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Ovarian hormones with notes on therapy

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THE OVARIAN HORMONES WITH
NOTES ON THERAPY

by

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INTRODUCTION

The term endocrinology, itself, suggests indefiniteness, vagueness, and, to many students of medicine in particular, actual distaste. The reason for this is probably founded, however, upon the defamation it has received from the extravagant claims of men like Brown Sequard, who asserted his ability to restore youth with his testicular substance, and upon the modern Steinach school and their inaccurate data. The popular conception of endocrinology appears to be that of a means to fulfill the individual's suppressed desires, of making old men young, and fat ladies thin.

It has been my attempt in this treatise to bring together, and correlate, the more recent and important, well founded scientific advances in the endocrinology of the ovary. Detailed function of the related organs has been omitted, and only their primary relation to the ovary has been considered.

This field of medicine has proved a stimulus for much research, with the result that many new observations are published daily. It has been estimated that for the past ten years an average of two to three thousand articles on this subject have been published yearly. There still remain many gaps to fill in before our knowledge of the subject will be complete.
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HISTORY

The study of endocrines as a science is of comparatively recent origin. However, abnormal gland conditions were noted as early as the first part of the nineteenth century, but with no understanding of the pathology involved or its mechanism of manifesting itself, the profession were unable to understand these conditions comprehensively. Scientific study of endocrines was first begun when Parry first noted exophthalmic goitre. In 1849 Berthold transplanted the testes of cocks. Addison, in 1856, gave pathological description and symptoms of tuberculosis of the adrenals. It was not until 1888 that Brown-Sequard began our present day concept with the spectacular and fallacious report dealing with the rejuvenating effect of testicular extract.

First evidence in medical literature regarding the possibility of an internal secretion of the ovary was through experiments made in 1896, at the Londau Clinic in Berlin, where extracts of the whole ovary were given orally. No explanation was offered as to the physiologic action expected. It was not until several years later that attempts were made to explain the rationale of this therapy. Jentzer and Buettner (1900) gave saline extracts to prevent the atrophy of the uterus following ovariectomy. Bucura used these extracts experimentally, but these were later shown to be ineffective.

Frannkel (1903) discovered the importance of the endocrine function of the corpus luteum, in that its removal terminated pregnancy. Marshall and Jolly (1906) demonstrated that the ovary produced
a hormone which caused the phenomenon of estrus. By the year 1912

many works had been published dealing with the effects of the ovar-
ian extracts on the accessory organs. Icavesco, by the use of fat
solvents produced enlargement of the uterus, at the same time real-
izing that breast changes were not adequate criteria to determine
the potency of the extracts. Fellner (1911-12) used ovariectomized
test animals and carefully examined the effects produced by his
active substance from the placenta, from ovaries without corpus lutea
and graafian follicles, which were soluble in alcohol, ether, and
acetone, and were probably of lipoid nature.

It was not until 1923 that Allen and Doisy completed their
memorable work and made possible the present day international test
for the standardization of ovarian extracts. Their experiments show-
ed that a unit of female sex hormone (estrin) was the minimum quanti-
ty which, given in three divided doses at four hour intervals,
produces estrus in castrated rats. These were known as rat units, and
one rat unit was equal to five mouse units. About this same time
Stockard and Papanicolaous noted cell changes in the vagina of guinea
pigs during the menstrual cycle.

Allen, Pratt and Doisy (1925) found that follicular fluid con-
tained the female sex hormone. Seitz, Wintz and Fingerhut claimed
to have prepared two different substances from the corpus luteum,
one promoting and one inhibiting menstruation. Herrmann and Fraenkel
emphasized the presence of estrus-producing substance in the
placenta, which was later confirmed by Frand and his collaborators.

The female sex hormone, named thus by Frank was identified in the blood by Loewe (1925), in the urine by Loewe and Lange (1926). Brouha and Simanet (1927) demonstrated it in the amniotic fluid, milk, liver, bile, testes, feces, grains, garden vegetables, yeasts, and flowers. Allen, Dickens, Dodds, and Howitt (1928) obtained the female sex hormone from the placenta. Doisy, Veler, and Thayer (1929) prepared it in the crystalline form. Allen, Pratt, Newell, and Bland (1930) noted its presence in the corpus luteum.

As summarized by A. S. Parkes (50) the history of ovarian extracts may be divided into three periods. First, 1912 there was an attempt to produce a substance which had an effect on the reproductive organs, especially on the ovariectomized animal, positive results depending upon its presence in the extracts; second, with the advent of material by Allen and Doisy in 1923, estrus was determined by cornification of the vagina of rats and mice; third, the more recent attempts to produce water soluble or pseudo-water soluble forms of the extracts.
HISTOLOGY

There is some confusion as to the exact embryological development of the ovary, but according to Fuss it arises from the coelomic epithelium in the ridge mesial to the mesonephron, and these primary germ cells wander through the mesentery to reach the anlage of the gonad. Pfluger believes that the ova are formed by the lining layer of the coelomic cavity. On the other hand in the chick, according to Swift, the primary germ cells can be traced from an extra-embryonal origin.

The ovaries, two in number, lie in the abdominal cavity with nine-tenths of their area free in the peritoneal cavity, and are covered by a single layer of germinal epithelium. They are composed of two main portions, the cortex and the medulla. The cortex is the superficial layer composed of, outermost, a single layer of low cylindrical germinal epithelium; next, a matted layer of connective tissue, and unstriated muscle fibers (tunica albuginiae); then the vascular stroma containing a large number of follicles. The larger follicles found toward the medulla. After they have reached a size of 0.5 cm in diameter further growth and enlargement takes a centrifugal direction, the follicles eventually projecting well beyond the surface of the ovary. The medulla is composed of many convoluted arteries and veins, as well as lymphatics and nerves which enter the broad ligament through the hilum. Nerve ganglia and unstriated muscle are found there also, as vestigial remains.
At birth the ovary contains from 3,000 to 30,000 primordial follicles, and in addition a few growing graafian follicles are usually encountered. With the gradual descent into the pelvis there is a slow increase in the size of the ovaries, they appear to lag behind the general body growth. Evidently some trophic influence is exerted by infrequent and not complete maturation of the follicles. At the onset of puberty a regular and well marked increase in the rapidity of ripening, and in the full maturation of follicles, takes place, and has been shown to be dependent on the activity of the anterior pituitary lobe.

At cyclical intervals a primordial follicle shows signs of growth, maturation and formation of a graafian follicle with cavity, discus, and avum. As this grows it projects above the surface of the ovary and ruptures (ovulation). The point of rupture of the collapsed follicle soon closes, and the cavity is first filled with blood which is later invaded by connective tissue. The epithelium of the follicle (granulosa) rapidly multiplies; its cells enlarge containing a lipoid of yellow color. This structure is now called the corpus luteum. The outer layer of the corpus luteum is divisible into two strata: the inner narrow connective tissue stratum (theca interna), and the outer vascular, almost cavernous layer (theca externa) which merges with the surrounding ovarian stroma.

The detailed histology of this structure reveals that the theca externa becomes vascular early, and that the theca interna
has many large clear cells loaded with lipoid (theca lutein cells), the epithelial layer becoming stratified. The cells are small, of cylindrical or spindle form, and show mitotic division. The follicular cavity may either be empty or contain serum or blood.

