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Anterior pituitary physiology

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ANTERIOR PITUITARY PHYSIOLOGY

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Endocrinology presents new evidences of its value in the field of medical research. The tremendous complexity of the interrelationships in the various endocrine substances exhibits a fascinating but laborious study. Recently, rapid progress has been made in the knowledge of these endocrine glands with invasion into the many fields of specialized medicine. Its significance, then, may only be realized with organized and diligent investigation.

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INTRODUCTION

Anterior pituitary physiology is so expansive in its subject matter, that its consumation would be voluminous. Therefore, an attempt is made here for a very brief consideration of the essential and congruous material. Corroborations and repudiations may be briefly mentioned depending upon their apparent influence or importance to the trend of the literature. Conjective articles without experimental or clinical substantiation may suffer complete omittion. With consecution in mind, the present organization of the theme was considered with deliberation.

The first section constitutes a brief resume of the non-physiological aspect of the subject, intended merely as a basis for the later more pertinent discussion.

History.

Among the earliest references made to endocrinology is the glandular therapy recorded by the Egyptians in their Agurvedic writings, indicating the use of orchitic substances in the treatment of impotence (Harrower 1914).

The Bible, according to Garrison (1922) contains descriptions which indicate acromegalic giants, such as Nephelim in Genesis IV.

Hypocrates of ancient Greece looked upon disease as the balance of various humors and the treatment was the use of organs of healthy animals. Paracelius (1493-1541) held also a similar theory, in that like cures like, heart cures heart, etc. (Harrower 1914).

It is difficult to say when the pituitary body was first discovered, but it was known to Galen, and at the time of Versalius (1543) it was thought to be the source of the mucus discharge from the nose. Because of this Versalius named it pituita. This function however, was disproven by Conrad Victor Schneider in 1660 (Engelbach 1932).

Bordeu (1722-1776) was one of the earliest to produce a conception of what internal secretions were like, although he thought each organ produced a sub-

stance which affected the body in some way. His work was soon followed by Hebenden (1745), who published satirical phamphlets against the polypharmacy of Bordeu (Garrison 1922).

The anatomist Sommering (1778) gave the pituitary its first recorded anatomical description and suggested the name 'hypophysis cerebri' (Engelbach 1932).

It was the work of Bernard (1835) that laid the foundation of endocrinology by his animal experimentation, so that this study could be carried out. He found that the liver transformed dextrose into glycogen, which he termed, 'internal secretion' in contrast to the bile which he thought was an external secretion. (Harrower 1914).

The embryology of the gland was established by Rathke (1838), who showed that the anterior lobe of the pituitary was derived from the buccal cavity. (Garrison 1922).

In 1840 Mohr described a case so well that we now know it to be pituitary obesity although Mohr did not associate it with the pituitary (Engelbach 1932).

Experimental implants was introduced into endocrinology by Berthold (1849), who transplanted a fowl

testes to a different part of its body with consequent retaining of its sexual characteristics (Garrison 1922).

Acromegaly and the pituitary was brought closer together by Marie (1886) who was the first to associate the lesions of the pituitary with the symptoms, although descriptions of the associated conditions was given by Klebs (1884), who confused it with thymic conditions and another still earlier, that of Verga (1864) who was perhaps less accurate. (Garrison 1922).

Evidence of a thyro-pituitary relation was brought in evidence by Rogowitch (1889) who demonstrated hypertrophy in the anterior pituitary following thyroidectomy in rabbits and dogs (Hertz 1936).

Oliver and Schafer (1895) showed that extracts of the pituitary, if injected, would give elevation of the blood pressure and increased force of heart beat. Howell in 1898 showed that the effect was due to the posterior lobe alone. (Engelbach 1932). (Camiron 1935).

A new pituitary syndrome was added to the literature in 1909 by Frölich, who described the condition known as adipose genitalis, and associated pituitary tumor with it (Engelbach 1932).

Bayliss and Starling (1902) discovered the principle

of hormone activity, and Starling proposed the name "hormone" for these substances, a Greek word meaning, "I arouse to excite" (Harrower 1922).

Operative technique on the pituitary was introduced by Paulesco (1908) who devised a temporal excision of the anterior lobe of the pituitary and showed that it was essential to life as its removal was fatal to animals. This was disproven by other workers as Aschner (1912) (Engelbach 1932).

Cushing and others (1913) showed that diabetogenic symptons as polydypsia and polyuria may be in some way related to the pituitary.

The growth hormone was demonstrated by Evans and Long (1921) from extracts of the anterior lobe and this resulted in a vast series of experiments in regard to growth, acromegaly and gigantism.

Smith (1926) showed that the anterior pituitary lobe contains a sex hormone, which caused superovulation. This, as the growth hormone of Evans caused considerable experimentation to the present day.

Aschheim and Zondek (1928) discovered another hormone which will cause luteinization of follicles thought to be another sex hormone. Use was made of this hormone

for tests in pregnancy.

In the same year Kamm (1928) divided pituitrin into two fractions, pitressin and pitocin. The former he shows as having blood pressure effects and the latter having oxytoxic effects.

The material according to its aspects will be taken up later under the various divisions of physiology.

ANATOMY OF THE HYPOPHYSIS

Embryology:

The hypophysis, or pituitary gland is composed of tussues which have widely separated origions. The anterior lobe, which has typical endocrine structure, is derived from the oral epithelium, as is the pars intermedia, while the posterior lobe is derived from the neural epithelium. (Atwell 1926).

More explicit is the following:

Anterior to the cephalic portion of the pharynx an invagination of the ectodermal epithelium develops, known as the stomodeum. The ectodermal epithelium meeting the endodermal epithelium of the pharynx forms a plate-like membrane, the oral membrane. (Arey 1931).

The superior portion of the stomodeal ectodermal epithelium, just anterior to the oral membrane, invaginates superiorly (or dorsally) now becoming a sac, known as Rathke's pouch. This pouch elongates, and comes into contact with an evaginating sac-like structure, the infundibulum, which is derived from the neural epithelium of the diencephalon. (Bailey 1932).

The neural tube of the early embryo becomes divided into three brain vesicles: the prosencephalon, mesen-

cephalon, and rhombencephalon. T he more cephalad division, the prosencephalon, immediately (at four weeks) divides into telencephalon and diencephalon, of which the latter is more caudad. In the floor of the diencephalon, the neural epithelium evaginates inferiorly to form the infundibulum which meets the posterior surface of the epithelium of Rathke's pouch. The distal portion of the infundibulum forms the posterior or neural lobe of the hypophysis, and remains permenantly connected with the diencephalon by the infundibular stalk. (Arey 1931).

Rathke's pouch flattens, then grows caudally about the neural sac, losing its connection with the oral epithelium, at the end of the second month. The lumen of the sac, while present in the lower animals, is usually obliterated in man. (Haberfeld 1909).

The cells in the anterior wall of Rathke's pouch poliferates rapidly, forming the anterior lobe of the hypophysis, while the posterior wall remains comparatively thinner to form the pars intermedia, later obliterated in the adult. (Kasche 1926).

Close to the stalk from the stomodeum lateral lobes bud off of Rathke's pouch, which later fuse into one structure of a glancular nature. This is known as the pars tuberalis. (Atwell 1926).

ANATOMY OF THE HYPOPHYSIS

Anatomy:

The hypophysis is a small spherical-like body lying beneath the brain in the sella turcica of the sphenoid bone. Its weight varies, but its average weight is approximately .57 gms. Its dimensions are about 10 mm anteroposteriorly, 13 mm. laterally and 6 mm. dorsoventrally. (Rasmussen 1928).

The hypophysis is covered by an extension of the dura mater. The superior portion of which forms an inclosing flat membrane called the diaphragma sella which is pierced by a small stalk uniting the organ with the brain. (Bailey 1932).

The dura mater also lines the sella tursica carrying with it the sub-arochnoid space which also encloses the organ as does the dura mater, except in the posterior extremity where the blood vessels enter the posterior lobe. This is possible as the anterior lobe becomes early separated from its bucal stalk. (Hughson 1924).

The pituitary body is usually divided into two gross divisions. The anterior and posterior lobes. The posterior division is, however, found to have an

inner neural core which is an extension of the hypothalamic region of the brain, and an outer epithelial covering which is composed of epithelial cells extending around the stalk and continuous with similar cells of the anterior lobe. The core is called the neural lobe and the epithelial layer is the pars intermedia (Bailey 1932). The pars intermedia is practically absent in adult human hypophysis. (Rasmussen 1928 a).

Histology:

The Pars Anterior:

The pars anterior is composed of columns of cells separated from each other by large numbers of vascular sinuses. (Bailey 1932).

