodged in the sella turcica of the sphenoid bone. It will be seen
from the diagrams (Figs. 1 and 2) that the infundibular process, as it enters the sella turcica, is closely surrounded by the diaphragma sellae, which is formed by a fold of the dura mater. The dura mater continues ventrally and lines the entire sella turcica, being closely adherent to the bone. The relations of the arachnoid are variable. It is usually reflected from the infundibulum to the diaphragma sellae, but it occasionally extends further ventrally and partially encloses the hypophysis as it lies in the sella. The two lobes can easily be distinguished in the gross specimen. The anterior lobe is large and firmer in consistency and partially encloses the posterior lobe in a hilus-like depression in its caudal surface. On section it becomes quite apparent that the two lobes are quite different in color, for the anterior lobe has usually a reddish tint, owing to its relatively high vascularity, while the posterior lobe is usually greenish-yellow, depending on the amount of pigment contained. On close examination of the anterior lobe, it is possible to define the limits of the pars intermedia, which is a thin epithelial layer between the anterior lobe proper, in front, and the posterior lobe behind. The pars intertuberalis, which is so distinct in lower forms, is only represented in man by an inconspicuous prolongation of the tissue of the anterior lobe along the infundibulum in the direction of the tuber cinereum, hence the term tuberalis." (18)
The blood supply of the hypophysis springs from two sources, from the internal carotids as they are passing through the cavernous sinus, and from the twenty-five small arteries from the circle of Willis. The internal carotids give off delicate branches which run to the anterior lobe. The posterior lobe is supplied by the Circle of Willis as is the infundibulum and, according to the general view now, there is adequate anastomosis between the two supplies. The important point relative to the blood supply is the greater vascularity of the anterior lobe.

Dandy, 1913, by use of intravitam methylene blue demonstrated numerous nerve fibers derived from the carotid sympathetic plexus and passing along the arterial supply into the gland where most of the fibers passed into the pars anterior but a single fiber separated from the others and passed down within the hypophyseal cleft where its branches spread out on the surface of the pars intermedia. Fibers going to the posterior lobe were remarkably few in number compared to those of the anterior lobe. At that time Dandy made note of color differences in the anterior and posterior lobes which may now be interpreted as due to the unmyelinated fibers so numerous in the former.

The embryology, taken briefly, shows that the anterior lobe is developed from an ectodermal pouch, called the pouch of Rathke, which grows upward under the brain from the stomodeal
epithelium. At about the fourth week Rathke's pouch comes into contact with the infundibular process, which is a downgrowth from the floor of the third ventricle, and which ultimately forms the posterior lobe. (75)

The anterior pituitary body is a compact of cellular elements of three recognizable sorts—divided by histologists on the basis of their staining reactions, into two principle types. One, those with a nongranular cytoplasm and two, those with a cytoplasm that is distinctly granular. Those of the former type are known as the chromophobe type, those of the latter as chromophile. The latter consists of two types, the acidophile and basophile, more correctly termed the alpha and beta cells. Whether these cells are fixed in character or represent different stages in the same cell is a matter of dispute. Remy Collin (26) a recent advocate of the unitarian view believes that the non-granular cell represents the primitive stage of an element which in the process of ripening acquires a granular cytoplasm that is primarily acidophilic but which may in turn become basophilic. When the ripened granular cytoplasm comes to be discharged, little is left but the nucleus and membrane of the cell which may then either degenerate or renew the cycle. The work of Severinghaus, as interpreted by Cushing (43) seems to disprove the thought of basophilic cells being further development of
the eosinophile as he has shown that a study of the golgi apparatus of the two chromophile cells indicates a difference that may be traced back to the mother cell. Rasmussen has shown that the average frequency of the three cells in the adult male to be: chronophobes 52 percent, cells with alpha granules 37 percent, and cells with beta granules 11 percent. The only known conditions which affects their frequency are pregnancy causing increase in alpha cells, and rutting season which causes increase in beta cells. The granules of alpha cells are coarse while those of beta a quite fine. A few fat globules can be demonstrated in the pars anterior and these appear to increase with age. Mitochondria have been demonstrated by Bailey and Cowdry. The connective tissue forms a loose network throughout the pars anterior, the fenestrations of which are smallest in the posterior superior part of the anterior lobe. The connective tissue is composed of collagen fibers with numerous reticulin fibers attached to them. At times the reticulin fibers cross from one band of collagen to another causing fibrosis of the individual alveoli. The number of cells in such a fibrosed alveolus is greatly reduced or may become absent. Such a process may proceed to produce a fibrosis of anterior lobe called Simmonds disease. (90) Cushing summarizes the anatomical phases very well; "indeed, its extraordinarily well protected position, its presence in all vertebrates and persistance
through life, its remarkably disposed and abundant blood supply, would of themselves be enough to stamp the hypophysis, an organ of vital importance." (41)

Our present day concept of endocrine therapy is to supply to the individual suffering from endocrine insufficiency, the desiccated gland in question or a potent concentrated extract of the same. The premature thought, as expressed by Paracelsus was that a person suffering from heart disease should be fed with the same organ "heart cures heart; spleen, spleen; lung, lung." (8) A close analogy to sympathetic magic of the homeopathic type as described by Frazer in the Golden Bough can be seen in Paracelsus' "yellow bird of jaundice." This primitive apotherapy was for a time buried beneath a prevalent theory that concoctions made up of many heterogeneous and often repulsive ingredients would give results in direct proportion to the number and the odoriferous properties of the constituents. To accomplish this everything from excreta to skunk secretion was used. (65) This filth pharmacoopoeia as it was later known, was permanently discredited by the satirical writing of William Heberden, in 1745.

