Anterior pituitary body and its relation to the reproductive function

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ANTERIOR PITUITARY BODY AND ITS
RELATION TO THE REPRODUCTIVE FUNCTION

SENIOR THESIS

BY

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COLLEGE OF MEDICINE
APRIL 1934
A. Hypophysis, Anterior lobe (female)
B. Genital Hormones
C. Growth Hormones
D. Synergistic Hormone
E. Thyroid Gland
F. Ovaition Hormone
G. Luteinization Hormone
H. Ovary
I. Suprarenal Glands
J. Graafian Follicles
K. Corpus Luteum
L. Cornification
M. Hormone "A"
N. Hormone "B"
O. Nucification
P. Vaginal Mucosa
Q. Inhibitory Hormone
INTRODUCTION

The outline of this work follows in sequential order the functional phases of the female mammalian organism—puberty, menstruation, pregnancy, lactation and menopause. These physiologic phases are mainly governed by the development, and later decline of ovarian function, which is in turn, controlled by fluctuations in function of the anterior pituitary lobe, and other related glands of internal secretion. This monograph is a survey of the literature the purpose of which is to correlate the evidence which leads to our present concept of the anterior pituitary body, and its relation to the reproductive function in female animals.

The clinical application of our present knowledge is limited and has led to many conflicting results. However, judging from the rapid advancement in the past, we are safe in predicting a very fruitful future especially with endocrine therapy.

I chose this subject to familiarize myself with a subject exceedingly fascinating and appealing, and, one which is rapidly becoming popular both in the early recognition of clinical syndromes as well as favorable therapeautic results.

Endocrinology is in its infancy and is in the experimental stage. Typical clinical cases relative to this particular subject were not available, consequently laboratory animals and experimental results have been substituted.
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HISTORICAL

Our earliest conception of the function of the pituitary gland came from Galen. His idea was that it acted as a filter for the sedimented waste products of the brain and that these passed out through the infundibulum as a "pituita" or slime from the nose. As late as 1631 Robert Flood explained the etiology of coryza on the principle of a siphon action between the ventricles and the nose. In Thomas Gibson's anatomy (1688) it is inferred that in animals such as calves, who have a large pituitary with rich arterial supply the gland seems to have the same relationship to the arterial plexus as the pineal body has to the choroid plexus; its purpose is to separate serous fluid from the lymph.

Very little progress was made in the study of the pituitary body until Pierre Marie (1866) (98) made the discovery that acromegaly was associated with tumors of the gland. This brilliant observation was confirmed by Minkouski (1887) and many other investigations since. It turned a new page in the history of hypophyseal physiology.

To be sure acromegaly and gigantism were recognized as clinical entities known to be associated with hypophyseal tumor-faction. (Pierre Marie (98) and Minkouski (41), but Pechkranz (1899), Frolich (1901), Axenfeld (1903), Muller (1905) (108) and others were calling attention to existence of tumors of the gland or its neighborhood associated with combinations of optic atrophy, amenorhoea, infantilism, adiposity, and often, diabetes insipious. A relationship between the hypophysis, and genitalia
was, consequently, inferred, but not understood.

As early as 1898 following the work of Howell (86) special attention was given to individual lobes of the gland. Much experimentation has been done since to determine the effects of extirpation of the whole gland or part of the gland, feeding the separate lobes together and separately and the administration of extracts of the various lobes individually and collectively.

Prior to the work of Paulesco (1907) (113) a Roumanian investigators, the generally accepted opinion was that the pituitary body was a vestigial structure and of no consequence to the organism. Total extirpation of the hypophysis of experimental dogs resulted in their death. Thus, he concluded that the pituitary gland is "essential to life". Crowe (25), Cushing (27) and Homans (1910) (85) reported the complete removal of the anterior lobe alone resulted in a characteristic train of symptoms termed, "Cachexia-phypophyaeopriva," resulting in death of the animals, therefore confirming Paulesco's (113) observations.

Before proceeding with the main issues of this paper it will be necessary to briefly review the anatomy and histology of the pituitary gland. It is an ovoid shaped mass about the size of a pea, situated within the sella turcica at the base of the brain just behind the optic chiasm. Upon sagittal section the gland is seen to consist of an anterior and a posterior portion. The anterior lobe or pars anterior is larger and has a glandular structure. Embryologically it does not belong to the brain but is developed from a pouch in the primitive oral cavity. It is without a duct, as it is one of the glands of internal secretion.