According to their staining reactions, two main types of cells may be found. The chromophobe staining very lightly; and the chromophibe which will easily take stains, and is due to the presence of granules in the cytoplasm.

The chromophiles may be divided into eosinophils and basophils because of their reactions to acid and basic stains. This not being always true, Bailey thinks it is better to call them alpha & Beta

respectively. (Bailey 1932).

Transitional cells have been described but most workers think the two types of granules are not found in one cell. (Bailey 1921).

The distribution of the different cells are not characteristic. There are, however, 37% alpha cells 11% Beta, and 52% chromophic. (Rasmussen 1929 a).

The alpha granules are large, spherical and distinct, being so closely packed as to obscure structural details of the cells. The Beta cells are larger than the Alpha cells and the granules are finer, less distinct. (Bailey 1932).

In the chromophilic cells a clear area may frequently be found, called the macula. (Rasmussen 1921). In this area the Golgi Apparatus may be found, more easily seen in the basophiles. (Addison 1917 de Beer 1926).

The chromophobe cells are of two types. The one has very little cytoplasm and is known or reserve cells. (Bailey 1932). This was determined by the golgi net by other workers. (Severinghous 1933).

The larger cells resembles the chromophile cells and is thought to be one that has lost its granules therefore called entgranulurten zellen. (Krause 1914).

Pars Tuberalis:

The pars tuberalis is very insignificant in the human hypophysis. In other animals, it contains cells columns and sinuses similar to the anterior lobe. The cells contain no granules, but may undergo hyalinization with formation of irregular cavities. (Herring 1908).

Pars Nervosa:

The pars nervosa or neual lobe, being a derivative of the brain contains neural elements, and a pial covering.

Three different cellular elements are noted: typical ependymal cells with their cell bodies or the ventricular surfaces and processes stretching to the pial surface; mossy neuroglial cells; and larger pyramidal or spindle shaped cells. (Berkley 1894). The last type of cells are characteristic to the pars nervosa and has been named pituicytes. (Bucy 1930).

There are hyaline bodies, which are thought to come from the pars intromedia which degenerates and invade the pars nervosa although they never seem to have nuclei. (Cooper 1925-Herring 1908).

The chief cells are usually in the center of the column of cells although may constitute one entire column as near the stalk of the hypophysis. Their cell boundaries are not always distinct and so they look at times like groups of nuclei in a common cytoplasm. In the larger cells complicated reticular patterns have been found. Small globules of lipoidal substances are found in all cells, particularly in the Beta cells. (Bailey 1932).

There are nuclei which are vesicular with scattered granules and other nuclei which are smaller and contain a heavy network of chromatin granules. (Bailey 1932).

Intermediate Lobe:

The pars intermedia, while present in the embryo cannot be indentified in the adult as it is occupied by alpha and beta granules. (Kasche 1926).

Frequently there is present numerous cysts of different sizes. (Cushing 1912). There are irregular cavities of various sized cells filled with hyaline and colloid material, often with degenerating cells. (de Beer 1926). Rarely, remnants of Rathke's pouch can be found in the form of mucus secreting cells and ciliated epithilium. (Rasmussen 1929a).

Vascular Supply:

The anterior lobe is richly supplied with blood vessels. (Ducet 1873) from the circle of willis and descend along the stalk in the pia mater of the infundibulum. (Dandy & Goetsch 1911). They break up them to form sinusoids.

The pars nervosa has a much less vascular supply which arises at its posterior inferior extremity which it is not invested by epethelium of the anterior lobe. (Herring 1908) formed fram a symmetrical branch of the internal corotid arteries. (Stevens 1936).

The pars intermedia is poorly supplied with blood vessels, although, numberous small vessles run in the connective tissue which separates it from the pars nervosa. (Herring 1908).

The sinusoids and capillary vessels empty into veins which go into the cavernous sinus or according to Popa & Felding (1933) into the hypophyseal stalk into the hypothalmus where small capillaries are again formed and these drain into veins emptying into the large basal vein.

Lymphatics:

Lymphatics have never been demonstrated in the

hypophysis. (Bailey 1932).

Nerve Supply:

Anterior lobe receives its nerve supply from the carotid plexus of sympathetic nerves by way of the numerous vessles which radiate to the stalk along the hypophyseal vessels (Dandy 1913 Beattle 1930); at intervals branches leave the vessels to enter the cellular columns transversely and end between the glandular cells. (Berkley 1894).

There seems to be a rich supply of nerves to the posterior lobe and pars intermedia originating from the supraoptic group of nuclei, (Beattle 1932) the latter of which were at first thought to come from the pars nervosa according to Pine (1926). (Bailey 1932).

The posterior hypothalmic nuclei send out fibers which descend to the upper thoracic cord levels from which preganglion fibers arise, pass along the carotid plexus to enter the anterior lobe as described. (Beattle 1932).

PHYSIOLOGY

PHYSIOLOGY

The Pituitary Hormones and Their Significance:

Functions Claimed for the Anterior Pituitary,

Evidence has been accumulating rapidly in the last very recent years that the small pituitary gland, in some way, influences:

1. The growth of the organism
2. The Control of Sex Functions
3. The Secretion of the Mammary Gland
4. The Hormones of the Adrenal Gland
5. The Thyroid Hormone
6. The Control of the Parathyroid Function
7. The Secretion of the Isles of Langerhans
8. The Control of Metabolism
9. The Function of (Collip's) Antihormones
10. Many other body processes to be mentioned later.

It is obvious that the large number of functions of the anterior pituitary some of which have more than one hormone claimed for it, the chemical nature of these substances must be very similar to be divided from such a small body. This is also suggested by the fact that there are only two types of secreting cells, the acidophils and the basolphils. However, as

will be shown later, there are reasons to think each type of cell produces more than one hormone.

Tissue Receptor:

It has been known for a long time that when injections of hormones were made they frequently failed to produce the response expected. For this reason some authors have suggested that it might be due to the responsive capacity of the end organ, or the receptive tissue of the hormone. (Smith 1935a).

This phenomenon is readily observed in the reactions of different species to the same extracts. Also, as might be expected, different species contain different amounts of the hormones in their pituitary glands (Leonard 1934). It is noted that the degrees to the same hormone, as in the rat with the growth hormone. Another factor is that of age. In extremely young animals before 13 days old there is not response to the gonadotropic hormone. Also there is found a physiological limit to the amounts of the pituitary hormones. These factors are all interpreted as tissue receptor capacities. They will be taken up under their respective heads later.

This concept of tissue receptor should not be

be confused with antihormones, which will be taken up later.

Mechanism of Operation:

The mechanism of operation of the various hormones is certainly a field of speculation. It is known that certain tissues react to them and if the tissue are not present the hormones accumulates, and in some instances is found in the urine.

It was Bayliss and Starling who discovered the manner in which the substance was transported so it could act on the distant tissues, and named this substance "Hormone". We know now that the hormone is produced in one tissue and taken by the blood stream to other tissues.

It was Collip's introduction of antihormones that added an inhibiting mechanism to the known stimulating hormone mechanisms. In this mechanism of balance Thomson suggests a number of possibilites:

1. That the two substances may chemically react so that the final action would be the result of this subtraction
2. These substances may react on the same tissue to produce inverse reactions resulting in ratio

relationship.

3. One hormone might act on the endocrine source of another hormone inhibiting its secretary activity, either directly on the gland or indirectly through the nervous system or through another hormone. (Thomson 1936).

This concept of Thomson is in agreement with Collip's principle of inverse response and antihormones to be taken up next.

Antihormones:

It was noted that animals would become less responsive when treated chronically over long periods of time with the pituitary hormones.

This effect was noticed by Collip (1934) in the use of growth extracts of the anterior in the use of growth extracts of the anterior pituitary of which time he formulated his theory of antihormones. On growth this does not seem to be true always as Evans and associates (1933) and Smith (1930) obtained good results over long period. It does seem to be true of the thyrotropic (Siebert and Smith 1930) gonodotropic (Collip 1934) and Lactogenic. (Riddle 1932).

Against this idea is the fact that patients do not become more resistant to thyroid and to insulin.

It is true that there are some resistant insulin patients but Black (1933) states that the blood of these have no greater power to destroy insulin than has the blood of normal patients.

According to the recent review by Collip (1935) he states that there are two groups of substances which act in the hormonal regulation of the organism. The one called hormones or stimulating substances and the other chalones or inhibiting substances. Based on this Collip states that:

1. The individual responsiveness to a given hormone varies inversely to the hormone production of his gland
2. For each hormone there is an antihormone
3. The absolute amount of the hormone and its antihormone determines the degree of the patients' stability with reference so the hormone in question. (Collip 1934 and 1935).

The evidences in favor of such a theory are numerous.