As already pointed out Galen's and Vesalius' conceptions were that pituitary gland was an organ which secreted a substance known as pituita, which then entered the nose and was from this organ discharged. Brilliant and
studious men accepted this for fifteen centuries. Excuses are numerous enough such as the lack of human material, instruments that were not suitable to dissection, the necessity or better the tendency to try and make one's findings coincide with prevalent beliefs on the subject, the lack of microscopic technique and others far too numerous to mention. However the primary reason for this misconception is brought out by Cushing who tells us that under certain conditions of disease there is such a drainage. This drainage is due to an adenomatous tumor of the body. (41) "From the time of Galen and Vesalius until the middle of the seventeenth century, knowledge of the pituitary gland and its functions, made little or no headway, the anatomists of this period following directly in the line of existing beliefs or casually - perhaps wisely - avoiding the subject. Even as late as 1631, in the Integrum Morborum, Robert Flood explained the etiology of coryza on the principle of the siphon action between the ventricles and the nose. Could he have known that the hypophysis is present in all vertebrates, and that in the low order of amphioxus a canal lined by ciliated epithelium affords a communication between the buccal and cerebral cavities, he would have had something more than tradition with which to substantiate his beliefs." (39) In 1665, we find new concepts as to pituitary function. The first man to cast a doubt on the prevailing theories was Schneider.
In his *Liber de Osse Cribiformi* (1665), he denied the
eistanc of any demonstrable communication between the
ose and the pituitary. However, he as well as Vieussens
and Willis, anatomists of this era, could not quite corre-
late their findings with the "facts" of spontaneous cerebro-
spinal rhinorrhea so dogmatically dictated to them by their
learned instructors. The question came up then what could
account for the rhinorrhea; influence and formulations of
Galen still persisted. It was Richard Lower who in his
remarkable work "Dissertation de Origine Catarrhi, 1672, was
able experimentally to disprove the Galenic doctrine. His
basic conclusion for this topic is "For whatever serum is
separated into the ventricles of the brain and tissues out
of them through the infundibulum to the glandula pituitana
distills not upon the palate, but is poured again into the
blood and mixed with it. (41) After this work by Lower the
trend of anatomical theory was towards the function of the
pituitary being to secrete the cerebrospinal fluid. It is
interesting to note here that Sylvius, a contemporary of
Vesalius, held this belief. That the importance or any
inkling of the importance, of the pituitary was not suspected
by the greater majority of the anatomists is illustrated in
the following paragraph from the anatomy of Thomas Gibson,
published in 1688. "In those creatures that have the glandula
pituita large, (as in calves for instance) the two carotid
arteries, meeting about the sella of the wedge-like bone, presently divide themselves into small twigs, which being interwoven—make on each side a notable plexus, called the Rete meriable... So that in these creatures the gland seems to be of the same use to the Rete meriable, as the glandual pinealis is to the choroid plexus, vis. to separate a serous matter from the arterial blood. But in man, (according to the best anatomists) this Rete is usually wanting; so that... the glandual pituita is of less use in him than in other creatures that have the Rete. (39) In 1664, Willis, who is known to the student of today for his dissection and naming of the circulation at the base of the brain—set out to finally clear up the vascular supply of the pituitary. Willis began to untangle the knot by describing the vascular circle surrounding the pituitary. Through these dissections he was no longer able to accept the Galenic doctrine, and encouraged by the work of Schneider, he made quite a remarkable conclusion. "The ramifications of the carotids into a reticulated plexus shows... that the blood...before it is let into the cerebellum takes some part of the superfluous serum of the pituitary gland and instils another part into the various shoots to be led back toward the heart." This statement is aptly commented upon by Cushing who refers to it as the "kernal of the modern conception of internal secretion, but the idea was stillborn." (42) The foregoing summarizes the
trends during the seventeenth century. In the eighteenth century the advancement was slow, but it showed some advancement nevertheless. The writers all along up to this period - as already stated - had shown a marked liking for the including of "humors" in their discussions of disease. This phase of their ideas can easily be seen as a forerunner of the hormone theories of today. Now came the new theory which was to influence the pituitary - this theory coming out as all theories do - based on speculative hypotheses which may be proven or disproven only after innumerable researches. This theory was that brought forth in Morgagne's "De sedibus" (1761) in which he focused the etiology of disease upon the solid organs. This immediately was supplemented by Theophile De Bordeaux ideas concerning the importance of the body fluids. Bordeaux reputation today is based on his doctrine that not only each gland, but each organ of the body is the workshop of specific substances or secretions which pass into the blood, and that upon these secretions the physiological integration of the body as a whole depends. This doctrine is contained in his "analyse medicinate du sang." (18) Evidence of the advance in the knowledge of the pituitary gland in the eighteenth century can be seen in the fact that Sommerling, in 1776, first applied the current name hypophysis cerebri, to this organ. Once again one may well quote from works of current anatomical volumes, James Drake in 1750 in
his anatomy book. "At the bottom of this cavity (third ventricle), just below the occlusion of the Optic Nerves, lies the infundibulum, which seems to be nothing else but a passage continued from this third ventricle to the glandula pituitaria, between the medullary parts of the brain, and lined with the Pia Mater; and therefore not properly to be looked upon as a vessel, but as an outlet for serosities; through this glandula pituita, to which it is continued, there seems no proper drain for them, however, it may have been esteemed hitherto. Underneath the infundibulum in that sinus of the skull which is called sella equina or turcica, upon the Os Cribosum, is situated the glandula pituita, so called from its supposed office of receiving and discharging the serous humors evacuated by the ventricles of the brain. But though the use of the part as of divers others about the brain does not plainly and distinctly appear to me, yet I cannot admit of this use, both because it is against the office of a gland to receive humors already secreted which a vessel of a more simple structure might more readily and easily perform; because it is the peculiar office of glands to separate humors before unsecreted, which two uses imply a direct repugnance not to be reconciled, but besides the structure of this gland which is firmer than any other of the body makes it absurd to think that it should, like a sponge, suck up humors, not only in contravention to its own use as a
gland but likewise in violence to its own structure which is more compact than that of other glands, especially of those of the brain. I do therefore imagine it does, as other glands, serve to secrete some humor or other, though to what purpose is not so apparent. This gland is very small in human bodies, but in brutes much larger, which difference may at some time or other, suggest to a man of happy sagacity something that concerns the true use of it. It is covered with two coats from the meninges of the brain." (48) The nineteenth century starts out with a decade of great confusion in regards to the pituitary and the other endocrines. Great steps were made by men who seemed only endowed with intuition and not with persuasive powers. In 1801 the French physiologist Legallois, put forth his beliefs concerning blood thus "V" (Venous blood), "A" (Arterial blood), "S" (Secretion.) When A and S are chemically know, A being constant, V will be known, or, when A and V are known S will be known. The V is always variable. (18)

