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## Relation of the anterior pituitary to ovarian function

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THE RELATION OF THE  
ANTERIOR PITUITARY TO OVARIAN FUNCTION

BY

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## THE RELATION OF THE ANTERIOR PITUITARY TO OVARIAN FUNCTION

In the last ten years especially, there has been demonstrated and proved, a definite relationship between the pituitary and the sex glands. This is of importance to every clinician, and gynecologist.

In order to understand these various phenomena produced by the internal secretion of the pituitary, it is advisable to give here a brief discussion of the anatomical structure, with slight reference to histology.

### ANATOMY AND HISTOLOGY

The pituitary body is situated in the cranium at the base of the brain, surrounded by a bony encasement the sella turcica. It is connected to the brain by the infundibulum, which passes through an opening in the dura lining of the sella. It almost completely fills the cavity of the sella turcica, and its weight in men is approximately the same as in women, except in pregnancy when it is markedly increased. Since we are discussing the anterior lobe and its function especially, we will briefly go further into its anatomy, and histology.

The anterior lobe constitutes the greater part of the pituitary as a whole, is kidney shaped, concave on the posterior side, firm in consistency, and is epithelial and glandular in structure. Biedl(I) alone has attempted to relate the histology of the pituitary to its function or the activity of its various hormones. He has recently attributed

to the individual chromophil, basophil, and eosinophil cells of the anterior lobe, the function of secreting differentiated hormones, which may influence the growth of the osseous or genital systems. The experimental work of Smith and Evans (2) tends to prove, as we will show later, that the anterior lobe definitely affects the growth of the osseous system, and the development AND FUNCTION of the genital system. It is the latter we are interested in, in this article, and with special relationship to the ovary and its function.

#### HORMONES IN GENERAL.

The student of the anterior pituitary soon becomes aware of the complexity of the hormones which are supposed to originate from this gland portion. It is true that all have not been accepted, but the maze is a confusing one. According to Bugbee et al (3), animal experiments have demonstrated eleven hormones in the anterior lobe, which I will name briefly, without comment at the present time.

1. The growth hormone. Stimulates skeletal growth, and said to be elaborated by the eosinophilic staining cells.
- 2-3. The Master Sex, or gonadotrophic hormones. Probably elaborated by the basophilic cells.
  - A. PROLAN A. Follicle stimulating.
  - B. PROLAN B. Luteinizing hormone.
4. Sex maturity hormone.
5. Specific dynamic acting hormone. Said to be responsible for the specific dynamic action of food substances.

6. Calorigenic Hormone (Thyreotrophic).  
Which stimulates the thyroid.
7. Hormone which lowers gaseous metabolism.
8. Diuretic hormone.
9. Lactation hormone (lactogenic).
- IO. The hormone which lowers the "NPN" in the blood.
- II. The hormone which initiates menstrual bleeding. This latter is responsible for the saying that "The pituitary is the motor of the ovaries".

Evans (4) only accepts at the present time five main hormones, The growth hormone, adiposity hormone, carbohydrate metabolism or diabetogenic gormone, the adrenalotrophic hormone, and the thyreotrophic hormone, and gonadotrophic hormone, are all mentioned in his article but in summary he states. "I can only state that fortunately at the present time, sufficiently sensitive test objects would appear to have been found for each of FIVE substances-- the growth, gonadotrophic, thyreotrophic, lactogenic, and diabetogenic hormones---, and that in many cases, but not yet in all, we have assurance of relative, even if not absolute freedom from any but a single effect".

From the above introduction it is instantly apparent that even in the light of present knowledge, which is meager, the complexity of the anterior pituitary hormones is one which is very confusing to the student, and not only this, but the nomenclature which has arisen also is a maze of many terms, some identical with many others, or near-like them. In the foregoing

text we will confine our words to the gonadotrophic hormone, only mentioning other hormones of the anterior pituitary where relationship is very close, or where experiments with other hormones, have brought out information in regard to the gonadotrophic hormone. We will also attempt to prove the very definite relationship between the anterior pituitary body, and ovarian function, as shown by clinical and laboratory experiments, and as the text unfolds, attempt to correlate the wide nomenclature under a single pattern, understandable to the student.

At this time it seems advisable to offer an explanation of some terms used, and their meaning, both as to changes brought on by the hormones we are to discuss, and as to the hormones themselves. A short chart of inter-related terms will also be given in order to avoid confusion.

THE OVARIAN CYCLE refers to the development of the graffian follicle, rupture, and discharge of the egg, corpus luteum formation, and regression in the absence of pregnancy. In cases of conception, the cycle becomes lengthened to a reproductive one, with persistence and growth of the corpus luteum, followed by gradual recession to the time of parturition.

THE FOLLICLE. The small vesicular sac imbedded in the ovary that contains the egg-cell or ovum. When they develop and ripen toward maturity they are called graffian follicles. A follicle that aborts i.e. from death of the egg, is said to be atretic, the process being named the follicle

atresia. The follicle is lined with one or more layers of epithelial cells called the granulosa. In the periphery of the sac, outside the granulosa, is a capsule like sheath, the theca interna made up of cells derived from the interstitial cells of the ovary. Outside of this theca is another sheath, made up of pure connective tissue, the theca externa. The follicle contains a fluid, the liquor folliculi, which is richly supplied with the hormone estrin or folliculin. When the follicle has matured and discharged its egg (ovulation), the follicle at once becomes a corpus luteum. The granulosa cells, and to some extent the theca interna cells become hypertrophied and assumeing a yellow color. This change in the follicle cells is called luteinization, and is supposed to be brought about by a specific hormone to be discussed later. The corpus luteum then secretes a hormone of similiar properties named by Corner as progestin, which prepares the endometrium for nidation of the fertilized egg. Sometimes the maturing follicle does not rupture but retains the egg imprisoned. Under these conditions the follicle may become luteinized, the luteinizing process taking place chiefly in the theca interna cells. A luteinized follicle of this nature is called a pseudo-corporis luteum. Such a body may become cystic and is then known as a lutein cyst. Pathologically a lutein cyst is associated with hydatiform mole, and chorion-epitheloma, and is evidently the result of an excess of the luteinizing hormone emanating from the abnormally growing placenta.

**THE FEMALE SEX HORMONE.** A term introduced by Frank, to describe the follicular oestrogenic hormone found in the ovarian follicles and elsewhere in the body( blood, placenta, etc). Is now given the more favorable term "Oestrin".

**FOLLICULIN.** The same as Oestrin.

**OESTRUS** or estrus. Originally meaning sexual desire, but used specifically to denote sexual condition of the female animal, at the mating season.

The above describes in detail terms which will be used freely in the foregoing text and is taken from Graves(5).

The following will give some idea of the present day nomenclature in regard to the hormones related to sexual function, and attempt very briefly to correlate them, one to the other.

**PROLAN.**

1. Prolan A, or Rho I. Anterior lobe.
2. Prolan B, or Rho II. Anterior lobe. Also put out as antuitrin-S (P.D. and Co.)

Both said to be profuse in extract of pregnancy urine.

**ESTRIN.**

1. Ovarian residue.
2. Whole ovary.
3. Agomensin.
4. Theelin(pure crystalline).
5. Theelol( P.D. and Co. Given by mouth).
6. Estrogin.
7. Folliculin etc .

**PROGESTIN.**

1. Corpus luteum.
2. Lutein.
3. Sistomensin.



With some idea of the nomenclature, and the meaning of the various terms used, we are now ready to study the literature as to the relationship of the anterior pituitary body, to ovarian function. In order to do this in a complete and coherent way, it is necessary to start back in the earliest literature, and gradually build up to the present knowledge. This I have attempted to do, and at various intervals through the years, stopped and reviewed with some of the leading workers of their time the knowledge to date. This will give an adequate correlation, but at times will briefly repeat what has been done before, or been said before. I however feel it is very necessary, and enlightening, to find that in this review as we go along, a definite line of thought which all of the authors, and workers of the time, seem to agree on. I will therefore ask the reader to pardon some repetition which will occur in this review by years, only allowing it to occur to show that certain facts have been accepted and been established by all the leading workers in endocrinology.

The first hint of the real function of the pituitary gland is conveyed in a paper to which Cushing(6) calls attention. This was written by Lower, and was called, "Dissertation de Origine Catarrhi", written in 1672, and contained this statement. " For whatever serum is separated into the ventricles of the brain and tissues, and out of them through the infundibulum to the glandula pituitaria,

distills not upon the palate, but is poured again into the blood and mixed with it". Here then, we have the precursor of our knowledge of hormone-therapy.