Vascularization stage: The external thecal cell changes persist, while the theca interna is less prominent. The granulosa cells become distended by lipoid and lutein contents; the nuclei are spherical and less deeply staining, and the innermost layer has a feathery margin. Spindle cells and red blood cells appear at the outermost edge of the granulosa cells (lutein cells), where these come in contact with the internal theca, gradually forcing their way to the follicle cavity. These isolated forerunning changes precede actual vascularization. They are followed or replaced by the formation of fine or dilated capillary vessels which penetrate between the lutein cells until the follicle cavity, which has been filled with serum or thicker fluid in the meantime, is reached. It is by way of these vessels that the internal secretion reaches the general circulation. The following stage, known as ripeness, is the one previously described as being the corpus luteum stage. At this time the theca interna and externa are barely definable, and are visible only in bases of the larger septa, which penetrate the lutein (granulosa) margin. With the increase in size and number of lutein cells there is an infolding, crenation in character, of the lutein edge. The cells are uniform in size, irregularly cuboidal, and pale with light spherical nuclei; the cell bodies contain-
ing lipoid granules and lutein. Between the cells and running toward the central coagulum are many straight capillaries accompanied by spindle cells. When these spindle cells reach the coagulum some spread along the surface of the epithelium and some spread into the clot. The connective tissue septa spread from the theca interna toward the centrum to meet the other septae, which arise from the connective tissue which has proliferated in the clot.

Grossly the next stage, that of regression, looks paler. The fibrous septae are firm; the capillaries are diminished in size; the lutein cells become smaller and vacuolated, with irregular or deficient staining. The central core of the corpus luteum is fibrous. This stage may extend over six weeks or more to the formation of the corpus albicans, which is merely a connective tissue overgrowth.

Thus the corpus luteum is a temporary structure and functions as a gland of internal secretion temporarily. In the abortive or menstrual cycle it is of short life, vascularity marked, existing at most, for two weeks after ovulation. The involution and obliteration rapidly takes place: first obliteration of the capillaries, then degeneration of lutein cells, later invasion and substitution of the lutein cells by stroma cells, forming a connective tissue scar (corpus albicans).

If, however, the ovum is impregnated and embedded in the uterus the corpus luteum is larger and more persistent. The first signs of loss of function of the corpus luteum appear about the fifth month, but full involution and obliteration do not become manifest until
after the birth of the fetus. According to Miller's concept there is an accumulation of colloid in the lutein cells, also an irregular distribution of calcium deposits. Fat is absent at all times. Regression takes place by necrosis.

The interstitial gland, if present, consists of scattered epithelial or epitheloid cells in large groups throughout the cortex of the ovaries of certain animals. No function can as yet, with any degree of certainty be assigned to this inconstant structure (27). In man the interstitial glands resemble the corpus luteum, containing similar lipoid granules which are prominent from the third month of pregnancy, if at all.

As will be shown in more detail later, there is a marked interrelation between the various endocrines. It suffices to state here that according to Englebach (18) in embryonic life, if thyroxin is normal there is normal pituitary function, and at birth subsequently there is normal development of suprarenal cortex. Any variation in this sequence causes an abnormality in the development of the gonads.

In animals it has been shown by Parenoff (48) that extrapolation of the uterus causes degenerative changes which are manifested in the ovaries. The ova perish. The granulosa cells are destroyed with the formation of vacuoles and pyknosis. Many follicles become cystic and many develop into pseudo-corpora lutea. Edema and general hyperemia of the gland follow, with later connective tissue degeneration of the ovaries supervening. The interstitial gland becomes enlarged.

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General Consideration: Ovaries are glands of external and internal secretion. The ova representing the external secretory product were first noted by Von Baer in 1827. Aschheim believes the theca interna of the follicles responsible for the internal secretion which is elaborated by the follicles. Wallert and Seitz believe that the interstitial gland likewise produces a hormone. Burch and workers concluded that the ovary had two secretions, estrin (female sex hormone by Frank) and the corpus luteum hormone. The present day concept, however, does not differ a great deal, the two secretions being estrin (folliculin) and progestin. More recent work has shown the stimulating effect of the anterior pituitary on the ovarian secretions.

In this discussion we shall first take up the specific hormones, their actions, their relation to the anterior pituitary, and later we shall correlate these facts in attempting to explain physiological conditions in relation to endocrine action in the human.

Experimental Methods: At this time we shall discuss briefly a few of the experimental means of determining the physiologic actions of the ovarian extracts. The four most common methods are all from the laboratory animal by study of (1) uterine mucosa, (2) vaginal smears, (3) growth or atrophy of the uterus and tubes, (4) maintenance of gravidy in castrated rats are the most widely used, and
the vaginal smears as indicators are universally accepted.

During the anabolic phase of the cycle in rodents, the epithelium of the vagina grows to a considerable thickness and a cornified layer similar to that in the epidermis develops. During the catabolic phase the outer layers of the epithelium degenerate and are removed by the leucocytes (thus a microscopic examination of vaginal smears is a reliable indicator of the estrual condition of the animal). These changes cease after double ovariectomy, and their induction by the injection of ovarian extracts constitutes a positive test for the efficiency of these extracts. It was on these principles that Allen and Doisy (3) brought to light the methods of testing and standardizing ovarian extracts. The present day standards which have evolved from these early workers state that 1 rat unit is the amount of hormone necessary to produce full estrus in 48 hours in a castrated rat weighing 150 gms. One rat unit equals four mouse units, Englebach (18). Parkes and Fellerby (53) define a mouse unit as the least amount of an extract given at one time required to produce estrus symptoms in an ovariectomized mouse. M.U.K. indicates mouse unit per kilogram of original tissue.

It might be well at this time to mention the Aschheim-Zondek urine test for pregnancy. The urine is injected into mice, which are autopsied on the fifth day. The ovaries are then examined for: (1) growth and maturing small follicles, (2) hemorrhage into the ovary, (3) appearance of corpus lutea. In interpreting this, the first finding may be positive in hemorrhage of climacteric,
amenorrhea, after total oophorectomy, and roentgen irradiation. While the second and third findings are positive proof of pregnancy.

In correlating experimental work on animals with the human cycle, it may be said that the proestrin and maturation of the follicles coincide, while estrus is the final reaction of the preparatory changes, which are probably due to the same cause, occurring during proestrin. Menstruation is a homologue of proestrin as distinguished from estrus.

**Corpus Luteum:** The rupture of the graafian follicle is followed by the formation of the corpus luteum, which has been discussed earlier in this account under the histology of the ovary. The persistence and function of the corpus luteum in pregnancy will be discussed later.

Many authors have tended to minimize the importance of the corpus luteum in the menstrual cycle; however, it undoubtedly has certain definite functions. Among the earlier workers Prenant, Beard and Fraenkel thought it to be the only gland of internal secretion, and attempted to explain all effects on this structure. Born's hypothesis that if the corpus luteum be removed early in pregnancy, the fetus would be absorbed; if late, would be aborted. In attempts to study the function of the corpus luteum in animals we find that its effects vary with the species studied. For example, in the rabbit and ferret no corpus luteum is formed until copulation has taken place; in the dog ovulation is spontaneous at estrus; in
the rat and mouse ovulation needs the stimulus provided by the act of copulation before the corpus luteum becomes functional. (Anatomically and functionally the active portion of the corpus luteum is regarded as an epithelial structure.)

Papanicolaou (47) in the removal of the corpus luteum in guinea pigs, concluded that it had an inhibitory action on ovulation and estrus. Parkes and Bellerby (53) confirmed this. Frank (24) states that the corpus luteum lengthens the sex cycle by interfering with the maturation of the growing follicles. Allen (2) prevented or delayed the occurrence of ripening follicles and the onset of estrus by injection of corpus luteum extracts. Pratt and Allen (56) believe that this substance is very similar to one probably excreted or stored in the placenta, and its continuous availability throughout the gestation period would account for the absence of menstruation during pregnancy.

During pregnancy Frank (24) and Anglebach (18) assume that nidation is assured by the reaction of the uterus. The stimulus for this reaction is called forth by the presence of a foreign body (ovum), with the resulting natural decidua formation. They also state that the corpus luteum enables the uterus to produce this reaction. Parkes and Bellerby (53) feel that the corpus luteum is the developmental cause of uterine preparation for the reception of the ovum. This was confirmed also by Meyer (43), who further states that this may explain delayed impregnation.