As further evidence of the confusion present in the ear we find that in 1842 Magendie in his "Recherches sur le Liquide Cephalo - vachéien" leaves the impression that the hypophysis may represent a sort of lymph gland interposed in the fluid pathway. In this work he remarked (p. 22)" Les autour anciens, tels que Bruner (Brunner?). Littre, Haller, out sans doute observed quelque chose d' analogue (i.e. a
pituitary tumor) l'ars'qu'els out dit que, L. Hydrocephale est
souvent causes par la glande pituitaire." (39) Only seven
years later 1849, A. A. Berthald is said to have transplanted
the testes of a fowl to another part of its body and still
kept the sexual functions in tact. This phenomenon he
inferred was due to "the productive relation of the testes,
i.e., to its effect upon the blood and thence, through the
corresponding effect of such blood upon the entire organism."
(18) This work, though it exerted no direct effect upon the
pituitary, brought the use of the terms "blood vessel glands"
or "blood glands" by the more advanced physiologist of the
time. A further significant observation came from Italy when
Vergo, in 1864, gave the post mortem findings in a case in
which the sella turcica was enlarged together with an enlarge-
ment of the hypophysis (20). Bernard in 1849, after doing
work on other ductless glands, discovered that a puncture in
the region of the fourth ventricle produced a temporary
glycosuria. Although Brown Séquard was doing notable work
at this period references to him will be postponed until
the period when he published his theories of internal secre-
tion. However, the modern period starts with the work of
Marie in 1886 - acromegaly - a work which he did not directly
associate this disease with the hypophysis, the features of
acromegaly were hitherto known - along with gigantism - and
were known to be associated with hypophyseal tumification.
Menkowski in 1887 followed Marie with a definite directing of this disorder to the hypophysis. From this stage until the present time the references to the hypophysis are too numerous and varied to relate but briefly, but briefly, but before doing so - it will be interesting to set down Brown-Sequard's theory of internal secretions published in 1893. "All the tissues, in our view, are modifiers of the blood by means of an internal secretion taken from them by the venous blood. From this we are forced to the conclusion, that, if subcutaneous injections of the liquids drawn from these tissues are injected, then we inject some of the venous blood supplying these parts... We admit that each tissue and more generally each cell of an organism secretes on its own account certain products or ferments, which through this medium influence all other cells of the body, a definite solidarity, thus being established among all cells through a mechanism other than the nervous system... All the tissues, glands or organs, have this a specific internal secretion and so give to the blood something more than waste products of metabolism. The internal secretions whether by direct favorable influence or whether through the hindrances of deleterious processes, seem to be of great utility in maintaining the organism in its normal states." (18) As far as theory goes nothing has been added up to the present time. One of the earliest methods of experiment was that of thyroidectomy; Ragawitch and Stada
1889, made many experiments and found a constant hypertrophy of the hypophysis. Another physiological approach to the study of the pituitary was that made by injecting pituitary extract. Oliver Schafer (1895) found the noticeable result, the rapid and sustained pulse that followed Howell (1898) disagrees saying that the glandular hypophyses are negative. He places the change upon the Vagus. (20) Now at this period many men were calling attention to tumors of the glands associated with optic atrophy, amenorrhoea, infantism, adiposity and diabetes insipidus. Among these were Pechkranz (1889), Frohlich (1901), Muller (1905), Bressand (1907). With this great number of articles concerning the hypophysis, operative procedure was considered and along with this the question went—was the pituitary necessary to life? Victor Horsley (1886) first attempted experimental hypophyseal ablation; all but two animals died, these lived less than a year. Dastio (1889) Gley (1891), Gemelli (1908), and Paulesco (1907-1908) all confirmed the belief that the hypophysis was necessary to life, the last two operators using the buccal and temporal routes respectively, Cushing with others at this time also believed in its essentiality. Removal and replacement effects have been studied by many giving results confirmatory of today's ideas of function. (50) Earlier unsuccessful attempts were made to extirpate this gland, but, since the procedure nullified the results, it was up to Paulesco (89) to do the
research by means of a technique of his own. He found that the loss of the pituitary leads to a typical death. Paulesco contention received support from Schafer (1909), Lemon (1909), Biedl (1910), and numerous others. The question, however, was not unanimous. (20)

Recognized Functions of the Prehypophyseal Hormones

There is now considerable evidence that the anterior pituitary lobe elaborates a number of distinct endocrine compounds which, (1) control growth; (2) control the gonads; (3) control the thyroid; (4) control the parathyroid; (5) control the islets of langerhans; (6) control adrenal cortex; (7) control the secretion of milk; and (8) control fat metabolism. It is obvious since there are only three types of cells, one or more of these must have a multiplicity of function; moreover, no other function can be ascribed to the chromophale cells other than their being precursors of the others. There is some evidence that the alpha cells furnish growth principle and that the beta cells elaborate principles controlling the gonads. (25)

Thyrotrophic

The early work indicating the relationship of the pituitary to the hypophysis came from the following experi-
ments. Rogowitsch noted that an enlargement of the anterior lobe followed thyroidectomy. Gudernotsch noticed that precocious metamorphosis could be induced in tadpoles by thyroid feedings. (69) Smith later proved that the thyroid is dependent on the stimulating action of the pituitary. It has been shown that removal of pituitary gland causes either reduction in development or atrophy of the thyroid (Adler, 1914; Allen 1916; Smith 1916; Foster and Smith 1926; Smith 1927; Richter and Weslacki 1930). Several of these observers noted a decreased metabolic rate and Foster and Smith (1926) and also Richter and Weslacki (1930) noted that the change can be prevented by injection of an anterior lobe extract. (32) Moreover, the addition of anterior pituitary extract into the fluid in which Axaloths are kept initiates a metamorphosis which is preceded by hyperplasia of the thyroid gland. (36) Loeb and Aron (13), in 1929, independently discovered that injections of anterior pituitary extract in guinea pigs produced in the thyroid gland a histological picture very similar to Graves disease. In 1930, Aron, repeating this work reports that there was a great hypertrophy of the parenchyma of the gland associated with liquification and final disappearance of the colloid; if the injections be discontinued the thyroid returns to original state. (46) Further evidence of the direct action of thyrotropic hypothalamic hormone upon the thyroid is gained through Paal...
who established a three fold increase of oxidation in thyroid fragments swimming in a fluid to which thyrotropic hormone was added in Warburg Chambers. (53) The more recent workers have stressed that injections of the thyrotropic hormone has only a temporary stimulating effect upon the thyroid gland and that retrogressive changes actually take place in spite of continued injections of the hormone. Biasotti and Mazzocco (73) report that anterior lobe extract actually cause a fall in blood iodine in thyroidectomized dogs. Others have noted that the B.M.R. reached a peak in ten days then returned to normal. Collip showed that after the fifth week of treatment the B.M.R. was 29 and the gland showed the same histological findings as the hypophysectomized animal. The reason for these apparently contradictory results is postulated as being due to an antithyrotropic substance. (27)

Guinea pigs injected with thyrotropic hormone of the anterior lobe over long periods of time show a period of thyroid stimulation and production of characteristic changes in ovary (cessation of growth of follicles), this followed after four to six weeks by a period of regression. After a refractory period the gland shows only a very transitory period of stimulation followed by a more rapid development of the refractory state. (83)

Collip and Anderson have shown that the blood serum of resistant animals does not exert a direct neutralizing
effect upon the hormone; however, they have demonstrated that the injection of such serum introduces into the injected animal reactions, the nature of which are unknown, which somehow contrasts the effect of the hormone for a period. (77) Clinically, pituitary insufficiencies show a tendency for basal rate to be low and conversely acromegalics show a tendency for higher B. M. R's (36). These results and observations of necessity selected, are all in agreement with the view that a principle of the anterior pituitary controls the output of the thyroid principle. What is known of this hormone and its modus operandi will be taken up later.