Histologically the gland is composed of three parts:
(1) the large anterior epithelial lobe, pars anterior; (2) a much smaller pars nervous or infundibular, pars posterior, and; (3) the pars intermedia. The ectoderm of the mouth (Rathkes pouch) originates the anterior lobe which soon becomes a glandular structure. An outgrowth from the floor of the infundibular pouch of the telmencephalon, the mid-brain, develops the posterior lobe. The posterior lobe consists of two parts: (1) the neuroglia cells and fibers with ependymal cells and; (2) the pars intermedia composed of epithelial cells from a diverticulum of buccal epithelia, the posterior pharynx and is ectodermal in origin.

The anterior lobe contains cells which are clear in hold, in their protoplasm varying amounts of granules, which stain deeply. It contains three kinds of cells: (1) the "hauptzellen," (2) eosinophiles, (3) basophiles. Erdheim and Stumme (51) call the eisinophiles or acidophiles and basophiles or cyanophiles because their protoplasm intensely takes the stains, the chromophiles, while the "Hauptzellen" they call chromophobes because their protoplasm is difficult to stain.

Rasmussen (115) by means of reconstruction of cross sections of many glands, determined the relative number of these cells. He found that the chromophobe cells make up the largest percentage (52%), the eosinophiles occurred in 37% and the basophiles 11%.) In advanced age the chromophiles were unchanged. The eosinophiles are located in greater number in the anterior portion of this lobe near the margins of the alveoli. The chromophobes and basophiles are located in the center of the columns and are present in large numbers in the posterior part and near the stalk of the infundibulum.
The importance of these cells in the secretion of the hypophysis, and their relationship to the general metabolism of the organism has been the subject of much speculation and experimentation during the past decade.

W. P. Covell (24) has shown that the growth in weight of the anterior hypophysis during embryonic and early fetal periods is very rapid. The hypophysis and its lobes grows in weight similar to the increased weight of such vital structures as eyeball and mid-brain. The hypophysis of the full term fetus, consists mostly of pars anterior, roughly 78% (2% pars intermedia, 20% pars nervosa.)

The generative glands of the embryo is under the influence of the maternal pituitary and the sex characteristics are developed up to an infantile state which is complete at birth (Benjamin.). Evans (1928) (44) and Smith (1929) (125) found by experimentation on pig fetuses that the growth hormone appears earlier than the sex hormone. The anterior lobe of the hypophysis of infants does not function as yet. The internal secretion of the infantile sex gland is dormant, the sexual characters do not develop to maturity. Now comes the "great intermission" (Benjamin) (11).

The meaning of this intermission can be understood if one considers that the infantile body is not equal to or capable of a sudden sexual precocity. During the prepuberal period the internal secretion of the anterior lobe is being utilized for general growth. (24) After the organism has been developed and strengthened, the pituitary assumes its activating functions. The incretions of the sex glands become lively and the sex characters rapidly grow to maturity. With the advent of puberty and corresponding falling off in the rate of growth, quantities
of the anterior hormone are set free for the promotion of ovarian development. The ovaries increase in size under pituitary stimulus (Engle) (32). It begins to secrete the oestrin-producing hormone which is responsible for the onset of puberty. This state of maturity lasts with individual variations up to senescence. Then the decline sets in, the pituitary grows inactive, the incretions of the generative glands cease, the entire endocrine system suffers through this cessation, the sex glands retrogress, thus causing the state of maturity to disappear. This sequence of events shows the importance of the pituitary in the mechanism of the development and establishes a "biological law of puberty."

The old concept regarding the hormones responsible for the onset of puberty, as shown by Mazer and Hoffman (102) and many others, was that they were derived from the Graafian follicle and its successor the corpus luteum. The old puberty gland theory of Steinach (11) attempts to correlate the seat of the hormone production in the interstitial cells of the ovary and testes which he claimed induced puberty and maintained sexual activity. These views were violently disproven by the modern concepts established by the rigid and fruitful experimentation of Smith (123, 124, 125, 126, 127, 128) Smith & Engle (129, 130) and Ascheim and Zondek, (150, 151, 152) and many other investigators.
IMPLANTATION EXPERIMENTS

Foa (109) as early as 1900 suggested that the periodic changes in the ovary depend upon some force external to and distinct from the ovary. He found that the ovary of the immature animal grafted into an ovariectomized adult soon attained the state of maturity. The association of these findings with the clinical observations of Marie (1889) (98), Frolich and Cushing (27) clearly pointed to the anterior pituitary lobe as the origin of the cyclic ovarian changes. The complete dependence of the ovary upon hormonal influence of the hypophysis was not realized however, until the independent and almost epoch making discoveries of Smith and Engle, and Zondek and Ascheim was effected. The independent work of these American and German investigators published almost simultaneously, represent one of the most brilliant advances in our knowledge of sex physiology.