Bachman (1935) found that the antigonodatropid hormone antibody production. Black and Assoc. (1934). shows that some animals are made resistant to the hetogenic principle derived from one animals pituitary

and is equally resistant to hetogenic principle derived from the pituitary of another animal.

Riddle (1932) has shown that purified prolactin is inhibitory to the gonads.

Loeb (1934) suggests that the antihormone-like action may arise from the effect of a protein from which the thyrotropic substance has not been separated.

There are evidences to show that there might not be antihormone formation Smith(1935a) thinks the mechanism attributed to the antihormones may be due to protein sensitization. He says that sex and species show some variability to the hormones unlike that to the other hormones (such as thryoxin).

Apparently more convincing is the work of Dushane and his associates (1935) who show that when two animals are united parabiotically, in which one female is castrated and the other is hypophysectomized, a constant oestrus is produced in the animal hypophysectomized.

Yatsu (1921) with female-male parabrosis also obtained constant estrus diminution of the activity.

Seyle and his associates (1934) find that when the ovary will not respond to pregnancy urine extracts

of the anterior pituitary.

Katzman and associates (1937) show that implantations of pituitaries the same species of animals do not cause the refactory state, and serum that the serum inhibitory to one extract if one species is not inhibitory to extracts of another. They also show that substimulating doses of heterozoic extracts and inoctivated extracts induce insensitivity while extracts from homozoic animals may not induce insensitivity.

These workers conclude that refractoriness is due to antibody formation.

Chemistry:

The peculiarity about the hormones of the anterior pituitary is the fact that many have been quite refined so they produce comparatively even results, but not one of them has been isolated in the crystalline form so that the formula may be known.

Collip (1935a) considers them tropic substances containing a protein-like structure which is so complex as to warrant it difficult to determine its nature. The protein nature of these substances would be reason for their forming anti-hormones.

Many workers have obtained the physical properties of these hormones but they have been so different that it is useless to obtain much definite information about them as yet.

Fate of the Hormones:

It would be interesting to know what becomes of the hormones when they activate tissues. Are they destroyed in performing their functions, or do they act as organic catylists, or do they unite with the cellular substances (tissue receptors) to form new substances which produce the process exhibited.

It is well known that the hormones are found in the body fluids, which might be expected as they are produced in one tissue and carried by the body fluids to affect distant tissues.

The condition that is harder to explain is why in pregnancy there is a spilling over of the hormone in the urine. It might be explained on the basis that in such conditions there is an overproduction of the hormone so the amount not used by the tissues accumulates, reaches the threshold of the kidney and is found in the urine.

Castrate and menopause urine may be explained in the same way. The tissues using the hormone has been removed (Castration) or decreased its affinity (menopause) for the hormone, and therefore it accumulates reaching the threshold of the kidney.

Zondek (1937) has another method of explaining the reason for finding the gonadotropic hormones in the urine. He finds that the pituitary gonadotropic hormone (prolan A or follicle-stimulating) is increase in menopause and in such secondary functional inhibitions as early amenorrhea. He finds that, in these conditions, the quantity of follicle-stimulating hormone (prolan A) decreases with injections of estrogenic substances. This is not true in the primary amenorrheas as castration and congenital absence of the ovary (or in cases where there is a lack of production of ovarian hormones. He concludes from this that the pituitary function is increased due to the release of inhibition by the extrogenic substances so that there is an overproduction of the prolan A which causes it to be found in the urine. As will be explained later, this is thought to be the mechanism in lactation.

The difficulty with this is that there is no inhibition in cases of absence of the ovary, as shown by Zondek (1937), which indicates the importance of the ovarian tissue in the use of the hormone. The fact that the hormone is found increased in the urine may be also explained by saying it accumulates there due to

lack of use instead of overproduction.

The whole situation may be summarized by saying that the hormones are used by their tissue receptors, and if these are absent or below par the hormone accumulates until it reaches the threashold of excretion. (Zondek 1937).

The Growth Hormones:

The Growth Hormones have been studied ever since the initial work of Evans and Long in 1921. The experimentation on the growth hormones was retarded for a long time due to the failure of the workers to see that oral administration might not be effective. (Evans H. M. 1935a).

Briefly, authors now think that there are two growth hormones: the one affecting osseous growth and another, more obscure in its action, which prevents wasting away of the soft tissues.

It is thought that the osseotropic hormone affects the osseogenic tissues, which in prepuberty consists mainly of the epiphysis, and in the adult these being closed, the remainder of the osseogenic tissue is the main site of action.

The site of action of the anticachetic hormone is not known, but as will be discussed later, it has some function in the adult as in the growing child.

There has been reason to think that the eosinophil cells of the anterior pituitary are associated with the growth hormone (osseotropic). (Bailey and Davidoff 1925)

The growth hormones will be discussed first, the effects of deficiency such as ablation and conditions associated with hypofunction, and second, the effects of the hormone including implantation, injection and conditions associated with hyperfunction.

It must be remembered that the discussion does not intend to leave the impression that there exists clinically or experimentally a deficiency in one of the hormones alone. Many conditions arise, as a hypersecretion in a few or many, a hypersecretion in some and a hyposecretion in others although this condition is rare and, lastly, a hyposecretion in a few or many. Experimentally, the secretions or the hormones are better controlled and the effects are noted with greater accuracy.

The two growth hormones are discussed separately in an effort to produce better understanding.

In discussing the hormone affecting the growth of bones, or the osseotropic hormone the entire literature on the subject cannot be covered, and so the object is to render some idea of its physiology by noting its action.

The Osseotropic Hormone:

It is well known that the osseotropic hormone apparently increased the appetite as noted by the increased consumption of food (H. M. Evans 1935) but it was conclusively proven that normal rats under the influence of this growth hormone will increase their body weight more than controls given the same amount of food and no hormone (Lee and Shaffer 1934).

Some workers find that while growth may be accererated to quite a rapid rate, there is a physiological limit, which when reached, the growth will not increase no matter how much the dosage of the hormone is increased. The rate does not at any time exceed that which is known for postnatal life. Nor will growth continue indefinitely, as it is known that slowing will in time become evident, and the epiphysis close to limit growth (Evans 1935).

An interesting finding, is that females show better response to the hormone than the males which is thought to be due to the difference in the ephiphseal plates, according to Smith (1935a). However, it is also known that the female matures earlier than the male, but there must be some latency in the case of the female.

It has been reported that the concurrent administration of the osseotropic and thyroid hormones gives greater skeletal growth in the rat, than the administration of the osseotropic hormone alone. (Smith, P. E. 1933 Shaefer 1936 Evans, H. M. 1935).

It is noted that some animals readily react to the hormones and others do not. An example of this is the dog which easily becomes acromegalic while the rabbit does only with difficulty. This phenomenon may be explained on an hereditary basis or on the tissue receptor as explained previously. (Evans, M. S. 1933 Smith 1935)

Clinical Aspect of Osseotropic:

Paultauf first described a condition we know now to be associated with a hyposecretion of the osseotropic hormone (Evans 1935b)

In the literature now there are many records of proven cases of pituitary hypofunction in man. (Engelboch 1932) These are merely small in stature and usually do not show any sex or mental abnormalities, when due to osseotropic hormone alone. This condition is due to the retarded development of the bones, chiefly that of size, usually the epiphysis remains open for

a longer time than in the normal child. This is of course, advantageous in the delayed treatment of dwarfs. (Engelbach 1932 Car and Evans 1934). (Schaefer 1936).

The growth hormone is not any more abundant in young calves than it is in adults so for this reason it is thought that it has some function in adults. (Evans 1935a).

Adult hyposecretion seems to cause thinning of the acral parts, subnormal growth, falling hair, thirst, amenorrhea, and acrocyanosis. (Brugsch 1927).

As mentioned before, the earliest accurate accounts of a hypersecretion was that given by Pierre Marie on the condition of acromegaly.

The result of a hypersecretion, in the prepuberic human, is a condition called gigantism in which there is quite definite proportions of all the bony features but an increase in size. There is then a stimulation of general osseous growth. (Cushing 1912 and Engelbach 1932).

The result of injections, in humans with infantile dwarfism, showed there was an increased skeletal growth, which in some cases exceeded the normal for that age, but at no time did it exceed a rate which

was equal to that of the age at highest rapid growth. (Engelbach Schaefer 1934-1936 Skelton Cavanaugh Evans 1934).

Another worker reports good results in the use of the growth hormone and that in addition some thyroid extract was also found beneficial. (Shaefer 1936).

There are a few rare cases of hypersecretion and the resultant production of acromegaly in children, thought to be due to closure of the epipheseal plates. (Atkinson 1931)

The return of hair is speedier over shaved areas when this hormone is present than when it is absent. (Evans 1935a).