**Adrenatropic Principle**

Evans has shown that certain pituitary extracts prevent or restore degenerative changes in the adrenal cortex of hypophysectomized animals, particularly in the zone fasciculata and zona reticularis. Such injections produced an increase in cell cytoplasm and partial recovery of lipoid granules. (56) Further he has shown that hypo-pituitary states show an atrophy of the adrenals. Unilateral adrenalectomy usually is followed by hypertrophy of remaining adrenals — but this is not so if the hypophysis is extirpated. (29) Conversely, adrenalectomy leads to marked changes in the anterior lobe. Collip believes he has isolated a
relatively pure adrenatropic hormone by further refining the
thyrotropic hormone. (28) Severinghaus finds the possibility
of control of adrenal cortex by anterior pituitary intriguing,
but points out that it leaves unanswered the question of in-
complete compensatory hypertrophy of remaining cortical tissue
after incomplete adrenalectomy, when the hypophysis is left
intact. Very recently A.C. Crooke and Dorothy S. Russell
have shown that in Addison's disease there is a conspicuous
paucity of basophilic cells and a series of abnormal transi-
tional basophilic cells. (35)

Gonadotropic Principle

The early evidences of the presence of a gonad stimu-
lating substance in the anterior pituitary came through the
fundamental discoveries of Smith in 1925 (107) and those of
Zondek and Aschheim shortly afterwards which showed that the
ovaries and testicles remained dormant unless stimulated by
a secretion of the anterior hypophysis. They also pointed
out that the gonadotropin substance activated the gonads
of both sexes alike. (64) Early experiments with complaints
of pituitary under the skin showed a production of a precocious
sexuality in immature rats. (55) The weights of these ovaries
are distinctly greater than those of controls of same age or
even of the controls that have reached maturity. This in-
creased weight being due to the formation of an increased
number of follicles. Recently authors have been inclined to consider the presence of two gonadotropic hormones of the anterior pituitary namely Prolan A and Prolan B. The accuracy of this interpretation has not yet been decided. Allen summarizes the situation thus, "Because of the ease with which ovaries of rats and mice may be luteinized by various extracts of gland or urine, most investigators have followed the lead of Zodek and Aschheim and have spoken of two distinct active principles. The idea of duality of gonadokinetic factors is not too convincing when it is considered that quantitative and temporal relationships vary the response. Since it appears that the best follicle stimulating extract tested to date will produce lutein tissue in the rodent with continued injections, the physiological state of the receptor organ rather than the nature of the active principle accounts for the dual response."

(5) Many believe that Prolan A and B are different stages of activity of a simple principle. (22) A gonadotropic substance found in pregnancy urine, though thought to be of chorionic origin may be from anterior hypophysis. Although in hydatidiform males and chorion epitheliomas this substance remains until growth is removed, some instances of persistence after operation indicate hypophyseal origin. (55) Gonadotropic substance found in blood or urine of ovarietomized or menopausal women is different than that found in pregnancy. The former has a follicle stimulating action on normal and hypo-
physeotomized animals while the latter does not. The former seems to have an almost pure gameto-kinetic action, whereas the latter seems to stimulate the interstitial cells of the testes and ovary. (108) In early years little or not gonadotropic hormone can be found in blood or urine. The amount excreted in urine of prepubertal persons in twenty-four hours is less than 2.4 to 3.7 rat units. In adults, the hormone is found in blood and urine in greater quantities, being greatest (25 rat units) nine days after the onset of the preceding period, growing less both before and after this date. (13) In the menopause the gonadotropic hormone may reach the high level of 500 rat units in the blood as compared with the 25 rat units of the cyclic females. In underfunction of the ovaries the gonadotropic principle is greatly diminished. In artificial menopause the substance is markedly increased. (64)

Lactogenic Principle

Riddle (96) obtained, by isoelectric precipitation of an acid extract of the anterior pituitary, a fraction which stimulates development of the crop gland in the male, female or castrate pigeons. Crude extracts of the anterior pituitary have been shown to produce copious lactation in virgin and dry goats (52) and in virgin heifers and in normal bitches. (81) Withdrawal of the pituitary hormone at any time
during lactation causes an immediate cessation of lactation. (115) Smith believes that prolactin causes onset and continuation of the secretory phase, but the essentiality of the pituitary galactophore he doubted because of the presence of phasic secretion present in hypophysectomized animals. (108) Allen and others in recent work upon rhesus monkeys concluded that complete sexual maturity and complete morphological development of the glands was necessary to obtain a positive glactin or prolactin reaction, mature animals responding positively, immature animals negatively. (9) Prolactin also seems to have a marked calorigenic action which unlike the thyrotropic hormone does not act through the thyroid but acts in a manner now practically unknown. The synergistic action in the O consumption that is greater than the sum of their separate actions. (95) Riddle et al, suggests through experiment that a growth hormone may not exist but rather that it is a combination of the lactogenic and thyrotropic hormone. (95)

Further discussion of this substance will be taken up under its modus operandi.

Parathyrotropic Hormone

The presence of a parathyrotropic substance in the anterior pituitary is not accepted by all writers as proven. Severinghaus terms the evidence rather meager. (106)
Houssay and Sammartino were able to show atrophic or degenerative lesions following the extirpation of the pituitary in the majority of dogs. The frequency and intensity of these changes were, however, increased by associated pancreatectomy. Smith, through a parathyrotropic substance that he has isolated showed that the substance induces hypertrophy but that continuous injections do not maintain this state. (108) Injection of anterior pituitary extract into male rats produces a hypertrophy of the parathyroids due to increase of chief cells. (71) Recently through the association of parathyroid adenomas with pituitary substance the belief in a parathyrotropic substance has been strengthened. Patients with a hyperplasia of parathyroids have been found to excrete in their urine a substance causing hyperplasia of parathyroids of normal rabbits. (32)