A student only has to read Ott's treatise on Internal Secretions (7), to find how little was known in 1910, of the relationship of the anterior pituitary to ovarian function. In a very few instances we can see that the same effects were there as described in our present day knowledge, but they were not comprehended. He states that the enlargement of the pituitary during pregnancy means an hyperhypophysy, and a diminished function of the internal secretion of the ovaries. He quotes also Marie, as having believed that changes in the functions of the sex glands were initial symptoms in acromegaly. He again states that the anterior part of the pituitary seems to be associated with growth of the body, with fat metabolism, and sexual activity. So we see that at this time, the earlier workers were suspicious at least, of a relationship between the anterior pituitary and the ovarian function, but at that time a very definite relationship was unknown.

In 1912 we find our knowledge took a decided leap forward, and much experimental evidence was stirring the fire to a more active flame. Under pathological studies Cushing (6) came forward in his book "The Pituitary Body" to state. "The genital organs of the female puppies remain infantile, and the ovaries show but few forming graffian follicles."

This statement followed the performing of hypophysectomies. Again on Page 211, under the heading "Cases showing a polyglandular syndrome", he states "There is probably a fairly definite symptom-complex for a primary involvement of each of the ductless glands, whether the involvement is of such a character to excite, on the one hand, an excessive secretion, or on the other, to diminish functional activity." He believes there is a polyglandular activity which must be present, as in most cases he cites, there has been evidence of participation of one or more of the ductless glands. He further states that that which holds true for the testis, applies also, in all probability, to the ovary namely, that there are two, and indeed possibly more, glandular elements to be considered. Far less is known of ovarian than of testicular function, and unquestionably the physiological complexities and the number of hormones are greater in the case of the female gland. Not only the process of ovulation itself, but the formation of the corpus luteum of pregnancy, is a factor to be considered. Further, after giving some cases, he states " In females as well as in males, the glandular element which is responsible for the physical changes of puberty, differs from that which is concerned with ovulation, and may, possibly, be a function of specific interstitial cells -----The relationship of hypophyseal disorders to the physiological activities of the ovary, other than those concerned with the acquirement of adolescent characteristics, is unquestionably a very close one, and amenorrhea is an early

symptom, whether the disorder is on the side of over function or under function". In many of the cases of acromegalic women recorded in the literature since Marie's early cases, menstrual irregularity or cessation has been noted as the first observed symptom.

So we see these early workers did not have their eyes closed to the possibilities that the anterior pituitary body, or least at first the pituitary body as a whole, was closely related, in some way, to the function of the ovary.

Following 1912, Sir Edward Schafer in 1914(8) gave a good account of pituitary syndromes, and dysfunctions. It was also known that certain growth changes, and changes in secondary sex characteristics were evident with this dysfunction. He describes the relation of the pituitary to the sexual glands as follows:"The relationship of the pituitary to the sex glands, and secondary sexual characters has been dealt with in considering symptoms associated with hypo, and hyperpituitarism, and besides the effect of these conditions on the state of development of the sexual organs, the latter appear to have SOME RECIPROCAL effect on the pituitary. Thus several observers have found enlargement of the gland and increase in the number of oxyphil cells of the pars anterior to occur as the result of castration-----Livingston, who has recently made experiments on the subject in rabbits, finds

that the effect which is produced is greater in females than in males, being practically negligible in the latter.

-----Moreover it is found that the condition of menstruation and pregnancy are associated with hypertrophy of the gland. Indeed, as the result of pregnancy, it may attain to twice or three times its normal weight."

So we see that the early workers at this time (1914), had some insight of a relationship between the anterior pituitary and ovarian function in general, but fuller knowledge was still some time away. There seems to be a lapse now in the work, or the workers were busy experimenting, because the following years to me, seemed to show a decline in the way the trend of thought had been running up to this time.

Gley(9), in 1917, three years later, came out with his book on "The Internal Secretions", and he did not tend to recognize in any way the relationship between the anterior pituitary and the ovary. Under extirpation of the hypophysis, and its effects, he does not mention that it has any relationship with the gonads, or their function. I feel that he had knowledge of the books and articles which came out before this time, but evidently Gley did not feel that there was sufficient evidence to warrant him to place them in his book.

Gley was not however alone, as Cobb(10) in 1918, in his book the "Organs of Internal Secretio", written in London, also fails to mention any evidence for which we are seeking.

He states, "It is a fact that the majority of the observers are agreed that the POSTERIOR part of the gland contains the active principle". In fact Cobb mentions the relationship apparent between the ovaries and the pituitary body, even less than did Cushing in 1912. He mentions all the relations of dysfunction of the pituitary, including amenorrhoea, but stops there as to any relation to the ovary. He does state however under a discussion of therapeutics that there is a relationship between the pituitary and the ovaries, and this should be remembered in the administration of extract of the ovaries in "disorders of the pituitary", a little reverse to our present thinking.

In a summary of Weil's (II) book, the "Internal Secretion", we know that in 1924 little was known about the anterior pituitary and its ovarian relation. The haze that was present at this time is especially noticed when one reads the chapter on Reproduction. After a discussion of the regulation of the events of pregnancy he discusses the process of labor and states that it is influenced essentially by one endocrine gland, the pituitary, but here he was talking about the contractions of the uterus, which we now know can be instigated by a posterior lobe extract, and nothing more is mentioned about the pituitary and ovarian relation.

To Pratt (12), in 1926, we must give some credit as to insight into possibilities for which we seek. He states, "That the normal menstrual cycle is largely dependent

on ovarian function is well established. The ovary cannot be considered alone, however, for interrelation of the ductless glands are ever present. The improved understanding of one gland aids in the interpretation, and function of others". He does not mention the pituitary, but there is more of a hint of the present day knowledge in the above statement, than seen by other authors to this time.

At this time came Smith(I3), working in 1927, and doing extensive work in transplanting pituitary tissue on young female rats. The whole gland, and the anterior lobe only were used, with results the same in either case. He found that sexual maturity was greatly increased, and that the opposite response was produced in the sex apparatus from pituitary ablation, the genital system remaining undeveloped. He states, "The invariable and rapid maturity which is induced by daily pituitary transplants speaks AGAINST the view of those who maintain that hypophysectomy does not interfere with sexual development or function, and indicates an important hypophyseal-gonadal interrelationship".

In the following year came the classical work of Zondek and Aschheim, to which reference will be made soon. However, I wish to state at this time that even with the work of these authors in 1927, as far as 1929 Cruschmann(I4) was not accepting the work of either Smith, Zondek, and many others. In his book Cruschmann under both chapters of "Disorders of the Pituitary", and "Disorders of the Gonads", has practically

nothing to say about the relationship of the anterior pituitary to ovarian function, which had been so very definitely, at least to me, proved by Smith, Zondek and others.

It was not until 1929, that we are able to find a definite correlation of the works up to that time and a new, generally accepted view, taking place. Bell (I5) apparently did not accept all works to that time, but from the side of ablation of the pituitary he states, "As we have seen-----demonstrated beyond a doubt, that the removal of a large portion of the anterior lobe may produce genital atrophy,-----that in the ovaries the follicles cease to develop, and that subsequently the uterus, and other parts of the genital tract atrophy. -----I usually found that profound changes in the ovaries follow extensive removal of the major portion of the anterior lobe, and compression or separation of the stalks".

At this time I will give the classical summary by Parkes (I6), published in 1929, with references of other authors, showing an agreement of facts that had arisen from various directed experiments, on the function of the pituitary. Parkes knew that in the normal animal, a regular connection is found between maturation of the graffian follicle, and the appearance of oestrous symptoms in the accessory organs. Since no uterine effect on the maturation of the follicles had been demonstrated, this functional correla-



tion throughout the whole lifetime of the animal could more easily be explained on the grounds that the oestrous cycle is regulated by the periodic maturation of graffian follicles. The question follows--Where is the oestrus producing cycle obtain its periodicity? It is known that oestrus has occurred after follicular ablation, therefore the graffian follicle is probably not the essential source of the oestrus producing hormone, and the periodicity of oestrus is not governed by the periodic maturation of follicles.

All this initial work paved the way for the discovery of the influence exerted on the ovary by the anterior pituitary body, and it is possible to assert definitely at this stage that the regulation of ovarian periodicity is controlled by the anterior pituitary, and that ovarian regulation is therefore external to the ovary itself. The same conclusion is indicated by numerous experiments on ovarian grafts.

It is true that many previous observations had been made that the ovary did not regulate its own periodicity by several workers. Some other substance was considered present by early the hypophysis was not thought as being responsible. Heape (17), thought that some substance was present in the body for both growth and development, and reproduction, but in such small amounts that only one process could proceed at a time. Hammond (18), in 1925, grafting immature ovaries in a mature animal, and noticing maturation, explained this reaction by stating that there is a "generative ferment", used

in the young animal for growth. When body growth stops however, the substance can be utilized by the reproductive organs, and their activity begins. He thought that there was only sufficient amount of this substance to ripen certain numbers of follicles, and if one ovary was removed, twice as much was then available, and that this explained the increased follicle development in the other ovary. Lipschutz (18), called this the "X-substances". An extension of this hypothesis was put forward to explain the absence of ovarian activity during pregnancy, the use of the substance for uterine and fetal growth preventing its use by the ovary. Though purely speculative at the time, this theory of somatic control began to have some vindication from the effect of the anterior pituitary substances on the ovary. Then came the forward step of looking to some somatic tissue for the source of regulation of the ovary.