Experimental Aspects of Osseotropic Hormone:

It was shown by Reichert(1929) that dwarfism could be produced in hypophysectomized puppies, which in comparison to the littermate controls, showed decided decrease in size.

Putnam and his associates show the production of acromegaly in dogs (Putnam Benedict Teel 1929) while others have found no results even with prolonged treatment. (Evans Meyers Simpson 1933).

In young rabbits hypophysectomy leads to inhibition of growth and genital development. (Sakamoto Satio 1932)

In rats Smith and others have shown the effect of hypophysectomy which produced infantile rats. (Smith 1926 1927 1930). Thompson (1932) showed that with adequate nutrition these animals failed to have the normal weight gains.

Complete restoration of stature in hypophysectomized dogs by use of anterior pituitary extracts contaminated with other hormones. (Riechert 1929).

In rats, the long continued daily intraperitoneal injections of the hormone extract, produced a decided increase in the growth curve above the littermate controls. Also there was continued growth in the treated

rats while the customary plateau was reached in the controls. (Evans and Long 1921).

The effect of anterior pituitary administration in rats swarfed by hypophysectomy showed that they returned to a normal rate of growth. (Smith 1930).

The effect on normal rats was increased rate of growth as shown by Evans and collaborators. (Evans Meyers Simpson 1933).

Anticachectic Hormone:

There was found that administration of the hormone caused a retention of nitrogen. A single injection in dogs caused an immediate fall of urinary nitrogen, which was a real decrease in excretion, persisting for several days. This period of retention is followed by a period of loss so Gaebler thinks it is due to storage of nitrogen and not to an actual building up of protoplasm. (Gaebler 1933).

This was proven not to be due to an increase in absorption of nitrogen from the alimentary canal or to renal damage because the non-protein-nitrogen actually falls in the blood. There is also an increase in water intake and output, the polydipsia preceeding the polyuria. (Teel and Watkins 1929, showing the former and Teel and Cushing 1930, showing the latter.)

Clinical Aspects of the Hormone:

Simmonds (1914) reports a rapidly wasting disease associated with complete sclerosis of the pituitary found at necropsy Some animals deprived of the pituitary develop similar cachectic states in various cases. Evans (1935a) thinks that it is a

separate principle because, while these animals are supplied with the growth principle, they continue in the cachexia until they die. However, if the crude anterior lobe extract is used in place of the more refined products, the condition is relieved. Also, it is not relieved by adrenocortical extracts, so it is not associated with the condition known as Addison's disease. (Evans 1935a).

Calder reviewed the literature on this syndrome and found weight loss progressive, cachexia, loss of axillary and pubic hair, mental torpor, trophic changes in the skin, and terminal coma. (Calder 1932 Silver 1933).

Experimental Aspect of the Hormone:

In the rabbit (Sakamoto and Saito 1932) report that in total hypophysectomy leads to cachexia and early death, although partial removal of the pituitary, there is survival with the inhibition to growth and genital development.

Lee and Ayres (1936) found that hypophysectomized rats lost nitrogen due to destruction of tissue because they showed a greater loss was found in these animals as shown by their body composition as compared to controls which lost more fat while retaining their nitrogen.

Gonadotropic Hormones:

Luteinizing and Follicle-Stimulating Hormones:

Experimentation was begun on the sex hormones after the initial work of Smith in 1926, who recognized that anterior pituitary tissue implanted under the skin or intramuscularly brought about signs of sexual development in immature rats or mice.

The literature seems to indicate the presence of two gonadotropic hormones in the anterior lobe of the hypophysis. (Fevold and Hisaw 1930 and Wallen-Lawrence 1934).

These hormones are apparently associated with the basophile cells. (Evans 1935 Witschi 1934) Others think both eosinophiles and basophiles are involved (Reese 1932 Chadwich 1936).

One of these hormones, termed the follicle stimulating causes the development of follicles in the immature female animals and superovulation in the adult female animals. In the male, spermatogenesis is initrated in the immature animal while the adult there seems to be increased activity.

Apparently, then, it seems to be the germinal epithelium that is stimulated in both the sexes. (Evans 1935 Smith 1935 Smith & Engle 1934 Smith, Engle,

and Tyndale 1934)

The other gonadotropic hormone, which has been labeled the luteinizing hormone, seems to stimulate the interstitial tissue of the male and female which results in the development of the accessory organs. (Evans 1935 Smith 1935)

The luteinizing hormone, discovered by Zondek and Aschheim, was found to be in the body fluids. The same authors found also that menopause urine contained mainly the follicle stimulating hormone but luteinization was obtained when the pregnancy urine was added. (Evans 1935).

The pregnancy urine principle was thought to be the same as the luteininzing principle of the anterior lobe of hypophysis, but reports have indicated this is not so, although many similarities are present.

The main differences are: it cannot stimulate the growth of follicles and corpora in the ovaries of animals with ablated hypophyses according to Reichert and associates (1931). It will not cause the development of Aviantestes as does the anterior lobe principle (Riddle 1931). It has only slight effects on the monkey ovary. (Engle 1933) The principle will not cause increase in weights with such ease as does the anterior

lobe principle. (Evans and associates 1929) Evans and associates (1934 a&b) extracted a substance from the anterior pituitary to make the pregnancy urine maximally effective and secured the desired effects, naming it the "synergistic" principle, while Leonard and Smith 1933 by the simple addition of the principle in pregnancy urine obtained identical results.

There is reason to think that the pregnancy-urine factor comes from the chorionic tissue according to Evans (1935). He gives evidences which shows the chorionic tissue has large amounts of the substance in it when none is found in the anterior hypophysis (Phillip 1931). The hormone is found in all types of chorionic tissue growths hydatidiform mole and chorionepithelioma, and it is found in very young chorionic tissue, before the pituitary shows any characteristic pregnancy changes.

It is thought the placenta produces estrogenic substance in pregnancy. (Hark and Cole 1934).

The substance found in castrate urine resembles that found in menopause urine and the peculiar basophil cells found in castrates, with increase in the pituitary of the follicle stimulating hormone and the development

of a constant estris in a parabiotic union between a castrated male and hypophysectomized female, seems to indicate these both to be from the anterior pituitary. (Leonard and Smith 1934).

It is to be noted that the use of the follicle stimulating fraction from castrate-urine and from the hypophysis results in the absence of cyst formation in the ovaries even though large dosages are used. (Smith and Engel 1934). On the other hand, the injection of unfractionated extracts from the hypophysis results in cyst formation thought likely due to impurities. (Smith 1935). The same castrate-urine principle will cause spermatogenesis without interstitial cell stimulation. Consequently, the secondary sex characters are not stimulated and the gonads retain the same size (Smith and Engle 1934 and Smith, Engle, and Tyndale 1934). A similar effect has been found to be obtained from the follicle-stimulation fraction of the anterior pituitary (Evans and Simpson Percharz 1934).

Some of these workers find it is necessary that there be follicles present in the ovary before the luteinizing hormone can operate (Fevold and associates 1933 Wallen-Lawrence 1934) which seems quite justifiable

as this happens normally in the ovary.

Cole and Hart (1934) find that pregnant mare serum contains large amounts of gonadotropic substances stimulating both the interstitial and the gametogenic tissues, and they think that both follicle-stimulating and luteinizing hormones are present. Extracts of pregancy urine is thought to be by some workers, to be similar if not identical with the luteinizing hormone of the anterior hypophysis (Smith 1935).

Extracts of the pregnancy urine will not cause follicular growth when injected with hypophysectomized rats (Selye and associates 1933 and Leonard and Smith 1934) but produces luteoid changes in the theca cells of the ovarian follicle and true corpus luteum formation result. This also occurs where there are large enough follicles to be acted upon (Flubmann 1934).

In the male, pronounced interstiteal changes are produced whether the animal has been hypophysectomized or not. (Smith and Leonard 1934) Some authors claim stimulation by this pregnant urine principle. (Evans and associate 1934) (Brosius and Schaefer 1933) but has been denied by Collip 1934).

Apparently the synergestic principle, of Evans and associate (1934), is the same as the luteinizing hormone of the anterior hypophysis and the former requries the presence of follicles, which with the latter is not so necessary, likely due to the principle being contaminated with the follicle-stimulating. In testing with implants and with test animals both should be considered. Smith and Engle (1929) found that the pituitary exhibited a cyclic variation in its capacity to stimulate ovaries of test animals which corresponds to the phase of the oestrus cycle.

The age of the animal is important as this will determine whether the ovary is capable of reacting to the hormones particularly to the pregnancy urine hormone. In the monkey and guinea pig the ovaries will respond to the luteining principle of pregnancy urine only after hypopheal or castrate-urine hormore stimulation. (Collip 1935).