Previous to 1921 many attempts to obtain a promotion of growth and the stimulation of the ovaries of laboratory animals with various preparations of the anterior lobe, and although one or two successful results were obtained the evidence on the whole was not conclusive. Klinger (89), Hofstatter (48), Clairmont (19) attempted with negative results, the transplantation of the fresh living gland. Smith (125) in 1926 used daily transplants of the anterior lobe with attempt to overcome the effect of hypophysectomy on white rats. He found that not only was he able to restore an almost normal growth rate, but in addition there was partial repair of the injury to sex glands. Smith (123), Smith and Engle (129) extended the study of anterior pituitary transplantation, using immature, female rats for recipients of
transplants from full grown males or female rats and mice and were able to promote sexual precocity in them by only four daily treatments. A whole fresh anterior lobe was implanted intramuscularly into the recipients. There was establishment of, with striking rapidity, the virginal canal, uterine hyperemia, oestral "accumulation of fluid, a formation of large follicles and corpora lutea. At autopsy the sex organs showed tremendous hypertrophy the ovaries gave evidence of ovulation and many ova were found within the Fallopian tube. The changes that took place within these precociously mature females corresponds to those normally occurring at sexual maturity.

Ascheim and Zondek (150) working independently and simultaneously with the above authors, also by a series of classical experiments upon young white mice, succeeded in producing sexual precocity by similar transplantations of anterior lobe tissue. They found that not only the glands obtained from immature and senile animals was effective, but those from human subjects and cattle as well. They used transplantations of thyroid, testes, pineal, thymus, adrenal cortex and medulla, and posterior pituitary body with no effect in bringing ovarian function into action. Only anterior lobe of pituitary gland was shown to produce effect. They conclude: "If an infantile mouse of six to eight grams weight receives an implantation of a small piece of fresh anterior lobe from man and animal then after 8 to 100 hours the mouse is in state of oestrus. By the implantation the active principle, i. e., the hormone of the anterior lobe is given to the mouse. The hormone of the anterior and only this sets in action the latent ovarian function and thereby brings the infantile mouse to sexual maturity." These outstanding
works of Smith and Engle and Zondek and Ascheim have received abundant confirmation from numerous sources: Biedl (12) Ehrhardt (42), Lipschultz (95), Brouha and Simmonet (17), and others. These works show that a substance is elaborated by the anterior lobe which stimulates the formation of corpora lutea in ovaries of normal, mature and immature animals.

Male anterior lobes are as effective as female ones: thus Zondek (150) implanted glands from a cow and a bull, from a man and a woman, and from a woman four years after climacteric, the glands being obtained shortly after death. In all these cases a positive result was obtained, oestrus occurring in mice together with enlargement of the uterus and ovaries.

Evans and Long (1921) (49) and Evans (1924) (43) reported remarkable results on the reproductive system of mice and rats by intraperitoneal injections of properly prepared extracts of the anterior lobe of beef pituitaries. The results consisted chiefly of an inhibition of ovulation, and stimulation of the luteal tissue of the ovaries, so that many corpora lutea were formed. These observations may have been the starting point of the newer knowledge of the subject, but are different from the classical studies of Smith and Engle and Ascheim and Zondek discussed above.

Slonaker (1927) (122) questioned the criterion by which Smith and Engle based their conclusions of sexual precocity—establishment of vaginal canal, uterine hyperemia, oestral accumulation of fluid, and formation of large follicles or corpora lutea—as an inadequate sign saying, "Smith apparently did not try the crucial test of sexual maturity by mating the
animals." He overlooked the fact that it had been clearly shown by Smith and Engle (1922) that mice mated as early as the 20th day of life after two daily transplants. Ovulation also occurred at time of copulation. Furthermore, Engle (35) reports that of 63 immature rats when implanted with anterior pituitary gland exhibit a ruptured vaginal plate three or four days after first treatment, thirty-seven of the sixty-three mated during the first oestrus, thirty of the thirty-seven were killed and found that ovulation had occurred in eleven. Succeeding oestrus occurred at a significantly later date than the first oestrus for normal mice, and also first pregnancy. He thinks that it is possible that induction of oestrus delays the appearance of normal cycle.

Daily injections of extracts of gland into female rats caused the immediate cessation of the normal oestrus cycle, the cycle remaining in abeyance during the period of injection. Examinations of the ovaries found them to be filled with substantial corpora lutea. Long and Evans (49) concluded that these extracts were not only toxic to developing ova, but also had stimulating effects on the growth of luteal tissue. This observation was substantiated by Teel (136) and also Bellerby (1928) (10).