For many years some connection had been assumed between the gonads and the other endocrine organs. Parkes (16), states, "For many years in experimental and clinical studies, the thyroid, thymus, adrenals, and the pituitary body had all shown some correlation between them and the ovary, and the testis." "The evidence was not sufficient that the thyroid, as shown by Zondek and Aschheim, or the thymus, as shown by Marshall (19), or the adrenals, as shown by Deanesley (20), could be the seat of regulation of ovarian periodicity." On the other hand very striking

experiments demonstrated a close relationship between the anterior pituitary and the ovary.

Various authors in past years had pointed out that disorders of the anterior pituitary itself resulted in marked aberration of sexual function, as well as in body abnormalities, such as gigantism. Turner (21) in 1932, gives the student a very good review of these syndromes, and only a slight amount of study brings to light the knowledge that these syndromes known as the Lorrain-Levi, Frohlich's, the adolescent type, and others, all seem to have a definite relationship to menstrual disorders, and sex characteristics.

Both hypo and hyperpituitarism had been described therefore in association with amenorrhoea and infantile sex organs in the human female. From the first work therefore by Evans (22), in 1924, then to Smith (13) in 1927, previously mentioned in early history, we find that the very important work of Zondek and Aschheim in 1927 came forth. Parkes (16) describes it as follows: "From the evidence that the ovary did not regulate its own periodicity a thorough search was instituted to find out the effect of other endocrine organs and body tissues upon the same reproductive organs. The following conclusions were made by these workers:

- I. Implantation of male or female anterior pituitary into the immature mouse brings forth precocious oestrus, including ovarian changes.

2. The effect is exerted purely through the ovary, which is caused to undergo precocious maturation and to elaborate the oestrus-producing hormone."

At about this time also Smith and Engle(23) did some more work, and found that the immature ovary after implantation of anterior pituitary might be ten times larger than the control in the rat, or nineteen times in the mouse. This is not due to any increase in the size of the mature follicles, as compared with the normal adult, but to a great increase in their number, and in that of the corpora lutea produced by ovulation. On page 171 of the same reference the authors tend to show that the condition is one of superovulation, and that the number of ova found exceeded by a great number the greatest number ever reported for these species. They go on to state in the summary: "The results secured by anterior pituitary transplantations in the normal animal are harmonious with those secured from hypophysectomy, and a replacement therapy. After hypophysectomy, the gonads degenerate, the large follicles become atretic, though the primitive oocytes are apparently unaffected. Pituitary transplants restore the gonads to a normal or nearly normal size, cause a resumption of follicular growth, and reappearance of oestrus in the female, and induce spermatogenesis in the male".

The result of injection of suspensions of

the anterior pituitary tissue is therefore essentially the rapid maturation of graffian follicles in the ovary, with the coincident appearance of oestrus changes in the accessory organs. The production of oestrin by the stimulated immature ovary in such experiments has been attributed to the hypertrophy caused in the graffian follicles, but the same effect has been observed when the injected immature animals have been sterilized by exposure to X-Rays, and therefore possess no graffian follicles. Also confirmed by Parkes (24), in which he reports that in such cases the production of oestrus, and therefore of oestrin must have been dependent on the stimulation of the tissue of the irradiated ovary.

The only important difference between the work of Zondek and Aschheim, and that of Smith and Engle seems to be that whereas the latter authors always found that hormonal follicular maturation occurred, the former found that atretic corpora lutea and blood follicles were also produced. In view of the earlier work of Evans (22) on the luteinizing effects of anterior pituitary, this distinction is of interest. The difference in the effects following the injection of Evans' sodium hydroxide extract and the injection of the macerated fresh tissue, led to the tentative supposition that two different anterior pituitary principles were involved, one causing the conversion of the follicular granulosa to luteal cells, and

another causing the burst of growth preceeding follicular maturation. Many authors and workers have disagreed, but the most serious criticism of the view, taken early, that two anterior pituitary substances are involved was forthcoming from the work of Zondek and Aschheim. These authors in investigating the effects of implants on the immature animal, found that three ovarian reactions were characteristic of this treatment. They are:-

1. In the majority of cases follicles matured, and ovulated, as found by Smith and Engle(23).
2. Other follicles, however, in the same ovary became atretic, and underwent luteinization, without ovulation in a manner corresponding essentially with that described by Evans.
3. A small number of follicles, in the same ovary, would become CYSTIC, and appear as "blutpunkte", on the surface of the ovary.

Zondek considers these results to show that ONE anterior pituitary hormone is involved, and believes that the complete luteinization caused by the sodium hydroxide extracts is due to the injection of relatively large amounts, while the characteristic ovulation effect of the suspensions results from the substances being present in comparatively small amounts. Since this article more recent experiments seem to refute this view, but to keep our trend of thought in sequence, this will be mentioned later, with more recent works.

Even Engle, (25) working also in 1929 states, "Previous work has shown that the daily transplantation of the anterior lobe into immature female mice, results in a marked follicular growth followed by ovulation. Treatment of immature mice, with the urine of pregnancy results in a follicular growth, with atresia of follicles and ovum, and effective prevention of ovulation by the transformation of the follicle into a corpus luteum, with retained ovum. It is difficult to consider the two types of response as being due to the same factor from the anterior lobe.

So we see differences of opinion were arising, which were the stimulus to more experimental work. Parkes (24) goes on to summarize the work to this time to state that the anterior pituitary body produces a substance, or substances which have a most potent action upon the ovary, and it is thus reasonable to suppose that the anterior pituitary plays a part in regulating normal ovarian cycle. The fact that precocious oestrus can be produced in the ovaries, and accessory organs of the normal immature animal, by administration of anterior pituitary substance, suggests that the first oestrus of puberty is brought about by some action of the pituitary. This, in itself, would not explain how the first oestrus is precipitated. The problem is merely transferred from the ovary to the anterior pituitary body. Since the anterior pituitary body from the male and female, young or mature animals, all are efficacious, it is difficult to explain how this stimulus to the ovary is liberated from the anterior pituitary. He states

further that Smith and Engle believe that the hypothesis of the periodic liberation of gonad-stimulating hormone of the pituitary may explain the periodic ripening of groups of follicles more satisfactorily than any previously advanced. Parkes takes the side of Engle at this time, in stating that if the anterior pituitary is directly responsible for the changes in the ovary, then some means must exist whereby events in the accessory organs can influence the anterior pituitary. For instance, since ovulation does not take place during pregnancy, some mechanism must cause the anterior pituitary at this time to stimulate the corpus luteum, and not the follicle. Similarly, it must be concluded that the absence of oestrus during pseudo-pregnancy in the mouse indicates that the anterior pituitary body reacts to sterile copulation, and exerts a stimulating effect on the corpora lutea.

Parkes carries this supposition in regard to the luteinization effect produced, whether by copulation or ovulation, into a later article when in conjunction with Margaret Hill (26), he comes to this conclusion after much experimental work. He states, "The fact that corpora lutea develop after ovulation induced without copulation, shows that the stimulus to luteinization of the ruptured follicle is initiated by the actual act of ovulation, and not as a delayed effect of copulation. Ovulation was produced freely in non-copulated oestrus rabbits by one intravenous injection of the gonad-stimulating principle of the anterior pituitary body



prepared from the urine of pregnancy by the methods similar to those employed by Zondek and Aschheim,"-which will be explained later, and which is at the present time the basis of the pregnancy test. It might be well to mention at this time while speaking of the work of Parkes to state that in 1932, Parkes working in conjunction with Hill (27), adds to his belief mentioned above, that the anterior pituitary is the chief controlling factor in this ovarian action. This work was at least two years later.

Frank (28) in 1929 also briefly sums up in a few words this complex experimental work by the statement, "The lack of influence of the female gonad itself (of the female sex hormone), is in marked contrast to the rapid and striking activation of follicle ripening, and luteinization which results from injection of anterior lobe extracts or implants in both premature and adult rabbits. Frank (29) again in 1930, in working with the female sex hormone, states, "Proof that the anterior pituitary lobe secretes a hormone activating the ovary has been offered by Phillip Smith with repeated implants of fresh anterior lobe, as well as by Aschheim and Zondek, who employed an extract of the anterior lobe. Injection or implantation into immature animals produces puberty, causes massive and rapid growth of follicles in the mature, and reactivates the ovaries if senility has already ensued. Thus the anterior lobe is shown to cause puberty." The work of Evans and Simpson (30), which was published in 1928 was also accepted by Frank, and they had demonstrated that

the anterior lobe secretes at least two hormones, the one producing a general somatic growth, the other the special gonadal stimulant, supposed to be derived from the basophilic cells. By means of excessive exhibition of the gonadal anterior lobe hormone, SUPEROVULATION, and SUPERFETATION, to an astounding degree can be brought about. At this time also Aschheim and Zondek had discovered the excess secretion of the anterior lobe hormone as well as of the female sex hormone, in the urine of pregnancy.