Growth

Evans and his co-workers, showed, in a series of publications commencing in 1921 that injections of potent pituitary extracts into rats produced gigantism. (54) Earlier experiments had shown that an immediate cessation of growth followed hypophysectomy - later and more exact work along this line showed that there was not a centimeter of growth in long bones after a complete ablation. (53)
Experiments with mice have shown that the growth principle produces correctly proportional growth of the whole body, as judged by the relative weights of the chief organs, and the percentage dry weight, fat content, ash content and phosphate and calcium content of the ash. (67) Clinically it is not impossible that all the forms of dwarfism and infantilism are due to inadequate pituitary function particularly the Frohlich, Lorain-Levi and Lawrence Moon - Biedl types. (55) (88) Acromegaly and gigantism are found as opposite types of pituitary dysfunction to those just stated. Acromegaly has particular interest in that various animals show distortion of entirely different structures showing a lack of that identical substance to which harmonious growth is due. (53) The work on growth hormone, being one of the first recognized is voluminous, but at the present time its existence as a separate substance is doubtful. If is now suggested that growth promotion is not the result of a separate hormone, but rather the consequence of several other materials - that is the hormones so far discussed. (104)

Incompletely Defined Pituitary Function

Of the incompletely defined pituitary function so grouped at the present time, the diabetogenic substance seems to carry the most evidence for its existence. The possibility of this pituitary function was first suggested
by Houssay and Gieling and their respective co-workers. (67) (72) (73) Houssay and Magenta, in 1924, showed that hypophysectomized dogs were hypersensitive to insulin. From this start further work was done on hypophysectomized animals with the following conclusions. (1) Development of hypoglycaemia leading to convulsions or death; (2) Increased sensitivity to insulin and (3) that in pancreatectomized dogs the diabetes was lessened. Attacking the problem from another approach pituitary extracts were injected into normal animals with the following results: (1), a glycosuria developed associated with decreased sugar tolerance and hypoglycaemia, (2), to produce the previous results injections for several days were necessary, and (3), that fat metabolism seemed affected along with the difficulties in carbohydrate metabolism. (55) The symptoms of pancreatic diabetes were greatly ameliorated when the hypophysis was removed from totally pancreatectomized days. Fasting blood sugar level in these animals ranged around 100 mgm./100 cc. - following feeding, values up to 300 mgm. percent are common; There is a glycosuria present but the amount of sugar lost is small. Ketonuria is at a minimum. When these animals are given anterior lobe extracts the blood sugar level is raised, glycosuria is increased and there is a return to Ketonuria. Suggesting that the decreased sugar tolerance may be due to tuber cinereum injury or perhaps a chiasmal lesion; we may
conclude that the general action of pituitary extracts is one of an antiinsulin character. (31) The finding that the anterior lobe extracts develop in the animal and acteonomia suggests a Ketogenic Principle. (31-55) Many authors have suggested and demonstrated a hyperplasia of the isles of Langerhans after administration of extracts of the anterior lobe. (108) These two points of view are hard to reconcile but perhaps the ideas of "master gland" or dynamic balance add some to its interpretation. Clinically it has been seen that obesity is associated with both Frohlich's and Cushing's syndromes. Raab, (92), at first concluded that pituitrin promoted the absorption and destruction of circulating fat by the liver through a nervous pathway starting at tuber cinerum and running through the cervical cord and abdominal splanchines to the liver. Recently (93) he has come to the conclusion that there is a special principle of the anterior pituitary involved. Anselmino and Hoffman (12) and Magistris had previously made such claims calling the substance oraphysin there is some evidence that such a principle is excreted in the urine.

Mode of Actions of Hormones

The glands of internal secretion are through at the present to secrete substances into the blood stream that have regulating action on distant tissues. As a group these sub-
stances are called Autocoids of which there are two types the hormones or stimulating substances and the chalones or inhibitory substance. (30) Thomson suggests that theoretically there are three possibilities as to the mechanisms of antagonism and synergism shown by the hormones: (1), there might be a direct chemical reaction, that is, they might chemically cancel out each other or perhaps the resultant action might be the result of subtraction; (2), two or more of the substances might act on the same responsive tissue producing opposite or incompatible reactions - here the relationship is more of a ratio; and (3), one hormone may act upon the endocrine source of some other hormone - in this manner it might inhibit its activity - and hence decrease the rate of secretion. This possible mode of action may be direct or indirect through the mediation of the nervous system or perhaps some third endocrine gland whose role has gone unnoticed. (115) Recently the term antihormone has become very prominent in the literature and though I believe, at the present time most authors believe this substance or phenomenon merely a simple immunological response to a foreign protein I shall present the arguments for the existence of an antihormone. Collip states his theory of inverse response and antihormones as follows:

"(1), Responsiveness of individual to administered hormone varies inversely with the hormone content or pro-
duction of the subject's own gland.

(2), For each hormone there is an opposite, an antagonistic or antihormone substance.

(3), The absolute amount of a hormone and its respective antagonist determines the degree of stability of the subject as far as this one particular endocrine function is concerned. (27)

Collip states that the active principle in an antiserum produced as a result of long continued daily injections of an extract may be regarded quite rightly as a possible antibody reaction to the administered extract or antigen. This author prefers, however, to think of it as an increase of the antagonistic principles which are normal to the blood. Further encouragement to this belief has been added by the fact that in certain human patients antithyrotropic and antimaturity substances have been found - these patients had not been treated previously but they had occurred spontaneously a hormone imbalance due to the predominance of the respective antisubstance. The antihormones of Collip seem to differ from the substance diiodotyrosine which Abelin (1) has found to antagonize thyroxine and also the Katechins of Blum (24) as the antihormones do not prevent a rise in B.M.R. when injected with thyroxine as do the latter two. (27) Further evidence of the possibility of an antihormone comes from Bachman (16) who working on the anti-
A. P. L. serum has shown that the antihormone effect does not parallel the antibody content. Rats have been made resistant to the maturity hormone of rat pituitary by continued implantations of rat pituitary. Further evidence comes from the work of Black (22) who has shown that rats made resistant to the ketogenic principle by a long period of daily injections of an extract from ox anterior lobes have been shown to be equally resistant to the ketogenic extract made from sheep or pig anterior lobes. Collip (27) has found that there is a spontaneous occurrence in the serum of certain individuals of a substance capable of inhibiting an anterior lobe principle. The site of production of these antihormones, if they really exist, is not known. The work of Collip and Anderson (29) seems to show that the target gland does not play an essential role in the production of the antagonistic hormone. Riddle (98) has recently shown that purified prolactin is definitely antagonistic to the gonad, and that prolactin has a definite inhibitory effect in the rat on the action of a maturity extract. Perhaps inhibiting or antagonistic effects of this type are of the same order as the antihormone effects. Collip sums up the situation at the present time "In view of the fact that a somewhat extensive search for evidence of the existence of antihormones to oestrin, to parathyroid hormone, and to insulin has failed as yet to demonstrate such,
it is possible that the antihormone theory should be applied only to trophic principles. (27) It must be born in mind also that a resistant state to a certain hormone may be due to a purely local condition and not necessarily to the presence in abnormal amounts of an antihormone or of a specific antagonistic substance. Thus it is now well established that the ovaries of the very young animals are more responsive to the anterior lobe maturity hormone. Certain hypoglandular as well as hyperglandular, states may be due to decreased or increased responsiveness respectively of the gland concerned to the specific trophic principle normally influencing it. The history and functions of the various anterior lobe hormones and their effects has been dealt with briefly but fairly comprehensively as far as present day beliefs direct us.