Clinical Aspects of the Gonadotropic Hormones:

The lack in the male human of the follicle-stimulating hormone appears to be associated with hypofunctioning of the germinal epitheluim or the non-production of sperms by the seminiferous epithelium

(tubules) and is apparently not associated with the condition producing the obvious sexual infantilism that results from interstial underdevelopment of the testes, because cases of endocrine aspeomia were found in which the secondary male characteristics were present. (Brosius and Schaefer 1933 Goldberg 1934 Huberman Israeloff and Hymowitz 1937).

The lack of the follicle-stimulating hormone in the human female apparently results in the absence of follicle formation and this results in sterility.

The lack of the luteinizing hormone in the male human produces a obvious effect. The testes are usually small and may be undescended (Rubenstein 1934) The size of the testes is due to the underdevelopment of the interstitial tissue, which is normally supposed to produce a hormone affecting secondary sex characteristics. Thus, underdevelopment of this tissue would produce such as: small amount of pubic and axillary hair, underdevelopment of the penis, retention of a soprano-like voice, and female-like distribution of adepose tissue.

The lack of the luteinizing hormone in the female adult would produce the disease described by Schroeder,

particularly if there was a sufficient amount or over-abundance of the follicle-stimulating hormone. This disease (Schroeder's) is characterized by excessive menstrual bleeding due to the lack of luteinization of the follicles of the ovary by the requied hormone, thus allowing excessive hypertrophy of the uterine endmetrium. It is conceivable that the retension of these large follicles as cysts may cause the symptom known as amenorrhea, thus it appears as though the whole mechanism of menstruation was closely associated with this luteinizing hormone. (Evans 1935).

Judging from the laboratory work underdevelopment of the secondary sex characters should be found with a lack of this luteinizing hormone. Thus possibly would the mammary glands be underdeveloped. No proof is found for this clinically however.

The effect of the follicle-stimulating hormone in the male would be the production of sperms while this may be theorically true, Huberman and his associates did not obtain convincing results. They injected the extract of castrate and in some menopausal urine, which contains almost pure follicle-stimulating principle, and in the ten males were able to increase spermatogenesis

and the motility of these gametes, but none of the men became fertile during the period recorded. (Huberman, Israeloff and Hymowitz 1937)

In the female, the work with this hormone is not very convincing Hamblin (1936) used anterior pituitary extracts and could not secure any ovarian change. He thought perhaps longer periods of injection might give results.

The luteinizing hormone has been more widely used. It is interesting to note that Brosuis and Shaefer (1933) obtained spermatogenesis in man with extract from pregnancy-urine. For this reason some authors think this urine contains some of the follice-stimulating hormone but in some way is masked (Smith and Leonard 1934 and Evans and collaborators 1934).

In sexually infantile boys and cryptorchism, a number of authors have gained some results with their efforts. Rubenstein (1934) and Sexton (1934) both used the pregnancy urine principle, while Golberg (1934) used an extract of the anterior pituitary (antuitrin).

In the female, the effect of the luteinization hormone is decidedly indefinite. One worker could obtain no response with the pregnancy urine extract (Hamblin 1936) and Geist (1933) could only secure hyalinization of the ovary.

Experimental Aspects of the Hormone:

[illegible]:

Because of the vast amount of work done on the rats, these animals will be considered first and will be used as a basis for the following animals.

Hypophysectomy in the rats of any age will stop gonadal development and cause actual atrophy of these organs, particularly in the postpuberic, while in the prepuberic the gonads remain infantile.

In the male, before maturity, there is a decrease in size of the testes and cessation of spermatozenesis, while after maturity, there is degeneration of the seminal epithelium. However, the residuim of spermatogonia undergo division for seve ral months after the anterior pituitary removal, so that, with the injection of extracts of the anterior pituiray, sperm formation may be reestablished. Also there is associated atrophy of penis, prostate, seminal visicles and occessory organs (Smith 1927). (Leonard and Smith 1934)

In the female, before maturity, the vaginal orifice may remain closed and the ovaries remain small, while in the adult, the follicles of cavity stage undergo atresia as do any other growing follicles. The ovaries become filled with interstitial tissue. Ova may presist for a long time and it has not been determined if there is a reduction in their number. No corporalutea are

formed. In the other organs, the uterus becomes thread-like and vagina reduced in size. The uterine and vaginal epithelium takes the character of the castrate, and the cycles cease. (Smith 1927)

Pituitary ablation in the dogs results in atrophy of the male adult genital organs and in the puppy there is a persistence of infantilism. These authors also showed the posterior pituitary removal did not cause these affect while the anterior removal did. (Crowe Cushing Homans 1909 Reichert 1928 a and b).

Allen (1927) found that hypophysectomy in the female adult monkey lead to cessation of menstruation.

Apparently there appears retardation in the sexual development of the immature rabbit.

In the mature rabbits there follows atrophy of the genital organs similar to that found in the rat. Implantation was used by Smith on rats as early as 1926. It was found that both rats and mice reacted equally as well to the implantation therapy.

Pituitary implants on normal immature female rats produced large ovaries, about ten times the size of the controls, and it was thought the size was due to the growth of the follicles. There occurred super-ovulation as many as forty-eight eggs in one tube.

It took the rats four and the mice three days to become sexually mature. The response was found to be more rapid when nearer to the age of maturity. The uterus and vagina also assumed the structure of mature animals. (Smith and Engle 1927 Evans and Simpson 1928).

These implants have the same effect on the mature animals except the response is more rapid.

Pituitary implants following ablation of the hypophysis caused growth of follicles and corpus luteum formation when the implants were stopped follicular atresia developed and the ovaries became reduced in size.

In all these implants it was found that the follicles developed beyond normal size and cysts would form. Luteinization would take place at the periphery to form solid corpora later. (Smith and Engle 1927). It was also noted that while ovulation would take place in abundance (Engle 1931 and Smith and Engle 1927) the eggs would even be fertilized, but no implantation would occur. This Engle (1930) though it was due to lack of sensitization of the uterus, Shelesnyak (1931) showed that deciduomata formed readily if the

animal received anterior lobe injections along with the pituitary implants. Smith (1927) could not see any difference between the uterine contractions at induced and normal estrus.

In immature males, the series of implants produced some increase in size of the testes but some authors think spermatogenesis was not any sooner than in the controls (Smith and Engle 1927).

There did not seem to be enlargement of the seminal vesicles prostate according to More and Price (1931).

In mature males, the result was about the same, as is true for the hypophysectomized males.

In the dog almost the same phenomenon resulted as in the rat. Cystic follicles and signs of heat followed treatment with complants six months after completion of hypophysectomy. It was also noted by one author only a slight body growth was obtained, likely due to sexual development. (Reichert 1928 a and b)

In the monkey, implants of monkey gland into immature animals produced pronounded follicular stimulation with enlargement of genital tract and mammary gland accompanied by development of secondary sex characteristics.

In the mature monkey little stimulation was obtained from implants from pig glands, although with regular cycles of this treatment obtained good results when a non-ovulating animal was used (Hartman 1930 Hartman and Squier 1931).

The extracts of anterior pituitary was shown by some authors to contain two factions, a luteinizing and a follicle-stimulating principle, the later seems to be necessary for the second one to act. (Fevold Hisaw and Leonard 1931).

Hypophysectomized rats (female) treated with follicle-stimulating principle of menopause urine produced the formation of follicles and when followed by pregnancy urine extract, corpus luteum formation resulted. (Leonard and Smith 1934 and Fluhman 1934)

In males pregnancy urine extract produced profound interstitial hypertrophy whether hypophysectomized or not. (Smith and Leonard 1934)

In mature rats with atrophy of the reproductive system due to pituitary ablation, injections of menopause urine apparently seemed to restore this condition producing sperm cell production, but no interstitial stimulation of ovary or testes (Leonard and Smith and Collip 1935).

Atresin:

Recently, a number of workers have found a substance they call "atresin" which they claim is a follicle destroying substance found in the pituitary of cattle sheep and pigs, and which will cause the rapid destruction of follicles in the guinea-pig. These workers say it is usually associated with the thyrotropic and the luteinizing fractions.

The state the action of this hormone may cover up the action of other hormones and that it might be the means of transforming the gland from one type to another.

These workers refer to P. E. Smith (1927) and Evans and Simpson (1928) in whose work it was shown that injection of the growth hormone extract produced inhibition of early sex maturity, usually which was usually induced in these animals (Rabbit and Rat). Evans (1928) at that time, interpreted this phenomenon as an antagonism between the growth hormone and the follicle-stimulating hormone. (Loeb, Saxton and Hayward 1938).