The above review, by Frank, and the work of both Aschheim and Zondek, and Evans and Simpson, given, tells a rather complete story of just what had been generally accepted up to this time. We are now in the work which began about 1930, and we find that the experimental fire was so aflame, that the work was directed along many tangents; Work was being done as to the relation of the hormone to menstruation, to hydatidiform mole, and malignant chorion-epithelioma, to the discovery of whether there were two distinct hormones acting as gonadal stimulating, as to its therapeutic value etc. I will attempt at this time, as 1930 seemed to be the year when most of this experimenting was going on, to give an idea of some of the work which was going on.

Hartman, Warfield, Firor, and Geiling (31) made some interesting studies and especially so as much of the work was done on human subjects. Their work was in regard to menstruation, and they came to the conclusion that a separate hormone, other than the follicle stimulating, and the luteiniz-

ing phenomena was present in the anterior lobe, which initiated menstrual bleeding, and therefore for the first time lifted the menstrual problem from the realm of theory and conjecture.

Fluhmann(32) also in 1930 states, " It is seen that from the anterior hypophysis originates three hormones, or at least, the substance of this gland can produce three distinct effects, and of prime interest to us are those two which directly effect the ovary. In the first place we find the influence of the anterior pituitary "ovulation hormone", in the development of the graffian follicle in the ovary, and the consequent elaboration of the follicular hormone which in turn stimulates the uterus to growth, turgor, and the proliferation of the basal layers of the endometrium." "The second anterior pituitary factor coming into play then causes a luteinization of the cells of the ruptured follicle, and the formation of a second ovarian (corpus luteum) hormone, which acts on the endometrium to produce the changes characteristic of the premenstrual phase, or in the case of gestation, to decidual formation".

Of interest at this time was the work of many authors, especially Mack, Catherwood (33), in regard to the significance of the lutein cysts of the ovary so frequently seen and associated with cases of hydatidiform mole, and chorionepithelioma. They felt that this was due to a pituitary-ovary relationship. They state, "Follicular development while usually at a standstill during the course of normal pregnancy

as a result of the apparent inhibitory action of the corpus luteum, often progresses at a rapid rate in case of hydatidiform mole and chorionepithelioma. Sections of these ovaries show many highly developed follicles which form cysts lined with proliferating epithelium, undergoing lutein transformation! "THERE IS CONSIDERABLE EVIDENCE POINTING TO HYPER-SECRETION OF THE PITUITARY AS THE CAUSE OF THIS CONDITION OF THE OVARIES". They further state that there is an association of the cystic condition with certain tumors involving the anterior lobe of the pituitary. Whether this excessive production of the anterior lobe hormone is the cause or result of this condition is not absolutely clear. It seems likely however, that the increased hormonal production is the result of the abnormal activity of the chorion. This conclusion was reached, and has been accepted however, that the amount of anterior lobe hormone in these conditions was greater than that normally in pregnancy, and that the anterior pituitary hormone is the etiologic factor in the formation of lutein cysts in the ovary.

The above conclusion is interesting in that it offers a different result as to action of the anterior lobe hormone on the ovaries, when the secretion is excessive. It is true that even at the present time this theory is not fully accepted by all, but it offers a separate line of thought than that was followed by others in 1930.

In the next year, 1931, Graves (34) came out with his book "Female Sex Hormonology," which up to this time

is the finest, readable summary offered to the student. The work of Zondek and Aschheim up to this time had progressed to a fine degree, but both being German workers, translation of their entire work is difficult to find up to the time of this work by Graves. I ask the reader to bear with me in quoting Graves' classical summary of the work of Zondek and Aschheim, and other workers to the time of 1931.

Graves states, " Next came the classical experiments of Zondek and Aschheim. They used single transplants, and not only of the hypophysis but of other glands, and finally reached this conclusion:-

1. The hormone of the anterior lobe of the hypophysis, **AND ONLY THIS**, sets the ovarian function in motion, and brings the infantile mouse to sexual maturity.

2. The hormone of the anterior lobe of the hypophysis which produces oestrus in the female infantile mouse, is present in both the male and female gland.

3. This hormone is present in the female hypophysis after her own ovulation has ceased i.e. after the climacteric.

4. This hormone of the anterior lobe that produces oestrus in the virgin mice is identical in animals and humans.

The next observation was the comparison between the anterior lobe hormone and the ovarian hormone (oestrin), in their effects on ovariectomized animals. It was shown by tests of certain authors, that the injection of

oestrin in a female castrated animal produced typical oestrus changes in the vagina and uterus. Secondly, oestrin injected into the normal animal at rest produces oestrus changes in the vagina and uterus, but no changes in the ovaries. On the other hand, anterior lobe transplantation, has no effect on the vagina and uterus of an ovariectomized animal. In a normal animal it causes oestrus changes in the vagina and uterus, AND ALSO OVULATION AND LUTEINIZATION IN THE OVARIES. From these observations Zondek and Aschheim drew the following conclusions:-

1. The hormone of the anterior lobe is the motor of sexual function.

2. This hormone is primary, the ovarian hormone is secondary.

3. The anterior lobe hormone brings the follicular apparatus into action, discharges the ripening follicle, and mobilizes secondarily the ovarian hormone in the follicle cells.

Furthermore they conclude, the egg does not play the chief role in this process as formerly supposed, since hormone production can take place in the follicle apparatus without the egg.

With this information at hand Zondek and Aschheim provided the pregnancy test after finding the anterior lobe hormone present in high concentration in the blood and urine of pregnant women.

The next stage in the evolution of knowledge regarding sex physiology was in the demonstration that the

anterior lobe hormone contains not one, but two at least, and perhaps more, active endocrine bearing substances. The problem of complexity of the anterior lobe hormone was studied separately by Zondek and Wiesner. They arrived at identical conclusions, but by somewhat different routes. Zondek and Aschheim had tabulated so far:-

1. Follicle ripening, ovulation, production of folliculin(oestrin) in the follicles, and thereby secondary oestrus reaction.

2. Blood masses in the distended follicles.

3. Luteinization (production of corpora lutea), and luteinized corpora atretica (ova imprisoned).

With this as a test they demonstrated the specific action of the hormone on the infantile animal, and were thus able to draw conclusions as to the significance of the hormone on the general organism. Finally they were able to isolate the hormone in a chemical form, and to this substance they gave the name of Prolan. They studied its different properties, and separated it as different from the growth hormone, and the hormone thought to have a regulating influence on metabolism.

Having this hormone so separated they began to unwind the preplexities of Prolan itself. It did not always have the same reaction. Sometimes it would produce normal ripening of the follicle, with rupture and deposit of ova in the tubes, and repress the formation of corpus luteum. This was known as REACTION I. Often, however, the follicles would rupture, the eggs would be retained, and the entire cell