Implantations of anterior pituitary gland into adult mice and rat causes an increased weight of both ovaries. Smith and Engle (129) state that the adult ovaries of rat may be doubled in weight by only six or eight transplants. This increased weight of ovaries is caused by the development of large number of follicles followed by super-ovulation in young and adult, by the excess number of corpora lutea which are formed after ovulation.
Hoffman (82) in studying the effects of hypophyseal implantations upon the ovaries of old sexually degenerated mice, concludes that the implants not only are capable of initiating ovarian function in immature mice but in old menopausal mice. Old non-oestral mice when once stimulated can be kept sexually active for considerable time without further stimulation. These implants may act by mobilizing the latent residual hormone of the senile ovary. In one experimental animal ovulation was restored and succeeded by the gravid state.

Allan (2) in attempt to extend these experiments on to primates made small subcutaneous implants of fresh pituitary lobes into flank of immature monkeys (Macacus rhesus). A total of four implants of two day intervals was made. In seven days the treatment there was a morbid development secondary sexual characteristics and considerable growth in the genital tract and mammary glands. The ovaries were markedly enlarged and contained many follicules filled with liquor folliculi. He interprets the marked effects on sexual characteristics and growth of genital tract and mammary gland, as being apparently secondary to the marked ovarian development, noted by Smith and Engle (129) anterior lobe implants have no effect upon castrated animals.

In view of the results of transplantation feeding experiments were begun by Wulzen (148, 149) and Goetsch (1913-14) (72). The former gave the fresh while the latter fed the dried gland to young animals. The results were entirely contradictory, for whereas, Wulzen found a retardation in growth of the young fowls, Goetsch showed that the feeding of anterior lobe to young rats resulted in the development of the sexual glands, as well as a stimulation to body growth. This latter investigator also reported that the ovary of the pituitary fed rats contained a large number of corpora lutea. Marimus (1919) (100) reported
somewhat similar results.

This work of Coetsch (72) has not been corroborated by other investigators. Schaeffer (1912) and more recent work by Long and Evans, Frank (65, 67), Sisson and Broyle (121) have shown that oral administration has no effect on date of maturity in rats. Clark (20) maintained that he was able to stimulate the ovaries in hens, as evidenced by increased egg-laying by feeding fresh anterior pituitary glands.
HYPOPHYSECTOMY

By pituitary ablation an opposite response of the sex apparatus results before sexual maturity. The complete establishment of the vaginal canal is delayed and the genital system remains undersized. Total hypophysectomy in the rat (Smith-(27) (123) causes an immediate cessation of the oestral cycle, which is reestablished when replacement therapy is instituted. The ovaries in these hypophysectomized animals show no large follicles in the various stages of development (Smith and Engle --27 (129).

Cushing (27) and his co-workers recognized the condition produced in full grown animals, was identical with the pathological condition dystrophia adiposo genitalia, in addition to the adiposity there was marked atrophy of the uterus, and whilst follicles disappeared from the ovaries there was persistence of the interstitial tissue. Furthermore, partial removal carried out in young animals resulted in persistent infantile condition of reproductive organs. Similar results have been reported by Oschner (5) Bredl (9) Dott (30), and Bell (12). The destruction of the pituitary gland by injections of chemical substances, also resulted in marked disturbances in the reproductive system (Smith) (126), Walker and Caeser) (140), Fraenkel) (68) and Ford) (63), after x-radiation of pituitary region in rabbits report hypoplasia of genitalia. Smith (126) has succeeded in restoring the normal condition of degenerated sexual organs of hypophysectomized rats by grafting into them portions of the gland.

The results of these investigators not only prove the endocrine nature of the anterior lobe of pituitary, but also show the development and activity of the reproductive system to be dependent upon secretions.
CASTRATES

Fischera (1905 quoted from Bell) (9) observed in various mammal that the hypophysis increased in volume and weight after castration. According to the same author an increase of the eosinophile cells both in number and size takes place in castrated cocks and certain castrated mammals (rabbits, guinea pigs, buffalo) Tandler and Grosz (1908). Kolde (1912) found that total extirpation of ovaries produced hypertrophy of the pituitary, the increase being due to the increase in eosinophile cells and a new type of vacuolated "signet rings," cells which they called "castration-cells."

Van Wagenen (1925) (139) pointed out that the "castration-cells" were basophilic elements. In 1927 Addison and others described findings of anterior pituitary in castrate cats. The changes consisted largely of an increased number of large basophile cells and also in appearance of the "castration-cells", mentioned above. Engle (32) related the increased gonad-stimulating potency of the castrates pituitary body to presence of the basophile "castration-cells", being "led to suspect that it is the basophile cells which elaborate the gonad-stimulating factor in the castrates". Engle also made clear that not only those basophilic cells increased in number after castration, but they also show enlargement and vacuolization of basophil granules, presumably due to storage of hormones.