The maintenance of pregnancy is due to the fact that the corpus
luteum renders the uterine mucosa immune to the contracting action of the posterior pituitary hormone, and according to Johnstone (35), he was able to conduct castrated rats through pregnancy.

The theory that the corpus luteum plays a part in the development of the mammary glands, is not well founded, although Parkes and Bellerby (51) concluded that this development is due to persistent corpus luteum in the case of mice.

Regarding the formation of estrin, Parkes and Bellerby concluded that the corpus luteum is certainly not the essential organ of estrin elaboration. However, S.S. Smith (63) deduced that estrin is excreted only when the organism has been exposed to the action of the corpus luteum. Thus it appears possible by this means to differentiate between persistence, irregular appearance and total absence of corpus luteum in the cyclic activity of the corpus luteum.

In summary, there are four main functions assigned to the corpus luteum: (1) inhibition of estrus and ovulation during pregnancy and lactation; (2) development and preparation of the uterus for the reception of the fertilized ovum; (3) maintenance of pregnancy; (4) development of mammary glands. (Progestin, the secretion of the corpus luteum according to recent research, will be discussed under a separate heading.)

**Folliculin:** That folliculin arises from the follicle has been confirmed by Parkes and Bellerby (52), Allen (2), Novak (45), and Frank (26). It is also generally believed that this substance is derived from the corpus luteum in pregnancy. Allen (2) believes
that folliculin is the principle ovarian hormone. In more recent years it has been extracted from widespread sources: chorionic vesicles, placenta, yeast, plants, etc.

Parkes (49) shows that in pregnancy the injection of folliculin during the early stages causes the rapid reappearance of estrus, and the termination of the pregnancy. If injected in sufficient amounts during the later stages, it nearly always terminated the pregnancy. Haupstein (32) was able to sterilize animals by injection of extremely large doses of the follicular hormone.

The outstanding effect produced after the administration of folliculin is noted in the accessory genital organs. Folliculin is also probably responsible for the maintenance of ciliation in the tubes and initiation of secretion in the uterus, and for the production of the secondary sex characteristics. It may even produce uterine bleeding, but not analogous to menstruation. Mazer (41) developed artificial endometrium in spayed monkeys, but it is not of progestational type unless progestin is administered following it.

The hyperemia of the genital canal is produced up to the time of the rupture of the follicle. After follicle rupture this is carried on partly by the remaining corpus luteum. Folliculin is the normal stimulant of rhythmic uterine contractions throughout the cycle. Later in the cycle this effect is inhibited by progestin. No stimulating effect of folliculin on the ovary or ovulation has been demonstrated; in fact evidence indicated that large doses are actually harmful.

Positive tests from fresh follicular fluid, removed from the ovaries
at operation, indicates that the amount of folliculin decreases before the beginning of the next menstrual cycle.

Folliculin must precede the progestin of the corpus luteum. With the rupture of the follicle and the formation of the corpus luteum, there is a continual elaboration of the follicular hormone; thus Allen (2) concludes that folliculin enters the blood stream with progestin. Prolan A (anterior pituitary substance) is responsible for follicle maturation and the activation of folliculin, or theelin.

Englebach (18) concluded that the action of folliculin, if any, upon the ovary may be by way of the hypophysis. Lutein activity of the follicle is affected by hormones as from the anterior pituitary, and probably suprarenal cortex, and during pregnancy from the placenta.

**Progestin:** Progestin is a secretion of the corpus luteum and this secretion is due to the direct action of the anterior pituitary (prolan B).

Progestin begins its effect on the endometrium after ovulation, carries the uterine mucosa through the secretory or pregravid phase, and reaches its height just before the onset of the next period. Its effect on the endometrium occurs only when the endometrium has been previously primed by folliculin (theelin). If the ovum is not fertilized the progestin has failed and the endometrium breaks down in characteristic menstruation. If, however, pregnancy intervenes, this endometrium becomes the decidua of early pregnancy.
Ovulation is inhibited, and as soon as the restraining influence of progestin is removed a new crop of follicles begin to develop. Novak (44), Dowell (17), Novak (45), Anglebach (18) are all of this opinion. Progestin inhibits the contractility of the uterine musculature, thus being antagonistic to folliculin, but this effect may be considered as supplementary.

Thus the effects of progestin are seen to be the same, practically, as those of the corpus luteum, which has previously been discussed.

Anterior Pituitary: From recent experiments dealing with the secretion of the anterior lobe of the hypophysis it has been concluded and recently confirmed that the pituitary (1) promotes growth to the extent of gigantism, (2) luteinizes the follicles, (3) inhibits ovulation and estrus. In transplantation experiments the anterior lobe has no effect on the vagina and uterus of an ovariectomized animal. In the normal animal it causes estrus changes, noted in the vagina and uterus, and also ovulation and luteinization in the ovaries. Thus we may conclude that the anterior pituitary hormone is primary and it is the motor stimulus of the sexual function; while the ovarian hormones are secondary; (von Arvay (69), Novak (45), Fluhmann (20)).

Allen (2) observed that there was a rapid growth of the follicles when they were under stimulation from the hypophysis, and that it induced the secretion of theelin, thus stimulating the growth phase of the accessory organs, including the mammary. Prolan recover-
ed from the urine of pregnant women was seen to have variable effects with different workers, which led to exhaustive studies to determine the different hormones present.

Thus the anterior pituitary has four main hormones: (1) growth hormone; (2) metabolism hormone; (3) Prolan A, or follicle ripening hormone, corresponding in action to folliculin; (4) Prolan B, luteinizing hormone similar in action to the corpus luteum (progestin). This hypothesis was advanced by Zondek, and confirmed by others.

Theories have been advanced that the action of the posterior hypophysis is entirely nullified by the follicular hormone, or that the uterus is sensitized by means of folliculin until parturition (when the threshold is reached and the posterior hypophyseal secretion "pituitrin" becomes effective).

We may now show the complete cycle. Prolan A stimulate follicle ripening and incites the theca cells to production of folliculin, which causes proliferation of the endometrium. Prolan B causes changes of granulosa and theca cells to lutein cells with the production of progestin which changes the proliferative stage of the endometrium to one of secretion (premenstrual stage).

Other Glands: Novak (45) is of the opinion that the thyroid and suprarenal cortex are of importance in reproduction, but little is known of the mechanism involved. In hyperthyroidism (artificially produced) in rabbits estrus, ovulation, fertilization, migration, and implantation took place, but in most instances resorption of the fetus resulted. Generally speaking Englebach (18) thought that
the thyroid had an inhibitory action on the gonads before and after puberty.

The intermediate action of the pituitary hormone through the adrenal cortex, or direct cortical action, may stimulate the folliculin and lutein activity in both pregnant and nonpregnant in its effect on the external genitalia.

Diagramatic representation of the inter-action of the female hormones. Taken from Englebach (18).
Prepuberty: There arises the question whether the sex glands of the fetus produce a hormone during intrauterine life, but this has never been answered experimentally. Carlson has demonstrated that the fetal pancreas functions. Bell found that the fetal thyroid contains a hormone. It is known that large amounts of female sex hormone are in the maternal circulation and can be recovered from the cord blood of the new born fetus. Thus both sexes are subjected to this female sex hormone influence in intrauterine life. From the early weeks of life until puberty, although the female gives the appearance of a sexual or neuter state, there is evidence of a continuous, although not large, secretion of hormonal substance from the gonad. Anatomically there is an increase in the number of the growing primordial follicles, which reach graafian size in development, but undergo atresia. Quantitatively the follicle ripening is still insufficient to initiate puberty.