It is now my intention to briefly sketch the more popular theories of interrelationship and operating methods of these trophic hormones along with what is know of their chemical composition and preparation.

Thyrotropic

The thyrotropic hormone has little known of its chemical properties. It is apparently protein in character readily destroyed by heat and alkaline solution. (29) Probably the purest preparation yet available is that of Anderson and Collip.(10) They commence with the filtrate and washings
from the calcium phosphate precipitate formed during the preparation of the growth principle. These are repeatedly precipitated with ammonium sulphate and the precipitate dissolved in alcohol or acetone, until finally a pure white protein-like substance is obtained. This may contain tissues of the adrenotropic principle but the growth principle is absent. The modus operandi of the thyrotropic principle is at the present only partly understood. The theories and suggestions leave such a maze that I shall only attempt an enumeration of the more recent and popular. It has already been shown in this paper that increased and lobe activity causes an increased response in the thyroid and, that after a period of stimulation a latent period is reached. Collip explains this phenomenon by antihormone production. Friedgood (66) in a recent article has pointed out that there is cyclic character in the departure of the thyroid gland from normal and that after a maximum change a spontaneous remission occurs, and that this remission progresses in spite of the continued presence of the stimulus. Severinghaus (102) puts this interpretation on Friedgood's work "This concept of cyclic response by the thyroid is helpful in explaining many phenomena, such as the temporary effect of using the thyrotropic extracts thus far available. But it is difficult to reconcile the cyclic concept with the well known essential constancy of the basal metabolism in
man and animals. It may mean that the thyrotropic substance
is not the normal stimulant to the thyroid seclusion, but it is
only a superimposed control for certain emergencies." Along
this line of thought is the work of A. Sturm and W. Schoning
(113) who discovered that the ovaries, adrenals, pancreas, etc.,
contain considerable amounts of thyrotropic substances, greatly
in excess of the "hormone deposits" in the hypophysis which
up to the present time was considered to be the only site of
production of these principles. This led to the question of
whether the thyrotropic hormone is specific to the hypo-
physis, a question best answered by their assuming that the
hypophysis is the site of transformation of certain chemical
impulses which, departing from endocrine glands with a def-
inite tendency to direction (thyrotropic, gonadotropic,
adrenotropic, etc. ) are conveyed to the hypophysis. The
relation of the thyrotropic principle to thyroid metabolism
is pointed out by Loeser (80) who states that it even con-
trols the taking up of iodine by the thyroid. Under the
stimulation of thyrotropic substance decrease in the iodine
content of the gland is paralleled by decrease in thyroxine
content (62) furthermore the active iodine fraction of the
blood is increased. (68)

Houssay and Artundo have proved that the anterior lobe
exerts its influence in the B. M. R. through the thyroid, for
they find that hypophysectomy lowers the B. M. R., but sub-
sequent removal of thyroid lowers it still farther, while after initial thyroidectomy removal of pituitary does not affect basal rate.\(^{(74)}\) The relationship of cyanide to the thyrotropic principle is put forward in Marine's \(^{(82)}\) hypothesis that cyanide inhibits tissue oxidation. Amongst other tissues the hypothalamic centers are affected. These stimulate the anterior pituitary so that discharge of its thyrotropic factor is increased, and the thyroid subsequently exhibits hyperplasia. At the same time the sympathetic system is stimulated, either directly or through the pituitary and a hypothalamic center, and thereby the pupillo-dilator and Muller's muscles are affected and exophthalmus results. It has been shown by a number of investigators that the thyrotropic principle produces exophthalmus in both normal and thyroidectomized guinea pigs indicating that exophthalmos is not dependent on a normal or an abnormal thyroid secretion. \(^{(112)}\) \(^{(79)}\) Quite recently Blum has announced his theory regarding "Katechins" which he designates as inhibitory substances adjusted to the hormone, this substance has a definite anti-thyrotropic action and is decreased in Graves disease. Blum believes this substance is formed in the liver. \(^{(24)}\)

Adrenotropic

As stated previously, it has been seen that in experi-
mental giant animals adrenal lesions may occur, and further
that in pituitary basophilism there may be adrenal cortex
involvement. The close resemblance between syndromes of
pituitary basophilism and adrenal cortex in itself suggests
a close interrelationship. Anselmino and Hoffmann (11) (27)
have shown that the principle can be separated by ultra
filtration (through eight percent, acetic acid callodion)
from the gonadotropic, thyrotropic, parathyrotropic
growth, lactogenic and fat metabolism principles. It is
present in the acid ultra filtrate, which only contains
in addition the diabetogenic principle. This substance
is water soluble, but insoluble in lipid solvents. It is
precipitated from aqueous solution by excess of alcohol or
acetone. It's properties suggest a relatively small molecule.
Collip (29), by testing extracts from the alcoholic mother
liquor from which most of the thyrotropic principle has
been removed found that they had excellent adrenotropic
activity. From a 75 percent acetone soluble fraction
he obtained on concentrating in the aqueous phase at a pH
5 to 6 a fine flacculent precipitate, which was removed,
extracted with dilute ammonia, and the ammonia removed from
the extract by vacuum distillation. The residue, tested on
hypophysectomized rats, had no thyrotropic activity, but
restored the atrophied adrenal cortex to normal in daily
doses of a quarter of a milligram. Collip considers this
as pure a preparation of any pituitary principle as he has been able to obtain. The mode of operating of the adrenotropic hormone is still in the conjecturing stage, it is known that hypophysectomy causes atrophy and anterior lobe, adrenotropic injections cause hypertrophy. Likewise it has been shown that the relationship is reciprocal and that cellular changes take place in the anterior lobe in adrenal cortex disease. That this adrenotropic hormone may have an effect upon other structures than the cortex is suggested by the fact that removal of either the adrenal cortex or pituitary causes atrophy of the gonads. This is repaired by pituitary injections in the absence of the adrenals, but is not by adrenal cortex injection in the absence of the pituitary. (103) Perhaps this explains the recent linking of the adrenals to a role in Cushing's syndrome. Further than this the authors fail to go on interrelationship of the adrenotropic hormone.