Lactotropic Hormone:

Grüter and Stricker in 1929 (and in 1928) demonstrated that the anterior pituitary contained a principle which was essential for lactation. By the use of various animals, some of which were ovariectomized, they showed that injections anterior pituitary substance caused secretion of milk in the mammary gland.

Later workers were successful in isolating the lactogenic hormone from the anterior pituitary to a fair degree, and demonstrated that it was independent of the gonadotropic, thyrotropic and growth hormones. (Riddle Bates and Dykskom 1932 a and b).

This hormone, named prolactin by Riddle and his collaborators (1932), and, galactin by Gardner and Turner (1933), has four known responses in animals according to Riddle (1935). These are:

1. Lactation in mammals
2. Growth of the crop glands in pigeons,
3. Broodiness in fowls and
4. Marked diminution in active gonads of adult pigeons and fowls.

Because of the mammary development associated with pregnancy it was first thought, later disproven, that

the ovary was necessary for lactation. Ovariectomy in various animals conclusively shows the ovary unnecessary. (Grüter and Stricker 1929).

The mechanism of action of the hormone according to Moore (1935), is that the estrogenic substances of pregnancy inhibit the action of the pituitary lactogenic hormone, while causing mammary tissue growth itself. The release of the estrogenic hormone allows the lactogenic factor to stimulate secretion.

Some authors think that the estrogenic substances cause poliferation of the mammary duct system and the loctogenic factor causes the development of the alveolar epithelum.

Other authors think that the lactogenic hormone is solely responsible as it is shown that the hormone is increased in the pituitaries in pregnancy, and the estrogenic hormone prevents full activity. Also it has been shown that full development of the gland may be obtained with prolatin in ovariectomized animals after sexual maturity has been reached indicating, at least, the unimportance of the ovary to mammary development of the ovary. (Corner 1930 Riddle Bates and Dykshorn 1933).

However, it is more likely that the ovary does play a part as we find that castration has in some cases growth effect on the mammary tissues particularly in puberty.

Some workers rather doubt that the lactogenic hormone is solely responsible for initiation of laction, because they found that lactation will take place in hypophysectomized animals, although they agree that the anterior pituitary is necessary for the continuance of lactation. (Seyle Collip and Thompson 1933).

Gomez and Turner (1936) found that in their animals, lactation ceased immediately with hypophysectomy. They also found that, while replacement injections were not effective, whole gland substance was.

The continuance of lactation may be explained on two mechanisms. It is known that emptying the mammary gland causes continuation and it is thought that this prevents alveolar stagnation with resulting regression (pressure atrophy) allowing the cells to go through their secretory phases. Also it is thought there might be a reflex stimulation on the pituitary lactogenic hormone. (Seyle 1934 Nelson 1936).

Many workers have found that the normal mammary growth during pregnancy was inhibited with hypophysectomy but did not atrophy until after partuition.(Pencharz and Long 1933 Seyle Collip Thomson 1933). while others have found that prolactin would induce full development and lactation in ovariectomized animals. (Corner 1930).

Clinical Aspect of the Lactogenic Hormone:

Evans (1935) states that nearly all mammary glands have been exposed to the estrogenic hormone as many new borns, as well as at puberty, the mammary glands show growth spurts which produces the growth. He also thinks that, after birth, there is a release of the estrogenic or lactogenic hormone to act.

This phenomenon, as is now apparent may be explained in two ways. Perhaps the mother produces sufficient prolactin which circulates into the fetal stream and produces growth of mammary tissue, and when the estrogenic hormones are released the prolactin in the fetal blood causes the witch's milk. This would agree with Corner's theory. (1930). On the other hand, the estrogenic substances may cause the mammary growth spurt and when released the amount of prolactin in the fetal blood would be sufficient to cause the mild secretion, which would be more in keeping with the ideas of Moore. (1935).

There are cases reported in which lactation occurs in cycles with menstruation or in place of it (Schweitzer 1923) which according to Evans (1935)

may best be explained in a cyclic secretion of the lactogenic hormone.

In pregnancy, a gradual growth takes place which might be explained by an increase in the pituitary lactogenic hormone. (Evans 1935).

Kurzrok and his associates have shown that they could produce lactation quite readily in some females who failed to lactate in six days. (Kurzrok Bates Riddle Miller 1934).

According to the findings of some authors, there seems to be atrophy of the breasts, or at least a failure of the breasts to secrete after partuition. (Kurzook 1934).

In menopause it is noted that in many cases there is breast growth and lactation showing that continued stimulation by the estrogenic hormone is unnecessary. (Evans 1935).

In some cases there may be lactation in males associated with pituitary tumor which Evans (1935) concludes it is due to hypersecretion of the lactogenic hormone.

Experimental Aspects of the Lactogenic Hormone:

In dogs Lyons etal (1930) showed that lactation ceased or failed to develop.

In young guinea pigs Nelson (1933 1934) showed that after pregnancy lactation would cease following hypophysectomy. This was also shown by Gemez and Turner in 1936.

Much work has been done on the rats by Seyle etal (1933) who shows that there was no lactation when pituitary excision and ovariectomy was made simultaneously or if lactation was in progress it stopped. The removal of the ovary seemed to enhance the secretion of milk.

The effect of the hormone may be shown by Lyons etal who gave pituitary injections and produced lactation in dogs.

This was substantiated in virgin guinea pigs by Corner (1930) who also used extract o f the anterior pituitary containing the hormone. Nelson (1934) also showed that extract with estrin caused inhibition of lactation in partuient females. Gomez and Turner thought it was necessary to have whole gland (anterior pituitary) extracts. In the rat Seyle etal (1933) produced development of the mammary glands in virgin rats but no secretion of milk but with the removal of the ovary they did obtain lactation.

Thyrotropic Hormone:

The discovery of the thyrotropic hormone was made independently by Loeb and Aron in the same year (1929).

Recent workers think they have been capable of distinguishing the cells that are associated with the production of the hormone. They state that they are basophilic cells, which can be distinguished from the basophil cells of gonadectomy. Also when the animal's thyroid is removed, the pituitary shows these characteristic basophile cells, when no gonad atrophy results. The think that these changes are due to the results of thyroidectomy which causes retention of the thyrotropic hormone in these cells. (Zweckwer 1935).

The action of the hormone is to stimulate the thyroid tissue with consequent enlargement of the thyroid gland due to hyperplasia. Excessive stimulation of the thyroid gland results in increased heart rate, exophthalmos increase basal metabolic rate, and decrease in the iodine content of the gland. (Siebert and Smith 1930 Schochaert 1932 Schochaert and Foster 1932).

According to some authors, who worked on man, the principle caused increase in basal metabolic rate in those having capable functioning tissue. Those with a low functioning thyroid could be brought up to normal and those with hyperthyroidism are made much worse. The effects were found to be temporary, however, as the final results were that they all returned to what they formerly were or worse. (Thompson, Taylor, Thompson, Nadler, and Dickie 1936)

It is interesting to note that nearly all (except the growth) hormones form antihormones according to Collip (1935c) This being so, and it is suggested by him that it might be the cause of some disorders, it should be possible to give such as those with Grave's disease the thyrotropic hormone and thus being about antihormone formation and cure the disease. The barrier to this would be, of course, the theorical possibility of the hypofunctioning or lack of the antihormone formation.

According to Starr and Rawson (1937) they measured the thyroid cells before and after administration of anterior pituitary injections and found a definite increase in size of these cells.

Clinical Aspects of the Thyrotropic:

It is well known that in cretinism and in myxedema there is a hyposecretion of the thyroid in the formation of thyroxin. In the former which occurs amongst children, there is usually associated dwarfism as has been suggested in the growth hormones.

There are various possibilites as to why the endocrine is low. The cause may be primary, in the tissue itself, as in the case of endemic goiters, or it may be due to a hypofunction of the pituitary (thyrotropic hormone). Collip (1935c) would introduce the possibility that the antithyrotropic is over-abundant, thus causing an inhibition of the thyrotropic action.

In cretinic and myxedemic humans a number of authors have noted enlargement of the pituitary (Boyce and Bradles 1892 and Macallum 1907). In some cases with pituitary cachexia it was noted by Graubner (1925) that the thyroids were small, atrophic and some sclerotic. In adults there was some proof of the existence of a pituitary hypofunction where there was a low basal rate, according to Thompson and associates. (1933).

It has been stated that some myxedmatous patients have a lack of the thyrotropic hormone. It is also found that other myxedematous patients have a high thyrotropic titer. It is thought that this is due to the primary insufficiency in the thyroid itself. (Evans 1935a).