Englebach (18) emphasizes the importance of the inter-relationship of the various endocrines for an individual to reach puberty. Growth in infantile and juvenile years is augmented by the growth hormone of the pituitary, and of the thyroid preparatory to gonadal activity, while disorders of the thymus, parathyroids, suprarenal medulla, and islands of Langerhan, may have an effect on the gonads both before and after adolescence. If the relationship of these various endocrines is normal then gonadal activity is normally established at puberty.
Puberty: Puberty is marked by somatic and psychic changes and culminates in the first menstruation (which will be discussed in detail later). The various endocrine interrelation still exists, and according to Frank (26) the female organism is also acted on from neonatal to menopause by both the prepituitary and female sex hormone; after puberty has been reached the female organism is acted on by the gestational hormone in addition. The actual exciting cause for the onset of puberty is unknown, but it is very possible that this is due to folliculin present previous to this and causing development of accessory organs, but not present in sufficient amounts to precipitate estrous symptoms. Parkes (50) concludes that the ovary has a basic internal secretion to which the cyclically active hormones are added at puberty. Many disorders do not appear until after puberty because of the beginning of additional hormones in gonadal activity, Englebach (18).

Experimentally Allen and Doisy (3) have produced sexually mature animals by the injection of anterior pituitary substance into immature animals, also by injection of ovarian extracts (known as precocious puberty). If castration occurs in the immature animal puberty does not take place and it becomes of neuter state (genital tract fails to develop, breasts remain undeveloped even atrophy, the epiphyses ossify late resulting in long extremeties). There is no reliable record in the literature of human female being castrated in infancy, and surviving to adulthood.
When puberty is reached the organism is sexually mature, although body growth has not yet been completed. During sexual life of approximately thirty years there are 360 menstrual cycles. Castration at this time produces artificial menopause. Menopause: The exact physiological process which occurs at the time of menopause is not well understood; whether the gradual cessation of menstruation over a long period of time in contrast to onset at puberty is due to exhaustion of follicles, or whether another mechanism comes into play has not been determined. Cessation of fertility may not accompany the cessation of menstruation, and the ovarian cycle may therefore go on longer than the uterine cycle. However, with the menopause there is an involution of the Mullerian system, the vulva, breasts, and some of the less constant secondary characteristics are similarly affected. The changes verge toward a neuter type as a result.

The above condition may take place naturally at forty-five to fifty years of age, or artificially by operative removal of both ovaries, or by X-ray of the ovaries.

Menopause may be divided as follows:

1. No ovarian hormone found in the urine
   a. Artificial (operative or X-ray)
   b. In some cases it is spontaneous

2. Ovarian hormone is present in the urine.
   a. In some cases of spontaneous menopause.

Thus our therapy must be modified to the type of patient we
we are dealing with.

**Menstruation:** It is now definitely established that menstruation is under hormonal control, but first let us consider the sequence of events in the menstrual cycle. Ovulation is usually stated to be the twelfth to the thirteenth day (Allen (2)) after onset of the preceding menstruation. According to Frank (27) ovulation or the extrusion of the ovum from the graafian follicle is caused by the increase in the ovarian tension, being entirely independent from nervous influence. Glots reported regular menstruation and impregnation in a woman with transverse myelitis. Schochet suggests a weakening of the follicular capillaries followed by rupture. Papanicolaou (47) states that in those animals that ovulate after coitus ovulation is due to the interstitial gland, and further concludes that it is the end result of follicle maturation accelerated by coitus, and inhibited by glands in the ovaries; ovulation is spontaneous; thus it has not been shown to replace the function of the cyclical corpus luteum. Following ovulation the ovum migrates to and through the Fallopian tubes to the uterus.

The uterus at rest is small and pale, the thin mucosa supporting straight simple glands with wide interglandular spaces. During this interval a slow growth of the mucosa takes place without secretion. Following ovulation (16-22 days) ovarian hormones exert their effect on the uterine mucosa which now has numerous tufts or papillae projecting into the glands; the nuclei of the epithelial cells assume a central position with no mitosis. The stroma cells

-24-
increase in size and form the upper compact layer and on the
twenty-fifth day edema becomes quite marked. At this time the
corpus luteum has reached maturity, and the ovum is in the immediate
vicinity of the uterus. Now one of two things may happen. The ovum
may become fertilized; if so, the pregravid endometrial changes
become the early decidua of pregnancy and the corpus luteum becomes
the corpus luteum of pregnancy; or if the ovum does not become
fertilized, the endometrium undergoes retrogression and degenera-
tion, resulting in the casting off of the upper layers, as the men-
strual blood. There is a rapid complete necrosis of the functional
layers (compact and spongy), the muscle only being covered by the
remaining basal layers, which contain merely the fundi of the glands.
The uterus returns to its resting state, previously described, also
the corpus luteum undergoes retrogressive changes, described in the
section on histology.

Now let us attempt to analyze this cycle from the hormonal
standpoint. It is generally understood that the endometrium is
stimulated to hypertrophy, which is found from the time the ovum
starts maturing until extruded from the follicle. Allen (2) states
that ovulation with corpus luteum formation is essential for the
premenstrual endometrium transformation. The corpus luteum is said
to have a "nidatory hormone" (progestin) which seems to sensitize
the uterus for the embedding and early growth of the fertilized
ovum. Dowell (17) concludes that progestin is the supporting
hormone of the endometrium from its appearance until the twenty-
eighth day of the cycle. If the ovum is not fertilized progestin fails and the endometrium breaks down with the characteristic menstruation. Allen (2) believes that the corpus luteum is not necessary for menstruation, but Novak (45), and Pratt and Allen (56) state that the decreased secretion of theelin (folliculin) causes the onset of menstruation, and theelin alone seems to supply the necessary elements for the phenomenon. Novak (45) also believes that the menstrual cycle is dependent on an internal secretory function of the ovary, which in turn is dependent upon the anterior lobe of the pituitary. While Hartman, Firo and Geiling in their work on monkeys (Englebach (18)) conclude that actual bleeding is caused by the anterior lobe of the pituitary after it has been stimulated by the ovary or some other endocrine link, Meyer (43) concludes that only the functional preparation of the mucous membrane intended for pregnancy should be regarded as physiological function, that menstruation should be regarded as a failure, and a passive non physiological process.

Pregnancy: Fertilization is the sole purpose of the gonads. The end result of all endocrine function depends largely on the secondary effects of the activities of the hypophysis, thyroid, and suprarenal cortex; however, great detail will not be gone into in this connection; merely the effects produced on this condition by the internal secretions of the ovary will be given.

In early pregnancy the corpus luteum plays the important role in the production of progestin, described previously. To review
briefly, it sensitizes the uterine mucosa, rendering it responsive to mechanical stimuli (resulting in the maternal placenta), also the inhibition of follicle formation and menstruation. As gestation approaches, according to Witherspoon (75) there is a release of an inhibitory factor, previously held in abeyance by the luteinizing factor in the ovary, placenta, and the anterior pituitary. The uterine sensitivity to pituitrin is stimulated by the release of estrin, becoming more marked and continuous until the threshold is reached, when labor is precipitated. Working on this theory Witherspoon (75) was only able to induce labor in 22.2 per cent of the series of pregnancies within thirty-six hours after administration.

Ovum: From extrusion of the ovum from the ovary until implantation in the uterus, it is not known whether the ovum has a functional effect; on implantation, however, there is no question.

Genital Tract: Iscavesco used lipoid extracts from the ovary, corpus luteum and placenta, and he found that when they were injected into rabbits there was a hyperplasia and congestion of the uterus and vulva. This was confirmed by Fellner 1912-1913. Pratt and Allen (56) were of the opinion that the ovarian follicular hormone started the periodic growth process in the female genital tract. Novak (45) stated that folliculin stimulated hyperemia until follicle rupture, and that following this the corpus luteum stimulated rhythmic contraction throughout the cycle, until progestin inhibited. In the hands of some the tonus of the uterus was increas-
ed, as were spontaneous contractures, by the use of the pure crystalline hormone; and with the use of folliculin the tonus of the uterus was decreased. Thus we may conclude that the effect of the ovarian hormone depends on the functional condition of the uterus. Parenoff (48) goes so far as to assume the uterus has a hormone which stimulates the ovaries, when he found it more difficult to induce estrus after the uterus had been removed for some time. Hartman finds relaxation of the pelvic ligaments in the monkey on the approach of parturition; he calls this substance relaxin, but he has been unable to identify it in the human blood.