Gonadotropic

Various methods for concentrating the gonadotropic principle has been described. They involve either extraction with acid or alkali or aqueous pyridine or aqueous butanol. No marked concentration seems to have been effected as yet. The principle is soluble in water, acid and alkali, and is moderately resistant to heat, although boiling purified preparations in slightly acid solution destroys it. It does not
dialyse and is probably protein in character. Zondek and Asohheim (120) believed from their earlier work that there were two gonadotropic hormones, one controlling and stimulating ripening of the ovarian follicles and aedius, and the other—the so-called luteinizing principle—stimulating the change of follicles into corpus lutea. This belief has recently gained support by the study of the relative effects of pituitaries of different species of animals as it is stated that in the different species the relative amounts of the substances vary. (78) (70) Femald and Hisaw (59) claim to have effected a partial separation. They extracted des­sicated sheep pituitary powder with aqueous pyridine, and treated the extract with water, obtaining two fractions. One, soluble in water was very active in stimulating growth of follicles in the ovaries of immature rats and rabbits, but relatively inactive in inducing luteinization. The less soluble fraction was practically inactive for the first effect, but produced luteinization. Before stating the more recent concepts as to the mechanism of the gonadotropic hormones it might be well to cite some conclusions reached by Smith (7) in his chapter in Allen's sex and internal secretions. The following will be partial quotations from his work. "Evans and Simpson (1929) reported that in rats the pituitary of the adult male is about three and one half times as potent as that of the female. Since the anterior lobe in the male
is smaller than in the female, it is evident that the potency is still greater per tissue unit. The age of animals in foetal or early post-foetal development at which the pituitary content of gonad stimulating hormone becomes sufficiently great to be detectable by implanting into immature rats or mice or by injection into rabbits has been reported by a number of investigators, Smith and Engle (1927) found this hormone present in rats five days of age. That this hormone, though present some time before birth, is not present in early foetal life in sufficient quantities to be detectable by the Mouse test is shown from the studies of Smith and Dorlstach (1929) on pig foetus. The gonad stimulating principle of the pituitary is also present in animals post active sexual life. A correlation of the content of the gonad stimulating hormone of the anterior pituitary with the stage in the oestrous cycle, has been reported. Smith and Engle (1929) having noted in earlier work that pituitaries of female guinea pigs varied greatly in their content of gonad stimulating hormone, suspected that this might be due to stage of the cycle at which the pituitaries were removed. They found that gland from guinea pigs in oestrous often gave no response when implanted into white mice, while those at mid dioestrus gave good responses. Wolfe (1931) in a similar study with the glands of the sow secured more uniform and extensive data. Using the ovulation test in rabbits
he reported that the capacity to produce ovulation was
greatest during pre-oestrus, was diminished during the
heat period, and was lowest at the succeeding lutein phase.
These experiments convincingly show a periodicity in the
sex hormone content of the pituitary correlated with the
cycle. Although the parabioses experiments of Kallas
(1929) show an increase in the liberation of the gonado-
tropic hormone into the body fluids of castrated rats
associated with the increased pituitary content of this
hormone, nevertheless, the fact must be kept in mind that
a liberation of the pituitary sex hormone paralleling
the hormonal content of this gland has not been demonstrated
under all conditions. It is the amount of hormone liberated
into the circulation by the pituitary, not that which is
contained in the gland, which is functionally significant.

The anterior pituitary works directly upon the
gonads as shown by the ineffectiveness of implants in
gonadectomized animals. The contradictory evidence upon
the alleged antagonism between the male and female gonads
has been explained by the work upon the hypophysis. Lip-
schutz and Krause (1923) showed that the amount of gonadal
tissue present was important in the fate of the transplant.
Visualizing that the apparent depressant action of one gonad
upon the other was not an acutal depression but a pituitary
deficiency phenomenon - Engle (1929) showed that the degree
of growth of an ovarian graft into the other sex, if equally vascularized, was dependant upon the amount of available anterior lobe hormone. With the growth of gonads of both sexes in the same animal stimulated by pituitary implants the effects characteristic of each sex developed."

As was pointed out by Smith in the previous quotation the gonads exert an inhibitory effect upon the secretion of the gonadotropic principle. Nelson (87) through experimental work concludes this suppressing action is upon the secretory phase of the anterior lobe basophilis. In the male the hypophysis is less easily influenced by gonad hormone, so that apparently it is never suppressed to the extent that the male reproductive functions exhibit cyclic characteristics. The explanation of this suppression of anterior lobe activity some authors have sought to prove the existence of a sexual center giving impulses to the hypophysis and the ovaries. Zondek (121) believes that a central regulation of the sexual function is possible but he thinks it has not been proved. The theory has in part been based on experimental work with rats and in fact it has been assumed to explain the negative prolact finding in pregnancy. The rise in the estrin level in pregnancy is supposed to bring about, by way of the cerebral sexual center, an interruption in the secretion of the anterior lobe, i.e. cessation of prolact production.
This theory will not be proved, Zondel thinks, until a suppression of ovarian activity can be demonstrated by shutting off a definite brain area. Frolan A or the follicle stimulating hormone has been found to be more potent when given with the luteinizing hormone or again when given with the pregnancy urine hormone. It appears therefore that development in the ovaries may take place as follows:

1. The follicle stimulating hormone produces primary follicles.
2. The luteinizing hormone then acts upon the primary follicles developing antra.
3. The follicle stimulating hormone then acts upon the antra containing follicles to produce macroscopic follicles and
4. The luteinizing hormone can again act to produce corpora lutea. (60)

It has been known that chronic administration of gonadotropic extracts from the pituitary or from pregnancy urine leads to the formation of substances inhibiting their action, and that a passive, resistance to both of these substances may be produced by administration of serum obtained from animals chronically injected with these gonadotropic substances. (15) Collip would interpret this as an anti-hormone reaction, however, the following experiment indicates an other interpretation. Litter mate female mice were united by parabiosis at thirty days. After fifty days
hypophysectomy was done on the right member, then after
maturity had been reached the left member was castrated.
The results of this experiment showed that the hypophysec-
tomized rat did not get enough hormone to maintain body
weight, thyroid, adrenals and ovaries at normal levels.
Castration of the normal female produces enough follicle
stimulating hormone that the hypophysectomized animal goes
into constant oestrus, the ovaries being obviously over
stimulated. However, not enough oestrin accumulates to
prevent complete atrophy of the secondary sex characteristics
in the castrate which is evidence that much oestrin leaves
the blood. This condition persists indefinitely showing no
loss of sensitivity in the follicle stimulating hormone.
Hence these authors conclude that prolonged stimulation with
gonadotropic hormone of heterogeneous origin is an immunity
reaction to a foreign protein. (49)