There are other causes with a low thyrotropic titer but have the clinical manifestations of thyrotoxicosis. Some authors suggest this to be due to primary over activity of the thyroid gland and not due to the amount of the thyrotropic secretion, but Evans suggests it conceivable that the thyroid demands so much of the thyrotropic substance in this condition (Graves disease) that the titer is unusually depressed. It has been reported, there has been some results in treating these hyperthyroid conditions with the anti-thyrotropic hormone. It is known that thyroxin renders the thyrotropic hormone inefficacious (Evans 1935a)

Experimental Aspects of the Thyrotropic Hormone

The lack of the hormone demonstrated by White (1934) by hypophysectomy in the rabbit. He showed there was some atrophy of the thyroid but not as much as might be warrated.

According to Smith (1930) and Collip (1933) there was considerable atrophy in the thyroid gland following removal of the anterior hypophysis of the rat. A low basal metabolic rate was obtained in the rat by the hypophysectomy according to Foster and Smith (1926).

The effect of the hormones in animals was shown by Benedict and Putnam (1930) who obtained enlargement of the thyroid and an increase in the basal metabolic rate in the dog.

In the rabbit Thurston (1933) and Scover and Spence (1936) showed increase in the size of the thyroid to pituitary injections.

In the quinea pig, Loeb and Friedman (1931) obtained exophthalmos with pituitary injections. Starr and Rawson (1937) showed definite enlargement of the thyroid by measuring the height of cells of the thyroid and concluded definite enlargement.

In the rat Collip (1935b) reported a raise of the basal metabolic rate to plus 26 and Thurston (1933) obtained enlargement of the thyroid with anterior pituitary extracts.

Parathyrothropic Principles:

Anselmino and his associates (1934) have shown that certain pituitary extracts cause hypertrophy of the parathyroids in normal animals. Hertz and Kranes (1934) soon after confirmed their findings. Anselmino also stated that long continued injections did not maintain the hypertrophy of the parathyroids.

The effect of hypophysectomy in animals causes atrophy according to some experimenters (Koster 1930 and Smith 1927) but others find no effect. (Aschner 1912) The removal of the pancreas along with the pituitary appears to lead to marked degenerative changes in the parathyroids. (Collip 1935b)

The effect of hypophysectomy on the blood calcium also varies with the work of different authors according to Collip (1935b).

Teel and Watkins (1929) find a fall in blood calcium in animals after treatment with growth hormone fractions of the anterior pituitary which is in contrast to Anselmino (1934) who find they get a raise, which does not occur in the absence of the parathyroids.

Clinical Aspects of the Parathyrotropic Hormone:

The work on these has been very little as yet. There might be some studies made on this hormone in relation to osteitis fibrosis cystica, and various parathyroid diseases later.

Hertz and Albright (1934) found that the urine of patients with diffuse hyperplasia of the parathyroids but not with adenoma contained a substance which caused parathyroid hyperplasia in the laboratory animals, by injection an extract of this substance.

Experimental Aspects of the Parathyrotropic Hormone:

According to Koster (1930) hypophysectomy leads to some atrophy in the parathyroid of the dog, as in evidenced by their smaller size. Removal of the pancreas causes more marked atrophy in the parathyroids with necrosis according to Collip (1935b). Teel and Watkins (1929) found a fall in blood pressure in the dog when injection of growth hormones was made.

In the rabbit, Hertz and Krames (1934) found changes in the parathyroids due to hypophysectomy.

The calcium excretion was considerably increased in rats, as the result of hypophysectomy. The excretion was mostly by way of the intestine althought the kidney excretion was increased several hundred times, but was small to begin with. (Perla and Sandberg 1936)

Teel and Watkins (1929) showed that with the use of anterior pituitary extracts they could obtain parathyroid hypertrophy in the dogs.

In the rabbit Hogben and Charles (1932) obtained similar results and there was noted a change in the blood calcium (higher) according to Hertz and Kranes. (1934)

In the rat, Anselmino, Hoffman and Herold (1934) obtained similar results by pituitary injections.

Interrenotropic Hormones:

The early work on the interrenotropic hormone was done by Smith, who showed that hypophysectomy would cause degenerative changes in the cortex of the adrenals. He showed that anterior pituitary implants would prevent this atrophy and there was frequently cortical adrenal hypertrophy in normal animals treated with pituitary hormones. (Smith 1930) His work was soon confirmed by Evans Meyer and Simpson (1932) in the use of extracts of the anterior hypophysis.

It was found that the use of growth hormones extract also produced cortical hypertrophy of the adrenals (Evans Meyer and Simpson).

It is stated by Evans (1935a) that there is marked hypertrophy of the one adrenal when the other is taken out, as a compensatory phenomenon. This change does not occur in hypophysectomized animals. Also it is noted that the animal will grow normally even if the adrenals are taken out if they are given cortical extracts, which does not occur in hypophysectomized animals.

In adrenalectomized animals (in dogs) and in Addison's disease (clinically) there appears to be a

diminution of the number of basoplils. (Evans 1935a)

The understanding of the interrenotropic hormone was made more difficult by the finding that non-specific toxins will also cause hypertrophy of the adrenals in normal animals. (Emery 1933)

The interrenotropic hormone was found to be associated with the thyrotropic hormone, and, with purification of the latter, the effects of the interrenotropic hormone became less. This led some workers to use the waste in the thyrotropic purification and they claimed they could obtain quite pure interrenotropic principle (Collip, Anderson, and Thomson 1933)

According to Mc Queen Williams (1934) the thyroid is necessary in the production of hyperplasia of the adrenal cortex with extracts or implants in normal animals. They find that while the thyroid is necessary the thyrotropic hormone does not take a part in it because extracts devoid of the pituitary thyrotropic hormone will produce the hyperplasia, while this cannot be produced by the thyroid hormone.

(Emery and Winter 1934)

Collip (1933), however, states the action of the interrenotropic hormone is a direct one and does

not occur through the intermediation of the thyroids, because this hormone does not raise the basal metabolic rate or prevent thyroid atrophy in some animals. (Collip 1933).

Clinical Aspects of the Interrenotropic Hormone:

The dysfunction of the adunal cortex may be theorically classified into intrinsic and extrinsic as to whether the factors are within the organ or external to it.

The intrinsic dysfunctions would be those related to the adrenal tissue itself, either being hypoplastic or invaded by pathology such as tumor and tubercular processes. Again there may be a hypertrophy as caused by a tumor or by a compensatory mechanism. This latter would be likely to be classified as an extrinsic mechanism, if one considers the pituitary as having a definite amount of secretion which is thrown on the remaining adrenal. The extrinsic mechanism would be associated with the pituitary and would be regulated according to the secretion of this gland. (Shumaker and Firor 1934).

Apparently, then, it should be possible to treat the adrenal-cortical insufficency or the hypopituitary

condition by their respective hormones, but it is obvious it would do little good to treat the adrenal insufficiency due to tuberculosis of the adrenal with a pituitary hormone.

In hyposecretions we find atrophy of the adrenal cortex as mentioned. It is interesting to find that in pituitary cachexia and in dwarfism, there was associated small adrenals. (Evans 1935a). There is found atrophy of the adrenal cortex in Addison's disease according to Wilder (1934) and Mackenzie (1932) reports atrophic lesions of the pituitary with evidences indicating a hyposecretion which was accompanied by extensive atrophy of the adrenal cortices.

The production of an excessive amount leads to hypertrophy and is often found in cases where there is found basoplilic adenomas of the pituitary (Cushing 1932) and is often associated with acromegaly (Cushing and Davidoff 1929) in which the adrenal cortex may reach enormous size.

Experimental Aspects of the Interrenotropic Hormone:

The experimental findings apparently are quite in agreement as to the findings due to ablation of the hypophysis and to treating normal and hypophysectomized animals with injections and implantation.

In the rat it was noted that hypophysectomy caused atrophy or involution of the adrenal cortex (Smith 1930 Collip 1933) and it was found that they could be returned to normal by intramuscular implants (Smith 1930) or by injections. (Evans Meyer Simpson 1932). It was also leared, in these animals, that implants and injections would cause hypertrophy of the cortex of the adrenal (Smith 1930 Collip Seyle and Thompson 1933).

In the dog Putnam and associate (1929) found that chronic administration of pituitary extracts caused cortical adenoma, while the growth hormone extract of Cushing and Teel (1929 and Teel and Cushing 1930) produced similar results.

According to Bauman and Marine (1932) very similar results were obtained in rabbits as was obtained of the rats.

Experimental Aspects of the Interrenotropic Hormone:

The lack of the interrenotropic hormone is shown of the hypophysectomized dogs of Houssay etal (1933) who showed that the adrenals were smaller in these animals than in normals. (Also Collip 1935b).

In the Rabbit, White, (1934) showed that hypophysectomy caused decrease in the cortex of the adrenals, likely due to the size of the cells rather than the number of cell decrease.