**Lactation:** Parkes and Bellerby (51) found that in the suckling mouse with more than two young does not come into estrus during normal lactation, but with injection of the estrus producing hormone they were able to produce estrus. They conclude that the inhibitory effect of lactation is set up via the ovary and probably by a persistent corpus luteum. Papanicolaou (47) concludes that the growth of the mammary is due to ovarian influence, (maturation of follicles and the activity of the corpus luteum). The same factors that produce the persistence of the corpus luteum probably cause the breast hyperplasia of pregnancy. Engelebach (18) has stated a general belief that the effect is produced by the anterior pituitary after it has been acted on by the corpus luteum.
The chemistry of these endocrines, the ovaries, is little understood even at the present time, while of the chemistry of the earlier substances used nothing was known. However, scientific study of this may be divided into three periods: first, little or no information obtained from the aqueous extracts and press juices; second, study of lipoid soluble substances; third, at the present time, study of the analysis of the water soluble and very active fractions.

There are no references as to the chemical nature of the aqueous extracts. However, in studying the properties of the corpus luteum Frank (24) states that it contains fatty substances called lipochromes. The active substances were thought to be lipoid by Brown and Ancel. Doisy and Butenandt independently and simultaneously obtained crystalline estrin, chemically known to day as triple unsaturated oxyketone with the formula $\text{C}_{18}\text{H}_{22}\text{O}_2$.

The characterization of alpha and beta follicular hormones as isomeric oxyketones $\text{C}_{18}\text{H}_{22}\text{O}_2$ was followed by the discovery of delta follicular hormone $\text{C}_{18}\text{H}_{22}\text{O}_2$. Later the follicular hormone crystal was prepared from urine by Girard, who isolated isomeric "hippulin" ($\text{C}_{18}\text{H}_{20}\text{O}_2$) and one oxyketone ($\text{C}_{18}\text{H}_{18}\text{O}_2$) the equilin. Recently Schwenk and Hildebrandt reported the discovery of two "dihydrofollicular hormones" $\text{C}_{18}\text{H}_{24}\text{O}_2$, which are presumed to be superior in
effectiveness to all known hormones of this type. Marrinn (1930) isolated "tri-hydroxyoestrin" from pregnant urine. Doisy (1930) prepared the substance "theelol" or "follicular hormonal hydrate". Collip (1931) isolated a product from the placenta similar to the follicular hormone, "emmenin" (C₁₈H₂₄O₃).

The question now arises as to whether these substances are identical or closely related isomers. The physical and physiological properties, render their identity questionable. However, all three show the same chemical properties, and supposedly have the same chemical composition.

<table>
<thead>
<tr>
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<th>Melting point</th>
<th>Absorp. in ultra-violet</th>
<th>optic rotation</th>
<th>Physiol. eff. on mice</th>
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<tbody>
<tr>
<td>Theelol</td>
<td>279-280°C</td>
<td>283-285 mm maximum</td>
<td>Identical</td>
<td>Same</td>
</tr>
<tr>
<td>Foll. Hor.</td>
<td>279-280°C</td>
<td>Same</td>
<td>&quot;</td>
<td>Same</td>
</tr>
<tr>
<td>Emminin</td>
<td>278°C</td>
<td>Same</td>
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<td>Greater</td>
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Thus Butenandt and Browne (13) conclude that they are identical, and that the hormone crystals isolated from the urine are formed in the organism. Parkes (50) demonstrates that folliculin is readily soluble in fat solvents, slowly in petroleum and ether; that it is resistant to high temperatures; oxidizing easily; is resistant to lipase of plants, pancreas and liver; and has some resistance to pepsin. It is non volatile, readily absorbed and destroyed on exposure to light.

Some findings indicate that hormone hydrate develops its activity in the body only after it has been transformed into the more effective forms of follicular hormone. This is probably achieved in

-30-
the ovaries.

Prolan: Prolan is damaged by heating to $60^\circ$ C, is destroyed by boiling, strong acids, or alkalis, is easily dialyzed, is insoluble in ether, is adsorbed by charcoal, and precipitated by alcohol. There is no demonstrable chemical difference between prolan A and B, Englebach (18). Dickens showed that it is effective orally in forty rat unit doses, although it is destroyed by pepsin and trypsin, and precipitated by ammonium sulphate and colloidal iron. Evans, Myer and Simpson believe it to be a hormone activator rather than a hormone.
For a more comprehensive understanding of the various preparations available at the present time, we shall point out the more common proprietary preparations correlated with the active principle. The names are often misleading and confusing. The estrin principle is contained in the following: agomensin (tablets), ammiotin (aqueous solution), estrogen (colloidal extract), menforman (aqueous extract) ovarian residue (tablets), pregonon (tablets), theelin (crystalline form), and varium (tablets). The progestin principle is contained in the following: lipo-lutin (emulsion), lutein tablets, and sistomen­sin (tablets). The proprietary preparations of corpus luteum are many. Many of them do not contain the lutein hormone. If they do, they are mixed with folliculin. According to Frank lutein is in the lipoid fraction and folliculin in the aqueous.

Emminin taken from human placenta is similar to Prolan A. Emminin (unaffected by the digestive enzymes) is potent orally as well as hypodermically. Emminin differs from theelin in that emminin is ineffective in castrates. This substance was extracted by Collip (15).

In 1930 Doisy and coworkers developed a new triatomic alcohol from the urine of pregnant women. It is closely related to theelin but differs in physical and chemical properties, and was called theelol. It is an oestrogenic hormone, and produces its effect when
administered orally. Englebach (18) has since doubted that theelin is a true follicular hormone. Novak (45) states that the active substance is a hydroxyl derivative of theelin.

Certain pharmacological actions are ascribed to the various preparations of the ovarian extracts, and a few of them will be cited at this time.

Central Nervous System: Herren (33) shortened the achilles reflex time in rats by increasing the concentration of the luteal hormone. He concludes that although sympathectomy does not alter the normal estrus cycle, it is probable that the ovarian hormone influences the higher nervous levels through the sympathetic connections, and is not a direct stimulus. While Badylkes (4) has shown that extrapolation of the ovaries leads to inhibitory processes of the nervous system, which is expressed in a decreased reflex excitability. In the case of the guinea pig, there is a prolongation of the latency period of the secretion of the gastric juice. During pregnancy the increased secretion of the acid value of the gastric juice reaches its climax in the lactation period. Badylkes (5) suggests that physiological and pathological processes in the female genitals cause numerous gastric disturbances of reflex nature, which are functional rather than organic. Menstruation is frequently accompanied by dyspeptic disturbances, easy fatigue, psychic lability, profuse sweating, salivation, and tachycardia. Mazer (41) states that these symptoms are due to hypersensitivity of the sympathetic nervous system, the same is true at the menopause. Badylkes (5) produced
an increased reflex excitability in normal animals by the injection of large quantities of ovarian products.

Thus it can be seen that the data is vague and nonconclusive, and that the literature is contradictory.

Non Protein Nitrogen: Bowman (10) states that the N.P.N. is lowered in the use of ovarian hormones in melancholia, simultaneously found that if the choleetrol had been previously lowered it was raised.

Calcium: Dixon (16) concluded that estrin and corpus luteum caused no change in the blood calcium in rabbits, dogs, and rats. Previously it had often been stated that the blood calcium was raised.