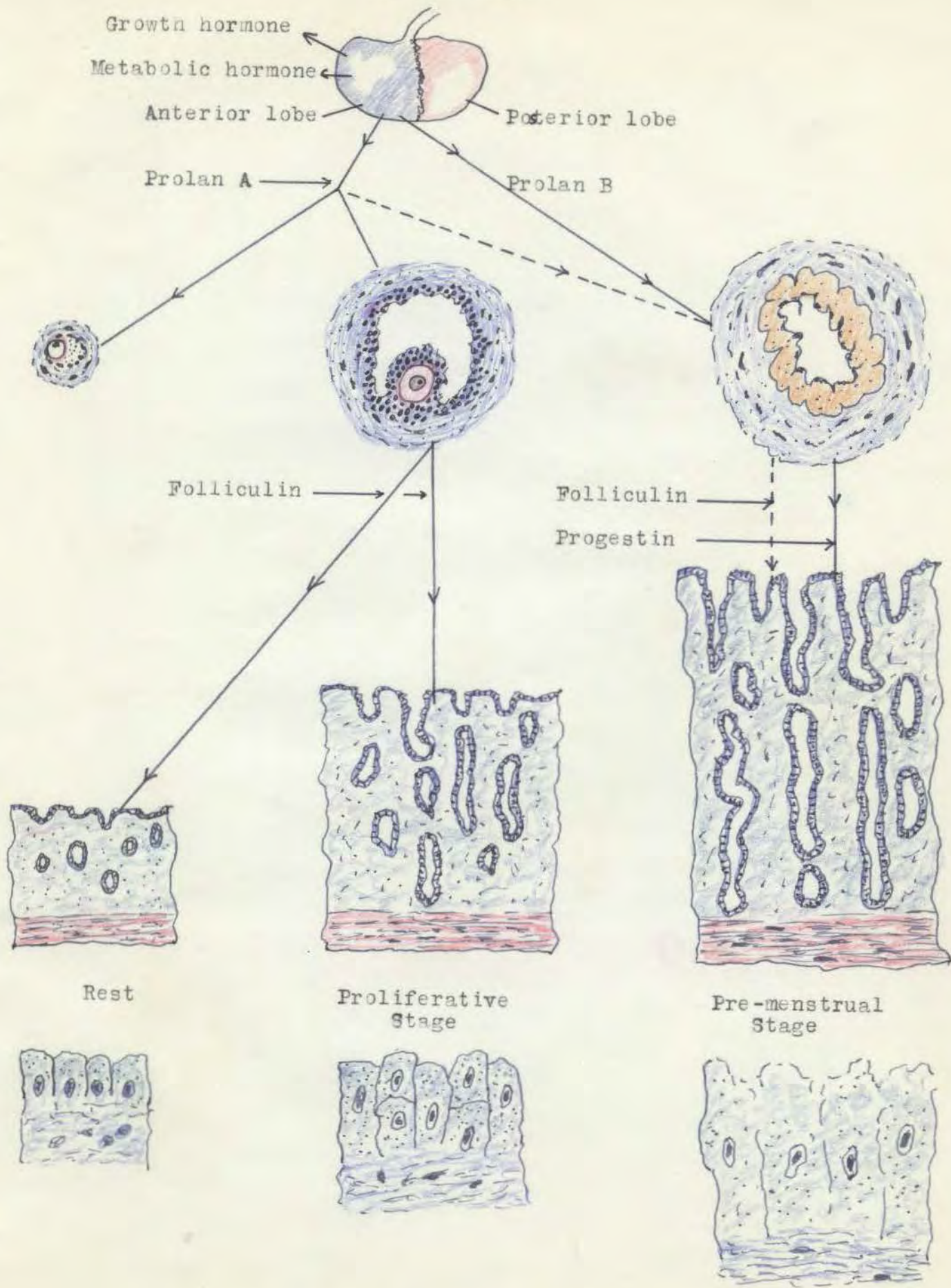
apparatus of the follicle would be luteinized. If the potency was increased, the entire ovary would be converted into a single lutein body (lutein cyst), in which case follicle ripening would be no longer possible.-----After some time Zondek was able to isolate a substance which would produce only follicle ripening (REACTION I), with no luteinization, and this product he named PROLAN A. The remaining luteinizing hormone being entitled PROLAN B.

He formed a comparison at this time which was enlightening. That is : Prolan A, and folliculin(oestrin) have properties in common, while Prolan B, and the secretion of corpus luteum (Progestin, lutin etc), are similiar."

This correlation is best seen in the following drawing. Prolan A starting from the hypophysis, stimulated the growing follicle to the production of folliculin, which in turn stimulates the proliferative stage of the endometrium. A small amount of the folliculin is excited in the corpus luteum, as indicated by the broken line. Prolan B stimulates the lutein cells of the corpus luteum to the production of progestin, which changes the endometrium to the premenstrual (Progestational) stage. The reciprocal relationship between the hypophysis and the ovaries, more recently described, and the other hormones are not shown other than the metabolic and growth hormones which we have mentioned in the preceeding text.



# THE PITUITARY



Graves continues on page 61 to state, " The correlation of Prolan A and Prolan B with the ovarian hormone , remembering the work of Zondek and Aschheim on the anterior lobe hormone, and Zondek's division of the hormone into two constituents, at the same time recalling the morphological events of the ovarian and endometrial cycles, we are ready for Zondek's summation". At this time I wish to stress on the students mind that essentially this is the final knowledge.

1. The female sexual function manifests itself in the following way. The anterior lobe hormone of the hypophysis is the motor of the sexual function and the hormones of the anterior lobe are the superordinated specific hormones of sex.

2. Prolan A sets off follicle ripening and incites the theca cells of the follicle to the production of folliculin which in turn induces the proliferative phase of the endometrium.

3. Prolan B effects the change of the granulosa, and theca cells to lutein cells, and incites in them the production of progesterin(lutein), which changes the proliferative phase of the endometrium to one of secretion (premenstrual, progestational, pregravid) stage.

Wiesner's contribution was practically along the same lines. He also felt that the gonadotrophic stimulating principles were in two phases, which he termed the Rho I, and Rho 2 factors. His nomenclature was entirely different, but these correspond identically to Zondek's Prolan A, and Prolan B.

Several investigators, notably Phillip (quoted from Graves), take the view that the anterior lobe hormone found in such quantities in the urine, especially during pregnancy, is not a product of the hypophysis, but of the placenta. Zondek emphatically denies this claim, and holds to the supremacy of the hypophysis, though he admits that if the placenta produces folliculin, it is conceivable that it may also aid the hypophysis in manufacturing the anterior lobe hormone. Zondek stresses the superordination of the hypophysis in the following words, which are well to remember.

1. Without the anterior lobe and its hormone, no sexual activity, no ovulation, no sexual rythm.
2. Without the anterior lobe, atrophy of the sex organs.
3. Without the anterior lobe, no conception.
4. With disturbance of the anterior lobe, death of the egg.

There is no doubt that greater knowledge than the above, in relation to the anterior lobe of the pituitary, and its action upon the ovaries, has not been forthcoming. The additional information which follows inquires further into the complexity of the anterior lobe hormone, and brings out some interesting assumptions, and above all more confirming experiments, at least to me, that Zondek's work will stand for time to come. We will move now to 1932, and take up some of the summaries which appeared in that year, plus additional experiments which were continually being formed as to this definite hypophyseal-gonad relationship.

Englebach (35) in his volume III, of Endocrine Medicine describes the pituitarisms of adolescent life, not related to tumors, and including the hyper and hypopituitarisms. He defines the hyperpituitarism of the anterior lobe as producing abnormal overgrowth of the entire body, caused by excessive function and unrelated to tumors. The hypertrophy of the organs internal and external, and of the genital system, are due to early hyperactivity of the anterior lobe. The skeletal growth, or overgrowth, remains permanent throughout adult age, although the hyperactivity changes to inactivity. In such event, the early virility, and normal menses are transformed into genital hypofunction as expressed in frigidity, and sterility, with amenorrhoea, in the female. The latter is interesting in the light of the preceding knowledge of the anterior lobe hormones. Under hypofunctions of the anterior lobe, he states, "Hypo function of the anterior lobe of the hypophysis presents just the opposite somatic manifestations --- It is never associated with pituitary tumor, and is free from adiposity. There is a hypoplastic genitalia, with ABSENCE OF FUNCTION, is rarely reactivated to a normal state, and never changes into a hyperactivity complex.

It seems from the work of Englebach above that we can understand more of the action of the anterior lobe hormones, when taken up in this light of hyper, and hypo function. On page 62 he further discusses the two

main pituitary hormones to genital development and function, and states the differences are not well defined. It is very probable he states, that the anterior lobe disorders, as hyper and hypo function, when not due to tumor, produces either a hyperplasia or hypoplasia of the eosinophilic and chromophobic cells of the lobe. The hormonal signs of the growth and sex hormones are based on the activity of these cellular elements. The ovulation hormone from the chromophobic and basophilic cells, has been fairly well established as having two important incretory influences. They are:

I. Through its effect on the graffian follicle it stimulates the production of the primary ovarian hormone (tneelin, ), which initiates the first endometrial phase of oestrus.

2. It is the most important maturity producing factor.

The luteinization or secondary sex hormone from the basophilic cells is related to the development and hormonal action and function of the lutein cells of the graffian follicle, before and after pregnancy. Its excess before ovulation , and rupture of the follicle results in hyperplasia of these lutein cells, with an imprisonment of the ova. After fertilization it causes a presistency of the corpus luteum by maintaining a prolonged hyperplasia of its lutein elements such as is present throughout gravidity. In either event hyperluteinization of unruptured graffian follicles, or that present in a presistent corpus luteum, inhibits, or prevents the normal

menstrual desquamation of the endometrium necessary for menstruation. These two pituitary hormones consequently have an opposite effect on ovulation and menstruation. The ovulation hormone, unopposed, provokes normal sexual maturity, and initiates, and probably carries the oestrus cycle throughout its initial phase to that of progestational proliferation of the uterine endometrium. A deficiency of the ovulation hormone, or an excess of the lutein hormone would delay puberty, and inhibit the normal endometrial changes of menstruation, producing amenorrhoea. A balance in amount, and sequence of production of these pituitary sex hormones, then, is necessary for the production of normal, rhythmic menstruation. For instance, the ovulation and luteinizing hormones must produce at the proper time, and in the exact amount, in order to facilitate their normal action upon the graffian follicle.