The rat was shown to have considerable atrophy of the adrenal cortex by McQueen-Williams (1934). This was substantiated by Smith (1930), and Evans (1932)

The effect of the hormone in the dog was shown by given injections of anterior pituitary extracts hypertrophy could be produced. (Houssay etal 1933)

Shumaker and Firer (1934) used implants of the anterior hypophysis and obtained corticoadrenal hypertrophy.

In the rat, implants were used by Mc Queen-Willimas (1934) who found the thyroid a necessary but not an absolute factor. He also found the hypertrophy was mainly in the zona reticularis and zona

fasciculata. They obtained compensatory unilateral adrenal hypertrophy following unilateral adrenalectomy. Collip (1933) found that extracts of the pituitary caused enlargement of the adrenal in normal animals but prevents atrophy in hypophysectomized rats. Smith (1930) accomplished very similar results with intramascular transplants.

Diabetogenic Substance:

Early writers noticed, that in cases of acromegaly, there was frequently an associated glycosuria (Goetsch, Cushing, and Jacobson 1911). This fact has been confirmed by recent investigators. (Eidelsberg 1932).

It was the classical experiments on dogs by Houssay that brought attention to the possibility of a Diabetogenic hormone in the anterior pituitary. He found that a pancreatectomized dog would develop symptoms of diabetes, but if the animal was also hypophysectomized the severity of the diabetes would be lessened. (Collip 1935b). This has been confirmed by Regan and Barnes. (1933)

The mechanism then, is that the hypophysis produces a hormone which antagomizes the action of insulin. It is found in animals that they are more resistant to insulin when simply pancreactectomized than when pancreas and hypophysis are both removed.

Collip (1935b), in his discussion of the theory of action of the blood sugar increasing principle states that Lucke believes this principle acts on the carbohydrate nervous centers thus stimulating the adrenals

reflexly, because he found that with denervation of these glands, he could get no response with the principle. He contrasted this with Houssay and Brasotti who did not get any change even with complete evisceration unless the liver was removed. Collip also presents evidence that might suggest the principle acts on nervous centers in that one author (Houssay) found a considerable period of latency with injection, but if introduced directly into the blood stream another author (Lucke) gets immediate response.

The Diabetogenic substances are composed of three hormones:

1. The Sugar raising principle
2. The pancreatropic principle
3. The ketogenic principle

There is not the definiteness there should be in the first two principles, because it is known that the pancreas controls the blood sugar also. The blood sugar raising principle is supposed to work directly on the nervous centers, as stated.

Clinical Aspects of the Pituitary and the Blood Sugar.

Goldzieher (1936) finds that 88 cases in his 112 series of hypoglycemic patients were due to the pituitary as evidenced by clincial findings and diagnostic therapy. Of this group of 88, there were 74 improved with organo and dietary measures.

De Wessclow (1936) showed that in humans with diebetes, there was found a hormone which would cause a raise in blood sugar of normal laboratory animals. The patients were on a dietary and not on insulin, treatment.

Salitowna (1936) showed that the insulin resistence in a woman (with acromegaly and diebetes) was reduced by the use of X-ray on the pituitary gland.

Torresini and Nicoloki (1937) show that while corticoadrenal extracts produce a hypoglycemia in old humans, anterior pituitary extracts causes a hyperglycemia.

Kenyon (1930) gave pituitary extracts (containing growth, gonadotropic and thyrotropic hormones) to one boy who had hyperglycemia but clinical evidences of hypopituitism.

Experimental Aspects of the Pituitary and Blood Sugar:

In the dog, it was shown that hypophysectomy would cause a hypoglycemia if the animal was fasting, otherwise when on an adequate diet, it would maintain normal blood sugar and liver glycogen. (Armor and Keller 1933 Corkill, Marks, White 1933).

In the rabbit, White (1933) produced loss of liver weight, and hypoglycemia, Evans, E. I.(1933) produced glycosuria and hyperglycemia in dogs by injection of anterior pituitary extracts.

In the rabbit, Baumann and Marine (1932) produced definite glycosuria by injection of extracts of anterior lobe.

The subject is comparatively new and very little experimental work has been done with this principle.

Ketogenic Principle:

Burn and Ling (1928, 1929, 1930) showed that rats developed acetone body excretion when kept on a butter diet and anterior pituitary extracts were administered.

It has been found that this principle is separate from any other, because it gives responses for this one effect. It has been shown to be active in thyroidectomized animals (Funk 1933) and so it cannot be the same as the thyrotropic. Collip (1935) states that Magistris claims the ketogenic and the diabetogenic principles are opposite in effect in that the first increases ketone bodies and decreases blood sugar particular in chronic administration, while the diabetogenic does the reverse.

Pancreatropic Hormone:

Koster (1930) states that the pancreas of hypophysectomized dogs is usually atrophic but no specific changes have been observed in the islands of Langerhans that would prove a relatory influence of the hypophysis on the histology of the pancreas. (Collip 1935b).

Anselmino (1933) believes that anterior pituitary extracts injected into rats causes an increase in the size and number of the isles of Langerhans, and attributes this to a specific hormone which he has named pancreatropic substance. He finds in the rat the liver glycogen dissappears almost completely after injection of a small amount of this substance.

Metabolism and the Anterior Pituitary:

Carbohydrate Metabolism:

The control of carbohydrate metabolism seems to be influenced by the anterior pituitary hormone as has been suggested by the diabetogenic hormones. (Collip 1935b)

Fat Metabolism:

This seems to be very similar to the anterior pituitary substance called ketogenic hormone by some workers. This substance apparently controls the lipema and the metabolism of fat in the body. (Collip 1935)

Protein Metabolism:

Gaebler (1933) and Lee and Schaefer (1934) showed the effect of the growth hormone on the retention of nitrogen as previously shown.

White (1934) showed that hypophysectomy in the rabbit leads to loss of weight.

Lee and Ayres (1936) showed that hypophysectomized rats lost greater nitrogen stores from their tissues than controls which lost comparatively more fat, when both were on the diet taken by the hypophysectomized animals.

Antidiuretic Hormone:

Gilman and Goodman (1936) think there is a hormone in the anterior pituitary which controls renal water excretion which normally passes into the urine and may be found there. They present evidence by showing that hypophysectomized rats dehydrated (to death) in forty hours failed to excrete this antidiuretic substance while control rats show appreciable amount, and that the urine and hypophyseal substances show the same properties. They conclude that the antidiuretic substance is secreted by the anterior pituitary, passes through the circulation and acts upon the kidneys. Normally it passes through the glomerulus and tubules and is found in the urine. The need for water conservation by the body is a stimulus for the secretion of this hormone.

Marshall and his associates (1933) show that pituitary extracts with water intake sometimes causes anuria. The find that the fish and chick varies with doses. According to these workers, the glomerulus plays a part in the water excretion, while the main action is in the tubules by a reabsorption process, because the glomerulus filtrate was tested and found the same while in the tubules it varies with the pituitary substance. Diuresis has been noted with the growth hormone. (Teel and Cushing 1930.)

Pituitary and Hemopoesis:

Hubble (1933) gives experimental and clinical evidence to show that the pituitary may influence the blood picture. He shows that:

1. Thyroid extract stimulates the production of red blood cells and lymphocytes and depresses the output of the granulocytes,
2. The adrenal cortex stimulates granulocytopoesis and the red blood cells,
3. The basophils of the anterior pituitary stimulates all types of circulating cells. He shows that a lack of the anterior pituitary would give the reverse, indicating this gland plays a role in Hemopoesis.

Wilson (1937) showed that injections of antuitrin-S or anterior pituitary lobe substances caused a marked leucocytosis but no change in the erythrocytes. It was also noted that with short intervals between the injections, they become ineffectual, but when ten to fourteen days are allowed to elapse, the initial response may again be obtained.

Pituitary and Hypertension:

Strecker (1931) had a patient with what seemed to be a hypopituitary condition which showed a peculiar sugar tolerance curve, hemiplégia and hypertension. Since then quite a number of clinical cases have been watched for pituitary disturbances when hypertension was present.

Cushing (1933) states that the hypertension may be due to the basophiles invading the posterior lobe of the pituitary, coming from the anterior portion of the gland, because he found some cases which indicated this. There were some contrasting findings; that is, there were cases of invasion where no hypertension was found and some with no invasion but had hypertension.

Close (1935) demonstrated a basophilic adenoma of the pituitary in which the only symptom was that of high blood pressure.

Blount (1936) in his experiments in hypertension in experimentally produced hyperpituitarism concludes that the thickening of the basement membrane is a result and not the cause of essential hypertention and that the pituitary has some effect.

Rasmussen (1936) in a careful cell study on the basophil cells of the anterior pituitary could see no relation between these cells and hypertension.

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