(1) Lactogenic

The lactogenic principle has been obtained by
Riddle. (96) By isolectric precipitation of an acid extract
of anterior pituitary tissue, a fraction which stimulates
development of the crop gland in male, female, or castrate
pigeons. The lactogenic hormone is apparently chiefly of
importance in the initiation of secretion after the breast
has been prepared during pregnancy by the ovarian hormones
or those placental products which replace or simulate them. Experimental work with this substance is rather scarce as it has shown itself to be rather polyvalent causing changes in both adrenals and gonads. The accepted mode of operation now expressed is that suckling seems to stimulate the secretion of prolactin through a nervous pathway not yet discovered. Hypophysectomy or withdrawal of pituitary hormone at any time during lactation cause an immediate cessation of the flow. (76)

Growth Hormone

The growth hormone, although one of the first anterior lobe extracts to be isolated, has now shown a tendency to join the group of indefinitely defined pituitary functions. Evans purest preparation of the growth principle (65) is made by extracting pituitary tissue with alkali, precipitating the extract with acetone (the ppt. which also contains the gonadotropic hormone) and extraction with 95 to 98 percent acetic acid, which destroys the gonadotropic but does not affect the growth principle. Acetone is added to the extract in presence of quinine sulphate, and the growth principle is thrown down, completely freed of gonadotropic principle. Collip (33) extracts anterior pituitary with alkali, acidifies, and filters. Ammonia is added to the filtrate to a one percent concentration, and then calcium chloride and sodium phosphate to give a suspension of calcium phosphate, which carries down the active principle. It is
extracted with very dilute alkali, the pH adjusted to 6.5, ammonia added to alkaline, and the material concentrated in vacuo to pH 7.5 to 8. A semi-crystalline material separates. This represents between 0.1 and 0.2 percent of the original material. This product has no effect upon the thyroid or on basal metabolism. Sometimes an effect on the adrenals is observed. It has no effect upon the gonads but does seem to contain a trace of prolactin.

As to the mode of operation of the growth hormone if such is its identity, the opinions of the authors vary considerably. Severinghaus (104) makes the following statement. "It is now being suggested that the growth promotion is not the result of a separate hormone, but rather the combined consequence of several other materials (those previously discussed in this thesis). Active extracts which promote the rate of skeletal and visceral growth of humans and animals are now in use. These mixtures may also contain some other biologic materials which have been demonstrated to produce growth (glutathione ?). They are known to be mixtures with some of the above mentioned fractions present. There are evidences of distinct effect on nitrogen metabolism with the use of such pituitary solutions. The varying pictures of gigantism, acromegaly, and dwarfism as well as the different types of infantilism may occur as consequences of varying disturbances of this one gland, with slight relative
change in one or more of the factors enumerated."

Evans, Pencharz, and Simpson (57) found that purified proportions of the growth hormone differed from the cruder extracts previously used in their inability to maintain the growth of hypophysectomized animals after about thirty to forty days. This may be accounted for by assuming that the crude alkaline extracts contain materials other than the growth hormone which are essential to survival in the absence of the anterior lobe. The theory of antihormones suggested by Collip and his collaborators thus becomes superfluous here. Such a theory, moreover, is inconsistent with the fact that the crude extracts do not lose their efficacy, and also that only animals deprived of the hypophysis become refractory. It might be well to note that at the present time there are only two such extracts marketed. The Squibb extract is of the more comprehensive type, the Parke-Davis extract, more highly fractionated one. This may influence the choice of an extract in a given case.

There is no evidence that the growth hormone acts directly upon widespread tissues of body that it stimulates to increase. It is possible that growth is due to stimulation to over-function of one of the other endocrine glands for example the thymus. Asher (14) obtains from the thymus a substance thymoresin which stimulates the growth of rats.
Others have noticed disproportionate hyperplasia of the thymus in dwarf rats when treated with the hypophyseal growth hormone preparations. The exact mechanism if the growth hormone is not known but significant beginning is made by an analysis of its effects. (1) There is a decreased nitrogen output indicating that nitrogen is retained to build up new tissues. (2) There is an increase in water intake, this is followed by polyuria which is a purely physiological effect. (3) There is found to be an increase in the respiratory and ventilation rate. (4) There is an increase in heat production which is due to an increased oxidation of fat. (5) Further studies of Lee and Shaffer (98) showed that treated animals do not possess the characteristic age changes that normal rats present (i.e. a decrease in the proportion of water, nitrogen, fat free dry tissue and ash and an increase in the percentages of fat.)

In concluding this paper I wish to point out some recent ideas relative to the hormones of the anterior pituitary and stress some findings already made. It has been made apparent in this paper that none of the trophic substance of the pre-hypophysis have had their chemical secret disclosed. This situation is quite in contrast to the hormones of the other endocrine glands; in these glands rather exact knowledge is available as to their chemical
structure. (45, 46, 47) Mention is made of this situation as it aids in making tenable the very interesting hypothesis of Arthur Jores who points out that it is not reasonable to suppose that the cells of the hypophyses are capable of producing fifteen different substances, especially since they are cells already differentiated, with function in a certain direction laid down. Theoretically, the most reasonable explanation leading out of this difficulty is to assume that the hypophyseal cells form certain basic substances out of which the separate hormones are later developed. Perhaps some of the extracting processes used to separate the various trophic hormones only serve to activate a mother substance. Likewise, this mother substance might be activated outside the pituitary or it may be activated through nervous stimulation in the hypophyses. Another point along this line of thought is the close relationship of the vitamins with the hormones. This relationship is only evidenced, as far as the anterior lobe is concerned, by the finding of greater unit concentrations of the vitamins (C particularly) within the gland. In other hormones (oestrogenic) a similarity of chemical structure and the chemical structure of the vitamins has been shown - both having a phenanthrene base.

Earlier authors termed the hypophysis the "master
gland" suggesting that this gland was the prime mover, and that all other endocrine organs dependent in some way upon it. Present information, such as the absolute necessity of adrenal cortex for life, the isles of Severinghaus and the manner in which thyroidectomy and gonadectomy influence the hypophysis, offers sufficient grounds for denying the independent mastery by the one gland.

Prof. E. J. Witzeman suggests that the hypophysis may still be "master": - he likens the gland to an executive who gives direction and coordination to the whole. "The mutual interdependence of the employer and employee is not violated by considering one the master of the situation." Just where the anterior lobe fits in with the recent work being done on the hormonal relationship to carcinoma is not known. Cramer has shown that the carcinogenic oestrogenic substance when rubbed on the skin of some mice produces a cancer; in these same mice changes in the anterior lobe are quite marked.
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