Engleback goes on to state that animal experimentation has established the two sex hormones provided by the basophilic cells of the anterior lobe. In the female rat injections of an excess of the ovulation hormone has been shown to produce superovulation of the ovarian follicle. The luteinizing hormone when injected into immature female rats in large amounts causes a hyperplasia of the lutein cells of the follicle. Imprisonment of the ova may result, preventing its expulsion by rupture, so that there is a delay or absence of oestrus, and fertilization does not occur. From

these known biological effects, a deduction is made that a deficiency of the ovulation hormone, and an excess of the luteinizing hormone of the anterior lobe, may have much the same clinical effect as that of amenorrhoea, and sterility. The reverse, a hypersecretion of the ovulation hormone, providing other incretions necessary for the mechanism of oestrus are normal, would produce diametrically opposite result, increased virility, without fertility. Therefore on the balance maintained by the two sex hormones probably depends the normal action of the ovary, which makes up the second link pertaining to normal ovulation, and the pregravid proliferation of the uterine, and vaginal mucosa of oestrus. Their proper interaction with the vaginal mucosa, through the ovarian hormones, must be obtained through the serial effects of the pituitary gland, through the ovary.

The elaboration of these sex hormones has done much to explain the genital symptoms of acromegaly with pituitary tumor. These pituitary tumors are frequently associated with complete amenorrhoea, although libido is retained. It is now known that this amenorrhoea is probably due to a superluteinization of the ovarian follicle, resulting from an excess of the luteinizing hormone from the anterior pituitary. The amenorrhoea decreases the probability of conception, which is rare in these cases. An imbalance of the two pituitary hormones may go far to explain the biologic reactions of the genital system found in adiposogenitalisms of juvenile and

early adolescent life. As is known in these cases there is a hypoplasia and decreased function of the genital system, associated with adiposity. That an excess of the luteinizing hormone, which inhibits in adult life, or arrests menstruation, may, when present in the prepubertal years of juvenility, also depress the metabolic processes to a sufficient degree to produce the associated adiposity, is a theory which may be tenable.

Englebach on page 482, makes this statement. "Many of these pituitary disorders had their start in juvenility, and that heredity plays a big part." Many of the pituitary hyperactivities he states produces abnormal stature development, and consequent effects in the non-endocrine systems, which could undoubtedly be prevented by the institution of treatment during juvenility, or early adolescence. This is also true of the hypopituitarisms, resulting in somatic, and genital infantilism, with absence of genital function. If these cases were diagnosed during juvenility, their growth and genital function could probably be restored, and maintained within the normal.

The above is interesting, in that it gives us some insight into excess, and decreased amounts of the anterior pituitary hormones, and their action upon the ovary.

Englebach in 1932, in his Volume I (36), gives us also some knowledge as from what cell source these hormones were obtained. He sums up his chapters dealing with gonadal and hypophyseal endocrinopathies as follows: "Convinc-



ing proof is offered that the eosinophilic cells supply the most important growth hormones to all the tissues and organs of the body. The basophil, and possibly the chromophobe cells furnish the most important gonadal hormones, resulting in ovulation and luteinization of the ovarian follicle.

Zondek, and Aschheim call the hypophysis the "motor of the ovary", and without the presence of these specific hormones from the basophilic cells of the anterior lobe, the histologic changes in the follicle, and the functional reaction of estrus cannot be accomplished".

Biedl (37), with animal experimentation associated the function of the basophils with the development and function of the ovary, and Latson (38) in 1933 states, "The basophilic or sex cells produce a hormone in the female known as prolan". Evans and Simpson(39), in 1929, showed that it is the germ element of the gonads, which when removed, caused the basophils to increase in number and enlarge. Englebach sums up this knowledge by saying, " It is apparently established that the eosinophils of the anterior lobe secrete the growth hormone, and that the basophils, and possibly the chromophobes of the anterior lobe secrete the sex hormone which stimulate the incretory action, and probably the development of the gonads."

I do not wish to leave with the reader the belief that the above source of the hormones is accepted fully by all workers. Barr (40) for example in 1933 comes out with the statement that the source of the gonado-trophic hormones

is as yet unknown. He states that several observers have suggested that it is produced by the basophilic portions of the gland, but while the hyperplasia of basophilic cells following castration lends some support to the belief, direct evidence is almost entirely lacking. He does state that the syndrome of pituitary basophilism does produce an accompanying atrophy of the sex organs, and amenorrhoea in women, and impotence in men. Such observations, he states, prevents us at the present time, from attempting any sharp differentiation between the functions of the eosinophilic, and the basophilic cells.

Personally however, I feel that Barr stands some alone in this, when such workers as has been mentioned seem to have the opposite view.

With the discussion of the exact source of these gonadotrophic hormones, came forth some other work as to a reverse action in this relationship between the anterior pituitary and ovarian function. Mazer and Goldstein (41) speak of it as follows; "A nonreciprocal relationship exists between the ovaries and the anterior lobe, extirpation of the latter results in complete suppression of ovarian function". It was also proved by Smith (42), that castration on the otherhand, is followed by increase in size, and function of the anterior hypophysis. Engle(43) and Evans and Simpson(39) and Fluhmann (44) also , all agreed with the latter statement. This observation would therefore suggest an inhibitory influence

of the ovarian secretion on the sex hormone producing cells of the anterior lobe. Which of the two ovarian hormones inhibits the function of the pars anterior is still a matter of conjecture. Hisaw (45) in working with rats, claims that progesterin inhibits the action of the anterior pituitary transplants in promoting maturity in rats. This would partly explain the periodicity of anterior pituitary lobe function and the consequent regression of the corpus luteum toward the end of the menstrual cycle. The experiments of Leonard (46) seem to indicate that excessive quantities of oestrin also inhibit the gonad stimulating function of the hypophysis. The unreliability of judging the degree of function of a gland by its hormone content is apparent, for some glands, like the ovary, store very little of the hormone which they produce. Mazer and Goldstein (41), later in their article after citing certain other workers as Schoeller and Danberg, believe that the latter effect, that of oestrin, due to the premenstrual high level in the blood, inhibits the anterior pituitary function, which results in the regression of the corpus luteum. As mentioned above, experimental work has not as yet reached an acceptable level to exactly say at the present time whether the anterior lobe is inhibited in its function at certain stages of hormonal cycles, or not, but it does seem in the present light that the ovarian hormones do have some effect. I believe that most authors have felt and believed that a certain interrelationship exists between all the endocrine glands, and that all to some extent exert a controlling effect on each of the others. This is however pure conjecture.

Some authors do however believe that the anterior lobe of the hypophysis is necessary for the development and maintenance of the endocrine glands. Dr. Houssay(45)A director of the Instituto de Fisiologia of the Faculty of Medicine of Buenos Aires states, "It is doubtful whether the hypophysis secretes a specific stimulating hormone for each gland. It is more possible that a general hypophyseal action is present, to which is added the effects of certain specific hormones". He carries this further by showing that ablation of the hypophysis causes certain changes in the thyroid, and suprarenals, as well as those known to occur in the ovaries. This is all interesting in light of the remarks which are made about the action of the hypophysis in regard to other glands, other than the ovaries, in that it tends to give the hypophysis a supremacy or control factor, in the endocrine system.

That the hypophysis has a large reserve surplus in its hormonal action is definitely shown also by Smith(46)A, when in experimental study on rats he found that changes in the ovaries, as previously discussed, were normal when thirty percent of the anterior hypophysis was present. This was true also in, sex cycles, mating, and reproduction.

We now move with the knowledge of the times to late 1933, where Evans(47) gives a good account of the present position of our knowledge of the anterior pituitary function. Under the section in which he speaks of the gonadotrophic hormone, with which we are interested, he brings up a general review of the previous works, but also brings up some existing arguments.

After a brief discussion of the action of hypophysectomy, and hyperpituitarism, which we have gone over in the preceding text, he reviews the work of Aschheim and Zondek. His concept of this work, and the relation to present knowledge is interesting in that he brings forth a new view as to the origin, or identification of the hormone found in the urine during pregnancy, named by Zondek and Aschheim as the same hormone as the gonadotrophic factor. A little space would well be donated here to lead up to the reason for his present belief.