Englebach (41) states that there are two histologic changes of the anterior pituitary which occur following castration, namely, (1) the appearance of the "cells of castration" and (2) a relative increase in the number of eosinophiles. He states
that these "cells of castration" are enormous cells two or three times the size of an eosinophile, basophile or chromophile. The protoplasm stains distractingly pink or neutral with eosin and methylene blue. Evans (43) believes they are basophiles probably derived from the chromophiles as their relationship to the sexual function would indicate their source. The investigations of Lehman (94) on the pituitary body of castrate animals show that the normal histological picture of the gland can be restored by injection of the follicular hormone.

It has therefore been conclusively shown by Van Wagenen (1925), Engle (1929) (33) Evans and Simpson (44) that the pituitary sex hormones are derived from the basophilic cells. In addition they have shown that the anterior lobes of castrated animals are more potent in producing premature maturity than similar lobes from normal animals. Also Fluhman (60) has shown that following total extirpation of the ovaries in women there is a large amount of anterior pituitary hormone in the blood which is readily demonstrable by the Ascheim-Zondek test.

The gonad hormones, of either sex exert a depressing effect upon the hypophysis which results in a diminished amount of the sex-stimulating factor available to the organism (Moore and Price) (105). Consistent with this observation Engle (1929) (33) and Evans and Simpson (1929) (46) demonstrate that the removal of the gonads—testes or ovaries—lead to a greater sex-stimulating capacity of the hypophysis. The depressing effect of the gonads secretion, only incompletely shown by the normal animal, becomes apparent when the gonads are removed. Fluhman (1929) (60) finds in women two months to sixteen years after ovariectomy, as well as women at the menopause. Meyers, Lenard, Hisaw, (30) (104)
injected normal female rats with oestrin for thirty days and the hypophyses of these injected females were far inferior in their ability to stimulate gonads than the hypophyses of their untreated controls. The prolonged administration of follicular fluid can produce histologic changes in the anterior pituitary lobe of guinea pig, (as manifested by hyperemia and increase in acidophilic cells (V. Bisceglie) (62). Kunde (92) stated that oestrin injected in a dog resulted in lessening the size of anterior lobe of hypophysis with diminution in the amount of cytoplasm in chromophobe cells.

Ovaries from immature female rats have been grafted into normal adult and castrated male rats. (Engle) (33). These grafts will grow in either the normal or the castrated male, if vascularization is established. There is not sufficient gonadal-stimulating factor from the anterior lobe of the host to cause a high degree of follicular development in these grafted ovaries. However, additional stimulus has been given by daily homeo-transplantations of the fresh anterior lobe. (Engle) (38).

It has long been known that complete compensatory hypertrophy of the remaining ovary will occur in rats and rabbits after one ovary has been removed.

Hansen & Boon (26) found that if the tubes of one ovary is tied off, but the ovary left intact, the other ovary produced no more than the usual number of ova. They interpret this to mean that the ovaries have a mutually inhibiting mechanism perhaps a new hormone by means of which each ovary inhibits the other from growing beyond a certain size or producing over a certain average number of ova per ovulation.

Lipschultz (95) in his law of constant follicle number which
is supported by a great deal of convincing experimental evidence clearly stated that the factor which causes follicular growth and compensation hypertrophy is to be sought from some extragonadal source. The experimental findings regarding the role of the anterior pituitary lobe on the development and regulation of the genital system of female indicate that this gland is the source of the factor responsible for follicular development and therefore the determining factor for compensatory hypertrophy of the ovary of the unilateral or subtotal ovariectomy.
THE SEX HORMONES

From the foregoing it is shown that the anterior hypophysis has no effect on the vaginal tract or uterus in ovariectomized animals. Moreover, the ovarian hormone when injected into normal animals does not produce any effect upon the ovaries, but apparently only acts upon the uterus and vagina. Lipschultz (1927) (95) suggested an extra-gonadal factor which he thinks responsible for initiation of the ovarian activity. Since the work of Smith and Engle and Ascheim and Zondek he concludes that the anterior pituitary tissue produces the X-factor. This same X-factor was responsible for the development of hetero-sexual ovarian grafts. Kraul (91) referred to the anterior pituitary gland as the "regulator." Zondek and Ascheim (150) made the following conclusion "the anterior lobe hormone is the motor of sexual function. The anterior lobe hormone is primary, the ovarian the secondary. The anterior lobe hormone brings the follicular apparatus into action, fires off follicle-ripening hormone and mobilizes the secondary ovarian hormone in the follicular cells. This then acts, in a specific way in the uterus and vagina."

Evans and Simpson (45, 46, 47) attribute the alterations produced in the ovary by anterior pituitary lobe to two hormones. These are first, a "growth hormone" which is closely related to the eosinophile cells of the pars anterior and a "gonad-stimulating" hormone corresponding to the basophilic cells. They state that these two hormones are antagonistic to one another and can be completely nullified by simultaneous administration.