Basal Metabolic Rate: It is the general opinion, and evidence confirms this, that the B.M.R. is increased by the administration of ovarian extracts. This reaction is probably due to estrus process and hypertrophy of the uterus; thus there is no increase when they are administered in male animals, or females in which the uterus, vagina, etc. have been removed. Von Arvay (69) working with four ovarian preparation, Verzar (68), Bowman (48) in work on melancholia, and Parkes (50) all conclude that the B.M.R. is increased.
Before attempting to prescribe an endocrine product, or to influence the cause of the derangement, its gravity and extent should be known. Otherwise treatment is purely experimental and usually futile. Thus a thorough examination is necessary. For practical purposes menstrual dysfunction, which is usually thought of as an ovarian hypofunction may also be a hypofunction of the thyroid or the anterior pituitary.

In diagnosis of these conditions the clinical history, general body make-up and general physical examination must first be considered, and if, properly evaluated, should lead to suspicion of endocrine imbalance. This may be confirmed by urine and blood tests (when the ovarian hormone is negative in the urine while prolana A is positive, the ovaries have ceased function; when ovarian hormone is positive and prolana A is negative the ovaries are functioning). Attempts have been made to determine the type of dyscrasia from uterine curettages. Hyperplasia of the endometrium result from the unopposed action of the estrus producing hormone, and is probably held in check by the corpus luteum hormone (ovaries lacking in corpora lutea in cases of hyperplasia). Absence of ovulation (absence of corpora lutea) could be due to some interference with normal activity of the hypophysis. This could be a deficiency in substance producing ovulation, or a failure in its release until gesta-
tion. This condition is due to the fact that changes preceding ovulation are the result of estrus, while those following ovulation are due to the combined action of the two hormones.

Before attempting to treat these conditions let us first review briefly the conditions with which we may deal.

Amenorrhea: Amenorrhea is one of the most common gynecological complaints, and it may be classified as physiological, pathological, and functional for our convenience. Physiological amenorrhea occurs: (1) before puberty, (2) during pregnancy, (3) during the first months of the lactation period, (4) at the menopause (natural or artificial), (5) in case of hysterectomy without gonadal ablation. Pathological amenorrhea occurs: (1) in endocrinopathies (hypopituitary, hypogonadal, and hypo and hyperthyroid group); (2) in constitutional conditions such as chronic debilitating diseases (tuberculosis, cancer, nephritis, diabetes, syphilis), blood diseases (lukemias, chlorosis), drug addiction, and nutritional disturbances; (3) in local pathological conditions. Functional amenorrhea occurs as in phantom pregnancy, anxiety states, etc.

In the conditions of hypo-ovarianism there is a subthreshold blood cycle, the lower limits in the blood and urine shows increased excretion at times coinciding with ovulation. There may be a negative blood cycle with the urine showing high concentration due, probably, to the abnormal permeability of the kidney. Or we may have an acyclic amenorrhea in which neither the blood nor the urine
show demonstrable quantities of the female sex hormone. Clinically these groups are indistinguishable.

**Menorrhagia:** Menorrhagia may be either physiologic as in the newborn; or it may be pathologic as in: (1) endocrinopathies, possibly in the first decade following puberty due to ovarian irregularities, and at the menopause due to ovarian hormonal irregularities; (2) occasionally constitutional as in acute infectious diseases; (3) in local pathological conditions.

**Menorrhagia:** Menorrhagia is always pathological, and is usually due to local conditions such as: malignancies, ulceration, abortion, placenta praevia, and hydatidiform mole. However, following the menopause it is due to senile atrophy, frequently, and thus may be on an endocrine basis, usually hypo-ovarian.

**Hyperovarianism:** In general this condition may present rather typical syndromes. In preadolescence the signs which ordinarily appear at puberty are accelerated and the anterior pituitary presses toward early sexual maturity namely: (1) menstruation begins early in life, (2) precocious enlargement of the breasts, (3) pubic and axillary hair appear early, (4) precocious development of the external genitalia, (5) precocious development of the bony skeleton. While in post adolescence with this condition the following present themselves: (1) uterine bleeding not explained anatomically, (2) prolonged menstrual flow, (3) nymphomania, (4) softening of the bones. In the puberty bleeding (menorrhagia or metrorrhagia) the blood level
of the female sex hormone is high, and the female sex hormone is also high in the urine. In the preclimacteric bleeding, the blood level of the female sex hormone shows a cyclic variation, resembling the puberty group. In maturity (menorrhagia or metrorrhagia) the blood cycle is unaffected and tests are negative.

**Hypo-ovarianism:** With hypoovarianism in preadolescence eunuchism results, with the following syndrome: (1) failure of the breasts and genitalia to develop; (2) general development is altered, tallness due to the increased length of the long bones, or obesity as in Frohlich's syndrome; (3) failure to menstruate, (4) hypotrichosis; (5) failure of the libido to appear. Eunuchaidism may be due to insufficient amounts of the ovarian hormone resulting in: (1) tallness, (2) menstruation absent or delayed, (3) Retarded or incomplete development of the secondary sex characteristics. Eunuchism in the adult presents the following syndrome: (1) atrophy of the genitalia, amenorrhea, and the appearance of hair on the face; (2) vasomotor disturbances (hot flashes, profuse sweating, alternate sensations of heat and cold); (3) physical phenomena including depression, restlessness, pessimism which may progress to state of melancholia. Late eunuchism (natural monopause) presents very similar symptoms to the adult eunuchism, but the symptoms are of a milder nature.

**Sterility:** The cases of sterility which have been studied usually show a subthreshold blood cycle level, or show a negative blood cycle and the urine cycle is present. Only a very small
percentage of the sterilities show normal hormonal conditions. 

Dysmenorrhea: Mazer (41) believes dysmenorrhea to be due to failure of the myometrium to empty the uterine vein, producing venous stasis, and pressure stimulation of the uterine nerves. This condition has been relieved by the administration of theelin combined with thyroid extracts. Gerhardt (28) believes that hormonal therapy is suitable in only those cases of dysmenorrhea, which are attributed to an underdevelopment of the uterus due to ovarian dysfunction.

Methods of Administration: For thirty-five years tablets, capsules, and powders of ovarian substance, ovarian residue, or corpus luteum extracts have been used in supposed ovarian disorders, especially concerning menstrual disorders. But with little or no results, to repay them for the materials used.

The following are the most common methods of administration: (1) tissue implants, which is a surgical procedure, and the results are indefinite and impractical; (2) orally, this method requires extremely large doses, due to the destruction by the gastric juices, but theelol is reputed to be quite effective by this means; (3) subcutaneously, which requires frequent office visits, but it is the most practical and effective for its dosage and absorption are certain; (4) intraperitoneally, but this method has no advantages over the subcutaneous method; (5) intravenously - is possible but it is impractical; (6) suppositories - vaginal and rectal are advocated by some, but have not become generally popular, due to
the indefinite amount absorbed.

Most authors agree that frequent and small doses are preferable. It is a common practice to combine subcutaneous and oral administration, which will no doubt come into more general use with the discovery of theelin. However, each specific case or type of disorder must be considered singly, and it is difficult to make generalizations, as to the dosage or type of administration.

**Theelin (Folliculin, Estrin)**

*Amenorrhea:* Although the results obtained by the use of theelin in this condition varies as to its effectiveness, theelin has been of some value in a large percentage of cases. Allen (2) and Hamblen (31) recommend its administration in all endocrine amenorrhea. While Fellner (19) found it effective in the amenorrheas of six weeks duration, but was less effective in menopausal amenorrheas even when combined with suppository administration. Gerhardt (28) obtained 100 per cent results in primary amenorrhea, but merely obtained breast changes in the secondary amenorrheas. Berger (7) and Mazer (41) found theelin of value in the oligonormonal amenorrhea but ineffective in the polyhormonal amenorrheas. Kurzrok (37) confirms this. In the cases which excreted the follicular hormone in slightly greater amounts than normal, there was no improvement. Ullmann (67) finds theelin is of benefit in early amenorrheas.