He states, "The circumstances which lead up to the detection of the sex hormone of the hypophysis came from Zondek and Aschheim, in 1926, seeking to influence the immature genital system of rodents, by various endocrine products, and transplants of endocrine tissues. They happened to introduce bits of the anterior hypophysis under the skin, to find the complete reestablishment of sexual maturity in these infants from three to five days. It is the ovary which gives a speedily ascertained, and unassailable picture of this effect, for large follicles, and above all, corpora lutea appear there for the first time. Just as it is possible to extract the growth hormone from the hypophysis, so also we can now extract the gonad-stimulating hormone from the hypophyseal tissue. Another and more convenient source of this hormone was THOUGHT to have been discovered by Aschheim and Zondek. During pregnancy, for reasons quite unknown to us, the estrous hormone, or folliculin, is produced by the body in great quantity, at a time, indeed, when

according to our present very limited ideas , physiologic demands for it must be nonexistent. It was encountered in the placenta, urine, and blood of pregnant women. What more natural thing than to search, not only for the ovarian, but for the hypophyseal sex hormone in the fluids, and tissues at the time of pregnancy. It also occurs, at this time, in great abundance in the placenta, and in the urine, and in contradistinction to the ovarian hormone, occurs so early in pregnancy as to constitute the means of recognizing conception as soon as the first missed period has occurred. This is NOT the sex hormone of the anterior hypophysis! He goes on further to state that our capacity to distinguish this particular substance, also a hormone-prolan- from the true sex hormone of the hypophysis, rests on clear evidence of a characteristic difference in the biologic effects worked by prolan and by the true anterior hypophyseal sex hormone. -----He goes on to show where many experimenters think that prolan is from the placenta, Phillip abroad, and Collip in this country, but he does not completely agree with them. Through certain experiments he has shown, with his workers, that there is prompt appearance in the blood and urine of males and females, of prolan, after complete surgical ablation of the gonads. He believes that it is of hypophyseal origin, but also admits that he will not be positive until he does simultaneous hypophysectomy, and gonadectomies. So we see here the first reference that there exists an argument as to the origin of

prolan. I will admit to the reader that this may cause some confusion, but a subject so new in its field, must be presented from every angle. Evans goes on to state that this much he is sure of however, that hypophyseal extracts confer on prolan a strangely increased potency, now comparable to, or exceeding the best that could be secured in extracts of the hypophysis containing gonadotrophic hormone itself. These facts he designated as the activation of prolan, which are also confirmed by Leonard(48), and it was also shown that extracts of the gland rich in gonadotrophic hormone itself, and free from the growth hormone, could equally well still further be activated in their gonadotrophic activities, and properties by the addition of prolan. In the recent months however, Evans et al (49), at the Rockefeller Institute claim that they have been able to show that this hypophyseal constituent is however, not the well known gonadotrophic hormone of the anterior lobe, but is a body having different chemical and biologic characteristics. This body, the so called activator of prolan, when it is added to the latter, confers a stimulus to the latter, or when added to the latter confers a stimulus on the gonads in excess of anything they have hitherto observed, save that produced by a highly concentrated gonadotrophic hormone of the pregnant mares blood stream.

The work of Evans and his coworkers, cannot be set lightly aside, when we are aware of his previous work on this subject. He does not commit himself as to the source of prolan, a largely debated subject, or exactly disagree that

the gonadotrophic hormone does not stimulate the production of prolan, but he does seem to believe that there is a separate anterior hypophyseal hormone, which acts as an activator to prolan, and the effects it is known to produce.

Latson, (38), in July, 1933, also states that it has been found that the urine from pregnant women contains a rich supply of a hormone very similiar in many respects to prolan. He states however a fact we know, that investigators differ in their opinions as to the source of this hormone. One school of thought claims that it is furnished by the anterior lobe of the pituitary body. The other claims that it is not from that source, but concedes that the extract is similiar in its biologic effect on the sex apparatus, to that of an extract from the anterior lobe of the pituitary. He does state that it has been shown that the pregnant urine does not contain the growth hormone. Regardless of the exact origin of the hormone in discussion, the Aschheim Zondek test for pregnancy is based on the presence of this hormone in the urine. Though prolan A and Prolan B have not been separated for therapeutic use, it has been found that small doses of the extract obtained from the urine of pregnancy, act on the ovary as a follicle stimulator, whereas large doses cause rapid luteinization. The latter point leads the reader and student to think that this hormone in the urine of pregnancy would have combined prolan A and prolan B, at least the effects, seem to be present.



Sage (50), in discussing the Aschheim-Zondek test for pregnancy states that these authors discovered that early in pregnancy, a hormone, APPARENTLY from the anterior lobe of the pituitary, is so freely formed in the mother's system, that it is actually present in the mother's urine in recognizable quantity, and upon the basis of this observation they have elaborated the pregnancy test.

There is a controversy that also still exists as to the duality of the anterior lobe gonadotrophic hormone. Loeb (51) opens a recent article published in 1933 with the fact that there has been much discussion in recent literature as to whether the anterior pituitary gland produces two kinds of hormones which act on the mammalian ovary, and through the ovary, on the uterus, vagina, and mammary gland, or also directly on the last named organ. He agrees with Zondek, and sites facts which he has established with previous work, as well as some only partly published at this time, that they assume there are at least two types of anterior pituitary hormones which act on the ovary, one of these which also effects the thyroid gland. The latter point is a new point to be considered in the complexity, in which we find ourselves placed. He states further, that pending the outcome of these investigations, we may provisionally characterize hormone I as responsible for the development of follicles to a large size, and for the maturation of the granulosa, and hormone II as inhibiting the growth of the follicles, and causing the degenera-

tion of granulosa in species in which the granulosa cells are very labile, and show some resistance to injurious factors. This hormone also leads to hypertrophic changes in the theca interna, and in certain connective tissue cells, especially those which are active during atresia of the follicles. He ends this point by stating that although we cannot be as yet quite certain as to the possible relationships of these effects to hormone I and II, it seems probable that the anterior pituitary of different species, each contain both hormones, but that the proportions differ much in different species.

Fevold (52), et al, in discussing as to whether there are two separate hormones state, "Many still hold to the single theory, saying that different absorption, or varying doses, either may produce a different response from the ovary." They however, by many experiments, fractionated an aqueous pyridine extract of dessicated sheep pituitary powder, into two preparations. One fraction which is characterized by being water soluble, is very active in stimulating growth of the follicles on the ovaries of immature rats, and rabbits, and relatively inactive in producing lutein development. The second fraction is more insoluble in water, and is practically inactive for the follicle growth, but is active for luteinization. Many tables and data are shown, and the authors are of the opinion that the development of follicles, and corpora lutea in the ovaries of rats, and rabbits is due to the action of

TWO separate principles, one which causes growth of follicles, and a second which changes the follicles to corpora lutea, and that these two factors have been substantially separated from one another, though the separation is not entirely complete.

Zondek in his original work was of this opinion from the start, while Wiesner, and Marshall(53) felt that it was impossible to explain the results as the action of one substance, and Evans and his collaborators(30) believed that experimental results suggested two well separated principles, even if the results could be explained on one active principle. So we see that Fevold and his workers had many of the same opinion as themselves, even if their work had not progressed to as fine an experimental state.

Allen (54) in his book "Sex and Internal Secretions", sums up the subject well at this time, under the article written by Engle. He states " Two closely related questions are constantly confronting the workers in the field. The first involves the unity or multiplicity of the active principle or principles of the anterior lobe affecting reproduction. The second question, largely dependent on the answer of the first, concerns the anterior-pituitary-like substance in the placenta, blood, and urine of pregnancy. Are they the same or merely similiar factors, and do they rise from the placenta or the anterior lobe? The one essential requirement for an answer to the question, as to the nature of the substance from the anterior lobe is an adequate biological test. For the

original work on implanted tissues, the rat and mouse were satisfactory. As test animals for extracts of either the gland or of pregnancy urine, they are not satisfactory.----- He further states that the active principles of the anterior pituitary, placenta, and pregnant urine are apparently very similiar on biological test, differences may exist, but the data is not abundant. The fractions seem to have more chemical resemblances than differences. Engle leaves the impression in this article that he is not so sure of whether there are two principles in the anterior lobe, which have to do separately with follicle formation, and lutea formation. He believes that the physiological state of the receptor organ more nearly accounts for the dual action of the anterior lobe, than does the evidence obtained by the fractionization of the gland. Even though it may be eventually shown that there are two gonadotrophic factors in the anterior pituitary, he states, the consideration of the gonad, as an actively changing organ, will aid in clarifying the concept of the nature of the stimulating substance. The evidence at hand does not justify, he thinks, a definite statement, either that there is but one gonadotrophic factor, or that there are two or more. Finally he states, "The relation of the gonadotrophic (gonadokinetic) activity contained in the placenta, blood, and urine of pregnancy, to the active principles of the gland, is equally unsettled."

At this time with the maze of evidence, both for and against the duality of the gonadotrophic hormone, and

to the origin of prolan, several workers tried the different extracts as an experimental therapeutics, to see if any confirmation for or against these theories could be discovered.