Bellerby (10) also believed that there are two anterior pituitary hormones, namely, an "estrous-producing" and an "estrous-inhibiting hormone," while Ascheim goes still farther
and attributes three hormones to the anterior hypophysis. (1) the growth hormone (2) the luteinizing hormone and (3) the ovulation hormone. Wiesner and Crew (143) substantiate Ascheim's findings. Phillip Smith of New York, who has done some most convincing work upon hormones of the hypophysis, is inclined to think that there is only one pituitary sex hormone, and that the cytological and hormonal effect upon the ovarian follicle are merely a continuation of the action of one active principle.

The effect of the ovulation hormone is the rupturing of the ovarian follicle and liberation of the ovum at maturity. The luteinization hormone causes the hyperplasia of the lutein cells of the persistent Graafian follicle during gravidity. In addition there is probably a reverse action of the follicle upon pituitary gland (Moore) (106). There is a potent active principle of the ovary which produces inhibition upon the hypophysis. This is important in so far that it would contra-indicate the use of gonad hormones as a means of stimulating either ovarian or testicular function. The injection of ovarian preparation for gonadal anomalies due primarily to pituitary disorders would tend to increase instead of diminish them.

That there are two gonad-stimulating hormones produced by the anterior hypophysis is the common opinion of the majority of investigators. The extraction and separation of these, however is another problem. Some investigators have succeeded in separating these factors. Evans and Long (49) state "if alcohol is added so that the concentration is brought to 50% and the precipitated protein centrifuged of the supranatant fluid induce ovulatory factor but not growth promoting factor. Alkaline extracts contain the
growth promoting factor and produce gigantism." A similar method has been reported by Fevold Hisaw and Lenard(53).

Aschheim and Zondek (151) have isolated a gonad-stimulating hormone extracts from the urine of pregnant women. These extracts have the combined physiological properties of follicle-stimulation and luteinizing factors which they term "prolan". They have also prepared factors said to have separate properties individually and call these "prolan A" and "prolan B". "Prolan A", follicle ripening or estrus producing substance motivates the ovarian follicle to production of "estrin", which in turn induces proliferation phase of endometrium, "Prolan B" is luteinizing principle which transforms the granulosa and theca cells into lutein cells and therefore motivates progestin (lutein) to change proliferative stage of the endometrium to a secretory one. (Pre-menstrual or pre-gestational stage) The chemical identity of prolan A & B is not understood. It is possible that we are dealing with different isomers of the same molecule. Prolan B is doubly important because it is the basis for the Aschheim-Zondek test and second because it is being used therapeutically with favorable results.

The luteinizing hormone cannot act on the immature ovary. The immature or infantile ovary must be stimulated to follicular activity by the gonad-stimulating hormone before a characteristic "mulberry" ovary can be produced. (Fevold, Hisaw and Lenard)(53) Hence the governing role of the pituitary over the ovary is characterized by a duality consonant with the duality of the pituitary and ovarian hormones (Novak)(111).
On the basis of the results obtained from implantation of the anterior pituitary gland. Ascheim and Zondek have evolved a test for the hormone which promises to be of considerable clinical importance. The substance to be examined is injected into an immature mouse and in a positive test evidence of estrus (vaginal smear, hypertrophic uterus) is observed in about one hundred hours from the time of the first injection. The animal is then sacrificed and serial sections of the ovaries are carefully examined. According to Ascheim (5) there are three morphological changes in the infantile ovary under the influence of hypophyseal hormone. The immature mouse ovary contains only primordial follicles and small Graafian follicles without cavities. The first change is growth of the follicle leading to rupture and discharge of the ova into the tubes, second occurrence of hemorrhages in many of the enlarged follicles which are visible to the naked eye as cyanotic spots, finally atretic corpora lutea are formed in the ovary by luteinization of the follicles which are not fully matured.

The criterion upon which this test is interpreted is as follows:

A.P.R. I. (Anterior pituitary reaction one) - The presence of ripening Graafian follicle or of recent corpora lutea.

A.P.R. II. (Anterior pituitary reaction two) - The finding of "Blutpunkte" small reddish pinpoint grossly visible in the ovaries & representing himorrhage into normal and abnormal follicles.

A.P.R. III. (Anterior pituitary reaction three) - The app-
earance of lutein cell transformation in follicles and the formation of corpora lutea in which ovulation has not occurred and the ovum remains imprisoned (pseudo-corpora lutea, corpora lutea atretica).

The finding of any one of these changes is considered a positive reaction for anterior pituitary substance, but it is of interest to note that the first reaction compares to that resulting from the implantations of fresh anterior pituitary gland substance, whereas the third reaction was obtained by Evans & Long (49) with their alkaline extract of bovine glands.