It has been concluded that theelin has no direct effect on the ovaries, but makes the uterus more responsive to whatever ovarian function may remain (Mazer (41)).
The administration of theelin in the cyclic ovary is useless; however, there is usually enough hormone elaboration to produce stromal and epithelial overgrowth of the endometrium. It is the inability for the ovary to complete its cycle (luteinization) or lack of stimulation from the anterior pituitary which is the underlying cause. After the administration of theelin and there is the resultant endometrial hyperplasia, the injection of progestin or anterior pituitary products, or irradiation of the hypophysis, is indicated.

Oligomenorrhea: Fellner (19), Hamblen (31), Gerhardt (28), and Ullmann (67) all conclude that theelin is effective and recommend it usage in this condition.

Polymenorrhea: While Fellner (19) advocates the use of theelin in this condition, Gerhardt (28) obtained negative results. Many authors even find the condition increased, which theoretically, we might expect. However, if the condition is due to the increased follicular hormone, and there is a lack of corpus luteum hormone (progestin) the use of the anterior pituitary hormone (prolan B) is indicated. Theelin has been found to be of no value in the bleeding of the menopause.

Menopausal Symptoms: Kurzrok (38), Gerhardt (28), Hamblen (31), Webster (70), Werner (71), Werner and Collier (72), and Novak (44) find theelin of distinct therapeutic value in relieving the subjective symptoms of the menopause in a high percentage of cases. While other results are reported, they are too variable to permit
conclusions. Werner and Collier (72) in working with five castrated, otherwise normal, females concluded that there was a definite relief of subjective symptoms; the cervix was more vascular; all subjects showed breast changes; four subjects had an increased libido, hyperplasia of the endometrium, and even presented subjective symptoms of menstruation with slight uterine bleeding (not comparable to the menstrual flow).

**Abortion:** In habitual abortion Zondek recommends the administration of theelin early until the sixth month of pregnancy. Erhardt accomplishes the same thing when he advocates transfusion, the donor being a pregnant woman. Fellner (19) advocates the use of theelin in abortions due to the hypodevelopment of the uterus.

Theelin has been advocated in hypermesis, frigidity, dysmenorrhea etc., but evidence is lacking.

The dosage of theelin advocated varies greatly with the extent of the condition present and the various preparations used. However, subcutaneous injection is generally accepted as the most efficient. With the development of Theelol oral administration will become more popular and the combined oral and subcutaneous administration, previously advocated by many, may be the eventual outcome. When theelin is given in large doses much is excreted, but Fellner (19) concludes that they are not dangerous since they are merely given for their stimulating effect.
Progestin

Theelin excites the motility of the uterus while progestin inhibits it. Thus Novak (46) suggests this as a basis for dysmenorrhea. The inhibitory effect of progestin is removed a day or so before menstruation, and its withdrawal may produce dysmenorrhea. In some cases there appears to be an actual imbalance between theelin and progestin. From the study of the physiology of the corpus luteum and progestin (previously considered in this paper) the therapeutic indications are self evident.

George van S. Smith used the luteinizing hormone and stopped six out of seven abortions, three of them subsequently lost their pregnancies. Engelbach (18), Allen (2), and Hamblen (31) further confirm the findings of Smith. Hamblen (31) used progestin in five cases of threatened abortion with excellent results.

Progestin may be of use in sterility, which is due to the lack of lutein activity, thus completing the cycle of estrus and menstruation.

Novak (44) and Allen (2) find progestin of value in hypermenorrhea. They also used it in underdevelopment of the mammary glands.

Progestin has not been produced on the market until recently, and at the present time it is too expensive for clinical use. However, the same results may be obtained by the administration of the anterior pituitary secretions, available clinically as
"antuitrin 'S'" and similar products.

**Anterior Pituitary Substance**

As seen in the study of the physiology of the pituitary and applied therapeutically, the anterior pituitary is of value in merely stimulating the secretory products of the ovary. Thus the use of the anterior pituitary substance would be warranted only in that connection, and would be of no value with a non-functioning ovary. Its indirect effects have been discussed in relation to progestin and folliculin.

Although not of therapeutic value the following may prove of value in the diagnosis of pregnancy. Injection of the anterior pituitary hormone intradermally in pregnant women is negative, while in the non pregnant there is a marked erythema surrounding a wheal at the site of injection. Dowell (17) suggests that this may be allergic; thus in the nonpregnant woman this is a foreign substance, while it is not, in the pregnant woman. Thus far his report shows it to be quite accurate in the determination of pregnancy.

**Female Sex Hormone**

The earlier investigators, for want of a better name, (originally introduced by Frank) used the name female sex hormone indiscriminately. Thus the literature is rather confusing. However,
female sex hormone usually implied folliculin (estrin, theselin, etc.). Its effects were variable, probably because of mistaken identity, and at the present time no definite effects can be ascribed to it, per se; but with the study of progestin and folliculin the effects usually attributed to it are completely covered.

Emminin

Emminin was obtained from placenta. Collip concludes that emminin does not alter the menstrual cycle, but corrects amenorrhea of recent origin, lengthens the cycle in polymenorrhea, relieves the symptoms of dysmenorrhea and recent menopause, but has no effect on castrates. Berger (9) used emminin in the treatment of migraine.

Specific Indications for Ovarian Therapy

Hereditary Diseases: Macklin (39) has called our attention to the female sex hormone in the male, associated with sex linked inherited diseases; in that it may do for the male what the extra sex chromosome does for the female. Thus he suggests that the female sex hormone be studied in hemophilia, thromboangitis obliterans, muscle dystrophies, and retinitis pigmentosa. By giving the affected male additional resistance he is able to suppress the disease tendency.

White (73), Birch (8), Hirst (34), and Ravina (57) have all
advocated the use of the female sex hormone in hemophilia. The normal male urin contains sufficient ovarian hormone, when concentrated, to produce estrus in rats. But the urin of hemophiliacs is negative in this respect. No definite dosage has been established, but bleeding is usually stopped promptly, and in some cases did not recur; however, repeated injections are often necessary. This treatment has been advocated by some, as routine preoperative treatment in hemophiliacs.

Other cases are reported in the literature on retinitis pigmentosa, thromboangitis obliterans, but no definite conclusions can be drawn. However, it is well to keep this possibility in mind, and await future work and probable confirmation of these results.

Migraine: It has been noted that the attacks of migraine often originate with puberty, are absent during pregnancy and after menopause, thus suggesting the possibility of the female sex hormone as a factor. Riley (58) found that in the females, the female sex hormone was usually absent or reduced in this condition, and in males increased prolan in the urin quite commonly preceded the headaches. With the injection of follutein characteristic attacks of migraine were precipitated. Berger (9) in the use of emminin reports 20 cases where headache was relieved in 10 days to two weeks time.

Acne: Rosenthal (60) in the treatment of acne in 34 women at the Vanderbilt Clinic found that the ovarian hormone was completely absent in 27 cases, normal in 6 cases and a slight amount in one case.
Induction of Labor: With the foregoing theoretical knowledge it might seem possible that labor could be induced by hormonal action. Rodway (59) in using ovarian residue (without corpus luteum) concluded that it was a safe uterine stimulant when the pains are feeble and infrequent, although the contractions were only slightly increased.

X-Ray: Using x-ray Hirst (34) found that in a large percentage of primary hypoovarian patients changed to regular menstrual periods, and conception occurred in many cases. Thaler (66) reports that four of seven cases of primary amenorrhea were improved, while in a large percentage a secondary amenorrhea satisfactory results were obtained. Although the roentgenologists disagree, the gynecologists explain this on an ovarian stimulation basis. Becles (6) made the observation that in irradiation of myomata of the uterus there was a disappearance of the flashes, increase in size of the fibroma, and reappearance of the menses. Associated with pituitary dysfunction Hirst (34) states that with mild exposures of the pituitary alone, and in some cases stimulation of the ovaries there is a resulting menstrual flow in eighty to ninety per cent, and an increase in the fertility in fifty per cent.