Mazer, and Katz(55), accepted the fact that intensive experimental evidence ,and clinical observations during the past decade had definitely established that sex function, and body growth depended totally upon stimuli from the anterior lobe, and that the latter to a degree, also stimulates the adrenals, thyroid and possibly other glands of internal secretion. They knew that in the absence of gonad-stimulating hormone, of adequate quantities, in pituitary extracts for therapeutic use, the discovery in 1928 by Aschheim and Zondek of a substance in the urine of pregnant women capable of evoking an ovarian response in the rodent qualitatively identical with that of transplants, and extracts of the anterior lobe tissue, met with the fondest hopes that a therapeutic agent for functional menstrual disorders was at least available in sufficient quantity to meet the needs of the medical profession. Disappointment followed the realization, that only ten percent of amenorrhic women responded to the treatment of the product when it is used as the sole agent. Function uterine treatment when bleeding was due to pituitary deficiency, responded quite favorably to prolan treatment. The difference in response of the two conditions, amenorrhoea, and functional uterine bleeding, to prolan treatment was at first explained on the basis that the product is purely luteinizing in affect, and therefore, incapable

of stimulating the inactive follicles of amenorrhoeic women to growth and function preparatory to luteinization. Without entering into a discussion of the unity, or duality of the anterior pituitary sex hormone, they state without reservation that prolan, which, as will be seen later, is not identical with the former, and is capable of provoking both phases of the ovary, in most experimental animals. The term prolan as used by these workers refers to the anterior-pituitary like substance obtained from the urine of pregnant women, commercially supplied under various names, such as folliculin, antuitrin-s etc.

From their work, they believed that prolan is a placental hormone, not identical with the pituitary sex hormone, that prolan probably stimulates the gonadotrophic cells of the pituitary to a moderate degree: that the anterior lobe of the pituitary apparently produces a pro-hormone which, in itself, possesses no gonadotrophic properties, but is readily converted into an active sex hormone by prolan. They do not believe that this pro-hormone is either the growth promoting, or sex stimulating hormone of the pituitary, however, their best clinical results were obtained in the injection of twenty-four women suffering from definite pituitary deficiencies, with a combination of pituitary extract, and prolan.

From the above we can see that we have stepped into the realm of therapy in an attempt to prove that some of the experimental evidence would effect a link with treatment.

Pratt (56) in discussing relationship of the pituitary and gonads, takes up what effect we see in humans, when so much has been done on laboratory animals. He states, "It seems quite fundamental to determine whether the follicle stimulating hormone of the pituitary when administered to women, causes great acceleration of the follicle growth, and an increased production of the ova. The answer to this should come through direct observation of ovaries in women to whom anterior lobe has been given". Hamblen (in a personal communication to Pratt) has injected anterior lobe hormone, which probably contains both the luteinizing, and follicle stimulating factors. Women waiting operation were chosen, so that the ovaries could be observed soon after the injection. His observations were similar to Pratt's, that there is evidence of the follicle stimulation. In most specimens observed, there were very few partly developed follicles. Primordial follicles remain and many large follicles were seen. Sometimes hemorrhage into the follicles, and luteinization was seen. The daily injection of 100 rat units were given from five to seven days before operation. These findings were suggestive but not conclusive because the condition found was not similar in all instances. Pratt states, "A large series should be studied, and the cases selected to represent various stages in menstrual cycle, and varying intervals of time before operation. Graded amounts of the hormone should be injected, and all details correlated. Until more data is obtained, a satisfactory foundation for the therapeutic use of anterior lobe hormone cannot be established".

At present there is no satisfactory evidence that a hormone derived from a gland, effects that gland directly, but it may supply a deficiency of secretion.

Considering its action therapeutically, he states, "The follicle stimulating, and luteinizing hormones of the anterior lobe are considered together owing to lack of evidence that they have been separated in preparations for clinical use".-----"The most conspicuous results obtained by use of anterior lobe sex hormone has been the relief of functional bleeding, associated with hyperplasia of the endometrium, "metropathia hemorrhagica" (Schroeder), a condition which occurs near the menopause. The condition of the ovaries found in this association is noteworthy since there are so many large follicles, but no corpora lutea. Not all cases act in the same manner, but in general the bleeding is satisfactorily treated, or controlled" He quotes Novak who in 1931 reported fifty-one cases successfully treated with material extracted from pregnancy urine. Anterior lobe hormones have been used for the treatment of amenorrhoea, both with, and without theelin, and in various combinations, dosage, and administration, but results obtained have not yet been constant. Up to the present time more convincing results in correction of menstrual abnormalities have been obtained by empirical use of thyroid, administered orally, than by treatment with any other hormone. A survey of the accomplishments in endocrine therapy, related to sex function, seemingly shows satisfactory establishment of



relatively few details. He does state however, that the psychotherapeutic effects are valuable.

Pratt's work, and conclusions are also accepted by Rowntree (57) 1933, who after giving a very well arranged table as to the origin of the female sex hormones, finally goes on to state, "The role of these products in animal experiments is generally speaking, clean cut. The rate of growth, the size, and the function of the ovaries, tubes, and uterus, and sexual behaviorism, may be tremendously affected by the administration of various products of sex hormones, from the ovaries, placenta, urine, amniotic fluid, the pituitary and adrenal glands. In the clinical fields however, little can be said to date on their practical value. They belong still in the field of controlled clinical investigation, and NOT, as some would have us believe, in the realm of established therapy. Even with pure hormones, chemical entities, or crystalline products, in our hands a decade at least, will be necessary to ascertain their full value in functional disorders of the female gonads!"

Even with the work of Novak and Hurd (58) and their treatment of fifty-one cases of menorrhagia due to what was thought abnormal pituitary function, and their apparent good results, the only true example of what appears to be conclusive evidence, we feel that we are safer at the present time to agree with Rowntree as to the therapeutic practicability of the hormones.

## SUMMARY

Due to the many branches to which the workers in recent years have taken us, in the study of the anterior pituitary, but which are necessary in that so little very definite knowledge has been established, a true summary is difficult at this time. However, I will attempt to sum up for the reader, briefly, the accepted facts to date which are generally accepted by the leading workers in the field.

That the anterior hypophysis is in some way related to the sexual cycle was long suspected, dating from the observations of Frohlich in 1901. Cushing, Evans, and leading up to Zondek and Aschheim in 1927, demonstrated that, of a large series of different tissues tested, the pituitary alone appeared to be involved in definite effects on the sexual organs. Continuation of these studies by investigators demonstrated the dependence of normal ovarian function on the activity of the pituitary.

The number of separate hormones produced by the anterior hypophysis cannot be ascertained, but those which appear to be fairly well established are:-, bearing directly on the ovary,

I. A growth factor, which is concerned with bodily growth, and antagonistic in a certain degree to the sex factor, inhibiting the activity of the latter during the period of growth.

2. A follicle stimulating factor, which induces

growth and maturation of ovarian follicles, with the production of the estrus-inducing factor.

3. A luteinizing factor, which is capable of inducing extensive luteinization of ovarian follicles (when in excess, even before ovulation).

Not all investigators are agreed as to the duality of No. 2 and No. 3. Some of the more recently accumulated evidence seems to indicate the existence of two separate factors, but species differences appear to play a large part in the relative predominance of the two effects. It is too early at this time to attempt an evaluation of these claims, and of others, for still other "hormones": of these, the existence of the growth factor, and the fraction having to do with follicular growth, and luteinization may be considered as well established.

Aschheim and Zondek have made extracts of the urine of pregnant women, these extracts have the combined physiologic properties of the follicle-stimulating, and the luteinizing factors. These they term Prolan: they have also prepared fractions said to have the separate properties individually, and call these Prolan A (follicle stimulating), and Prolan B (luteinizing). The latter they considered identical with similar preparations made from the anterior hypophysis but this appears to be dubious, particularly in view of the observations of several workers, that substitution therapy and urinary prolans failed after hypophysectomy.

Aschheim and Zondek have utilized the presence of the prolactin fraction in the urine as a test for pregnancy as determined by the effect on the ovaries of immature mice. The same method has been used for testing for the presence of the prolactin fraction in the blood and urine, in the normal state, and various pathological conditions (mole, and chorio-epithelioma), and in estimating the amounts of estrus-inducing factor in these fluids.

In brief summary the following actions have been ascribed to secretions of the anterior pituitary, in acting on or through the ovary:-

1. Induction of ovulation.
2. Stimulation of ovary to secretion of estrogenic substance.
3. Production of luteinization in follicles, either with or without ovulation, leading to secretion of "Progesterin"; The anterior hypophysis is essential to the maintenance of the corpus luteum during pregnancy.
4. Luteinization may also be induced by direct intra-follicular injection of the urine of pregnancy.  
(Whether the pituitary enters here is dubious).

The most essential factor now, it seems to the writer is a summary of the nomenclature, correlated by a committee, and introduced to the profession so that it is possible for the average reader to keep abreast of the literature without previous study of what the author means by the terms used.

Finally the the reader is refered to the work of Van Dyke and Wallen-Lawerence as to the chemical preparation of the gonad-stimulating principle of the anterior lobe of the pituitary body (59), if there be a desire to do experimental work, and thus add to the minute knowledge which we now possess as to the relation of the anterior pituitary to ovarian function.

THE END.

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