These three morphological changes are available as an exact test. (Ascheim-Zondek Test), for the presence of anterior hypophyseal hormone and thus have made possible to study the relation of the anterior hypophysis to the organism. It was by means of this test that Zondek isolated the anterior lobe hormone extract, "prolan".
PREGNANCY CHANGES

The effects of the gonads on the pituitary gland during pregnancy has been noted since Comte' (1898) described a hypertrophy and hyperplasia of the pars anterior, the pars posterior remaining unaltered. Erdheim and Stumme (1909)(51) observed the anterior pituitaries of pregnant women and showed that the hypertrophy is accompanied by histological changes and called attention to peculiar cells-Schwangerschaftszellen--noticing that they differ from the basophile and eosinophil cells, and suggest that they arise from the chief or Chromophobe cells.

(Reserve cells of Addison)(1) These cells have no demonstrable granules (Evans)(43). Cushing (27) reported similar hypophyseal findings in pregnant dogs, cats and rabbits; Kolde in guinea pigs, Lehman(1921)(94) in pregnant rats.

The hyperplasia of these "cells of pregnancy" is sufficient to cause an enlargement of the hypophysis during pregnancy (Englebach)(41) Coincidentally, with their appearance there is a decrease in chromophobe cells.

In addition to the increase of "pregnancy cells", the cytoplasm of the new cells become faintly acidophilic (Erdheim & Stumme)(51). The pituitary change of pregnancy as compared to the normal are now interpreted as a hyperplasia of eosinophiles the addition of the specialized "cells of pregnancy" (Englebach) (41). Little reference is made in the literature relative to their origin. Kraus (90) considers them a type of eosinophile.

The recent developments of the function of both the chromophobes and basophiles definitely relate them to chromophobe. It is probable that they are a type of basophil cell, directly developed from the chromophobes.
Pregnancy-type pituitary bodies may be produced in normal female mice through luteinization of the ovaries by means of continuous anterior lobe implantation. (Hotereu & Charypei)(75) The ovary is an essential intermediary agent as indicated by the fact that similar pituitary implants in castrates animals were ineffective in inducing pregnancy changes (Teel)(136). The hypertrophy of the anterior pituitary lobe during pregnancy is possibly a direct effect of the ovarian follicle hormone, which is present in abundance in blood during course of gestation.

The "pregnancy change" of the pituitary may also be produced in non-pregnant castrated and non-castrated females by injection of placental extracts (Berblinger)(13). In this connection the effects of implantations of the anterior pituitary gland in pregnancy is important. The treatments invariably produce an abortion (Ehrhardt & Wiesbader)(42) especially if given during first 2/3 of gestation.

Daily transplants of the fresh anterior lobe to mice and rats in first trimester of pregnancy prevents implantations of ova or lead to abortion, if treatment is begun during the mid-trimester of the period of gestation resorption or expulsion of fetus takes place. Pregnancy is interrupted less often when treatment is begun in the last trimester of pregnancy. (Engle & Mermod)(39) The gonad-stimulating hormone of the anterior pituitary introduced by the fresh transplants results in the production of a large number of ovarian follicles. (Evans & Simpson)(48) (Engle)(34). The ovarian hormone thus produced causes a proliferation of the uterine mucosa bringing about a condition
similar to that of normal oestrus. Pregnancy seems to be incompatible with this condition. Parkes (112) and Bellerby (10) suggests two possibilities for the mechanism responsible for upsetting pregnancy with follicular hormone. They are inclined to regard the large number of resorptions occurring as due to an inhibition or over-ruling of the action of the corpus luteum, and also the local disturbance of uterus consequent upon an effort to assume an oestrus condition.

Different authors have emphasised that the corpus luteum is a gland with an internal secretion, which causes by its hormone action, the cyclical uterine changes of mens truature and the changes which the uterus undergoes in pregnancy. Frauenschel (68) showed that pregnancy can be brought to an end in a rabbit if the corpora lutea are destroyed by cauterization during the first six days after conception, furthermore he demonstrated that the next mens truature can be prevented in man by cauterization of a fresh corpus luteum has in all mammals the same glandular function. Hammond also confirmed these results.

Removal of the hypophysis ends all functional activity of the sex glands. Without the hypophysis there is no follicle maturation, no impregnation. If on the other hand the sex gland is removed, the anterior hypophysis keeps on functioning but indeed puts out more hormone (prolan). With prolan, Ascheim (150) was capable of initiating every phase of the genital cycle. The follicle is made to mature and to rupture. The liberated ova migrate through the tubes into the uterus. Zondek succeeded in fertilization of such ova in an infantile animal and thus preg-
nancy was produced in an infantile rat by means of prolan. With "prolan" they were also able to induce follicle maturation and lib-
eration of ova even in pregnant animals and thus to annihilate the
general accepted law of ovarian dormancy during pregnancy. By
means of prolan in senile animals the quiescent ovarian activity
can be restored with rhythmic return of the estrus.