Hyperfunction, especially in over sexed, puberty and climacteric hemorrhages are benefited by the use of irradiation according to Hirst (34). If the flashes and bleeding are present at the
same time the hemorrhage is pathologic in origin, according to Beclere (6).

Great caution must be exercised to avoid exposure of the ovaries and the pituitary together in primary ovarian failure, or in thyroid deficiency. Care must be taken not to over-irradiate these structures, the ovaries, in particular.

**General Measures:** The general therapeutic measures indicated in the hyperfunction of the ovaries is as follows: (1) puberty (Menorrhagia and metrorrhagia) diet, proper environment, curettages, possibly transfusions and x-ray may be used, while removal of the ovaries is of no value; (2) the bleeding of maturity - curettages, roentgen therapy, or rarely intrauterine application of radium; (3) premenstrual tension - good elimination with calcium therapy gives a few good results.

In hypofunction of the ovaries, where there is a lack of the female sex hormone in the blood and an excess of the prepituitary maturity factor, we may result to: calcium in high dosage, good elimination, and occasional venesection. In this condition the administration of theelin may cause some regression of the anterior pituitary.

Temple Fay called attention to the suppression of the menstrual flow in the reduction of the fluid intake to 30 ounces per day. He also stressed vitamins, particularly "E" and minerals including manganese.

Verzar (68) has pointed out that in addition to the effect of the hormone ovarian function is dependent on the vegetative nervous
system, the ion concentration, and the colloid condition of the blood. If the ovarian hormone is present in the urine, Kurzrok (38) suggests the use of triple bromides and calcium lactate to depress the irritability of the vasomotor center in menopausal disturbances.

With follicle cytosis as a result of pelvic inflammatory condition this mechanism inhibits the formation of corpora lutea, and prolonged diathermy is indicated.

Exercise, hygiene, and diet should accompany any endocrine therapy, to obtain the best results. In dealing with the endocrine disturbances there is always the psychogenic factor to be considered, which may or may not be present; thereby causing much confusion and uncertainty as to the therapeutic value of specific extracts.
SUMMARY

The menstrual cycle is dependent upon the internal secretory function of the ovary, and the latter, in turn, is dependent upon a normally functioning anterior pituitary lobe. There are two definitely demonstrated hormones produced in the ovary. The first of these is known as folliculin or theelin. It is produced by the graafian follicle, but has been found to be present in many other body tissues and fluids. The substance is found in steadily increasing amount in the blood of pregnant women, so that, toward the end of gestation, large amounts pass over into the urine. In so far as the genital tract is concerned the chief effects of folliculin are to produce certain growth changes and hyperemia. It is the normal stimulant of the rhythmic uterine contractility, although, in the latter portion of the cycle, this effect is to a greater or less extent inhibited by the progestin which is then produced. Theelin differs from theelin in certain physical and chemical properties. It is an oestrogenic hormone, but it produces this effect even when given orally.

The other chief ovarian hormone is progestin, which, so far as we know, is produced only by the corpus luteum, and is responsible for certain histological changes exhibited by the endometrium in the latter part of the menstrual cycle. Progestin produces no effect upon the endometrium unless the latter has been previously primed with folliculin. If fertilization occurs, this built-up endometrium
is not cast off, but becomes even more highly developed and constitutes the decidue of early pregnancy. It also has an inhibiting effect upon ovulation, as soon as its restraining influence is removed, a new crop of follicles begins to develop. Progestin is of importance in: the maintenance of fixation of the ovum in the early stages of pregnancy, and an inhibitor of uterine muscle contractility. Folliculin and progestin may be considered supplementary, one to the other.

Folliculin has no stimulating effect upon the ovarian function, in fact evidence indicates that a sufficient dosage is actually harmful to it.

The anterior lobe of the hypophysis produces several hormones: the growth hormone from the acidophile cells, and the sex hormone from the basophilic cells. Prolan A is spoken of as the follicle-ripening hormone, while Prolan B designates the luteinizing hormone. The pituitary hormones are readily recoverable from the urine of pregnant women, also are present in large amounts in the placenta.

Other endocrine glands, especially the thyroid and the suprarenal cortex, are of importance, but we know very little about the mechanisms involved. In some cases thyroid extract gives much more satisfactory results, especially where there is some evidence of hypothyroidism.

The possibilities presented in recent publications indicates that ovarian therapy may be of great value in the treatment of hemophilia and in some hereditary diseases.

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With portions still unsolved in the complex endocrinology of the ovarian cycle, it is necessary to make a gynecologic and endocrinologic diagnosis, before attempting the management of the disorder, whatever it may be.
CASE HISTORIES

Case I. Female age 35 yrs. Menses began at the age of 16 yrs., were normal and regular and lasted 3-4 days, until her marriage at the age of 23 yrs. At this time the periods became scanty, and she began to put on weight. After a period of two yrs. pt. had not conceived, no contraceptives had been used. The Dr. who examined her at this time, found her B.M.R. to be normal, but placed the patient on thyroid. The Ruben test was also neg. 6 mos. later pt. became pregnant, went through a normal pregnancy and a normal delivery. Following this pt put on more wt. up to 220 lbs. The periods first became scanty and then irreg. until the age of 35 yrs. when she again consulted a Dr. At times would have amenorrhea for 3 months intervals. At this time the general physical examination was entirely negative, the B.M.R. was plus 6 and plus 8. The patient was then placed on Progynon. This preparation was given orally 1 tablet t.i.d. for 10 days, this being a series. The menses became normal after the first series. And since this therapy was started in Oct. '32 the pt. has continued to menstruate normally as long as the progynon is continued. At the present time the pt. has lost 15 lbs. in weight, and the menses are regular; a series of progynon being taken every other month. However, if the pt. deviates from this routine, and does not take the progynon, the menses become scanty, and irregular.

Case II. Female age 28 yrs. Menses began at the age of 19 yrs., periods were irreg. every 3-5 months were very painful and were of 3-4 days duration. At the age of 22 yrs. pt. married. Following this the periods became normal and regular, 4-5 days duration, for the next four years. However, during this interval the patient increased in weight from 120 lbs. to 190 lbs., and weighed 235 lbs. at the age of 28. With the increase in weight the periods became first scanty and then irreg. at times amenorrhea for 2-3 months. At the age of 28 consulted a Dr. thinking she was pregnant (Feb. '33) there had been complete amenorrhea for 3 mos. Examination at that time revealed that the cervix and uterus were both small, no masses in the adnexa at wt. 235 lbs. B.M.R. plus 12. Progynon therapy was started (same dosage as in case I) after a month menses have become regular, but the flow is scanty and lasts only about two days. There has been no loss of weight, neither has there been a gain.

Case III. Female age 28 yrs. Menses began at the age of 17, flow was regular and normal. Was married and had normal pregnancy and delivery at the age of 20. Following this in a period of 18 months increased in weight from 130 to 360 lbs. With the increase in weight, the periods became scanty and irregular.
At times would have amenorrhea for periods of from 3-6 mos. Pt. consulted Dr., who administered a mixed glandular therapy (the exact nature of which is not known), and "hypos" of ovarian extract. Following several months of this therapy the periods became regular, normal flow, and weight reduced to about 250 lbs. For economic reasons the pt. was forced to discontinue the therapy for a period of about 18 months. The periods first became scanty and then irregular. It was 18 mos. after she had discontinued treatment that the patient came to the Uni. of Nebr. Dispensary complaining of amenorrhea for a period of 6 months, increase in weight, and a mass in the abdomen which was progressively enlarging. Her weight at this time was 250 lbs. Examination revealed pregnancy of about 5 months.

Cases I and II were taken from the office files of L. S. McGoogan M.D. Case III was taken from the dispensary records of the University of Nebraska.


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* Indicates data taken from abstracts of the original article.