In general the hypophysis increases in size and weight (pars
anterior) at the end of pregnancy the "Hauptzellen" cells are in-creased so much in number that the eosinophiles unchanged in num-
ber take the second place. After delivery these "pregnancy cells" de-
crease and at end of second year after delivery the eosinophiles
are again predominate. The number of basophiles remain the same
during pregnancy. The "Hauptzellen" cells in time atrophy, how-
ever, during succeeding conceptions they reappear in larger num-
bers than in previous one (Englebach)(41). It is claimed that
skilled histologists can diagnose a former pregnancy from the pit-
utary gland.
LACTATION

Implantation of the anterior hypophyseal substance into senile male rats causes a definite increase in sexual activity and increased weight of the accessory organs of reproduction (Evans & Simpson)(43). During recent years much work has been done on lactation mechanism. Since the mammary gland normally undergoes enlargement and histological change preparatory to the secretion of milk during pregnancy only the cause of this modification has seemed to lie in some effect exerted by one or another of the three new structure, which appear in the pregnant animal, namely the fetus (Halban 1905)(83) the placenta and the corpus luteum of gestation (Boian 1911)(15) of the conjecture and experimentation have been devoted chiefly to the corpus luteum.

Evans (43) has shown that implantation of the anterior hypophysis substance into senile male rats cause a definite increase in sex activity and increase in weight of accessory organs of reproduction. Implants or extracts of the anterior hypophysis substance cause marked hypertrophy of mammary gland in the rat when ovary is present but they are incapable of doing so after ovariectomy.

Parkes (1929)(112) in an ingenious application of the discovery of Evans showed that alkaline extracts of the anterior lobe of hypophysis induce in female animals luteinization of Graafian follicle and also cause persistence of pre-existent corpora lutea.

Evans & Simpson (43) states that the corpora lutea is not responsible for the stimulus of mammary hyperplasia. Mammary hyperplasia is notoriously easy to produce in rabbits, but much more difficult to provoke in rats (67). Evans & Simpson injected
spayed virgin rats with alkaline extracts of beef anterior hypophysis for 20-30 days. The results were that the mammary glands of castrates did not respond.

Corner (23) tested the effect of his luteal hormone "progesterin" on the mammary hyperplasia with the spayed and now-pregnant female rabbits with negative results. On the other hand he secured mammary hypertrophy and active hyperplasia on injection of an extract of sheep's hypophysis in virginial spayed animals. The presence of ovary did not increase or alter the extent of the reaction produced. He concludes that the extracts of sheep hypophysis produce change in the mammary gland of rabbits resembling those occurring in pregnancy and leading to secretion of milk. The effect doesn't depend on ovaries for it can be produced in animals spayed at beginning of the experiment. Very likely (he added) the mammary gland must be first subjected to the influence of Fecestrin" (ovarian follicle hormone) and thus be brought into full prepubertal condition at time of spaying and beginning of injection.
MENOPAUSE

In all species at a certain age the cyclical phenomena gradually becomes less marked and eventually cease, whether this cessation is due to exhaustion of the follicles or whether another mechanism comes into play, has not been determined. The fact that Steinach (11) and Hoffman (62) have been able to reactivate senile females by implantation of anterior lobe pituitary fragments speaks for a more complicated mechanism than merely cessation of function due to exhaustion of follicles. Fluhman (60) and Goldstein (101) have shown that the anterior lobe assumes increased function with the advent of the menopause. It is not known definitely, however, which type of hypophyseal cell is responsible for the excess production of the hormone in menopausal women.
CONCLUSION

Therefore it is seen that the existence of a definite relationship between the anterior pituitary gland and the female pelvic organs has been established. The administration of the gland produce profound changes of the ovary, the transplantation of the fresh gland stimulates the immature ovary to activity, during pregnancy and following castration there is a gross hypertrophy of the anterior lobe and an increase in the amount of the hormone in the blood and urine of the patient. Hypophysectomy results in an atrophy of the genitalia. A simple test for the anterior pituitary hormone, which is of value in the diagnosis of early pregnancy, has been developed. Fore-going reports leads one to believe that an active preparation will in time be available and the indications for its use understood.

Undoubtedly a great deal yet remains obscured, but the tremendous advances of the past few years lead one to anticipate a new era in our conception of the physiology and pathology of the female sex glands and of the interrelationship of certain other endocrine glands.
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