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THE ENDOCRINE GLANDS AND THEIR RELATION TO
ABERRATIONS OF THE MENSTRUAL CYCLE

BY

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The application of our recently acquired wealth of knowledge on endocrine physiology to the problems of the menstrual cycle involves much "sifting of the chaff in seeking the grain". Though we have made great strides forward in recent years in the field of endocrinology, many gaps still remain in our concepts. The whole mechanism of endocrine inter-play as we interpret it today is liable to change within a short time for several reasons. One of the outstanding weaknesses of our present conception of the endocrines is that only a few of the relationships are known facts. The greater portion are in reality assumptions based on clinical experience, a method of investigation prone to fallacy because of the variability of factors which are difficult or impossible to control in the human being. One real value of this method, though, is that the work is on the human and by the time the work is completed, there is no need to transfer findings from one species to another. Another weakness lies in the fact that controlled experiments are for the most part on animals. The blind transference of animal findings to human physiology is a common fault of "laboratory technicians" and creates much fal-
lacious "knowledge". Though it is true that broad generalizations usually may be applied from species to species, isolated fact tends to be species specific. As a medical subject, we will of course stick to human findings as closely as possible in this paper. It is the aim of this paper to attempt to clarify as much as possible the present status of the endocrines in relation to the menstrual cycle and to abnormalities of this cycle from etiological, diagnostic and therapeutic standpoints, emphasizing the first and last more than the diagnostic angle.

The history of endocrinology is a comparatively recent one. Though the ancients back as far as Hippocrates postulated the humoral theory of physiology and the suggestions of ferments in the body are found in the writings of Sylvius, Willis, and others in the seventeenth century, it was not until the nineteenth century and more particularly the last twenty-five years of that period that we can list much in the way of true endocrine knowledge or research. Berthold, Bernard and Brown-Sequard are probably the original founders of modern endocrinology. It was Brown-Sequard, who in 1888 created a great interest and furor not only in the medical profession but among the laity as well by his announcement of a rejuvenating process by use
of extracts of animal testes. The biggest contributions to our knowledge of the endocrines has been from the experimental work completed since the turn of the century. Until more recently, many of the profession were very skeptical of the endocrines and their complexity. The recent past has seen some remarkable work so that now the glands have many converts. It would appear that the wave of enthusiasm is in its ascendancy at this time.

It is necessary to thoroughly understand the basic normal physiology of these structures before we can clearly evaluate the pathological entities. We must therefore discuss the present conception of the hormones of menstruation and their inter-play before we attack the problem of anomalies of this cycle.

Since the ovary is the principal endocrine of the female that distinguishes her from the male, it will be our first concern. The ovary has two main functions, the production of ova and its endocrine activity. Both of these actions, though racially important, are not essential to the life of the individual in contrast to many of the other glands of internal secretion such as the hypophysis, the adrenals, the pancreas and others. Profound metabolic disturbances follow removal of the thyroid, the parathyroids, the pituitary and other glands while removal of the ovary at any epoch of life
produces much less striking effects on body functions. Both of the ovarian functions, however, are intimately a part of the normally balanced endocrine system.

The ovary produces two types of sex hormones, the estrogenic hormones and the corpus luteum hormone. The estrogenic substances are three in number. The names which are recommended by the Council of Pharmacy and Chemistry of the American Medical Association are:

1. Estradiol or dihydrotestosterone. This is most probably the hormone that is actually evolved by the follicle. (MacCorquodale, Thayer and Doisy, 1935)

2. Estrone or theelin. This hormone is found in urine and is probably an excretion product formed from estradiol.

3. Estriol or theelol. Another estrogen found as an excretory product in urine. These three substances all have similar but not identical properties.

Estrogenic substances have a very wide distribution, not only in the animal kingdom but also in the realm of inanimate organic substances. It is found in the ovary, in the blood, in the excreta of all of the vertebrates; in invertebrates and in plants; and in such organic substances as lignite, coal and petroleum. Zondek showed that the theca, the granulosa cells and the corpus luteum all produce the follicular hormone. Chemically these
substances are closely related to the sterols, the male sex hormones and the carcinogenic hydrogenated phenanthrene ring compounds, a subject we will comment on later. Since about 1930 voluminous literature has appeared on these hormones. The estrogenic hormones were the first known of the ovarian hormones and were thought for a time to be the sole hormone of menstruation. Considerable argument was rampant from 1926 to 1928 as to whether there was another hormone of menstruation. Doisy, et al (1929), obtained and published an article on folliculin from the urine of pregnant women. Crystalline estrone was isolated in 1929 by two men working independently of each other. Doisy and Butenandt obtained their pure crystals from the urine of pregnant women. Since then estrogenic substance has been isolated from mare's urine (Laqueur, 1930), from palm nuts (Butenandt and Jacobi, 1933), from coal, petroleum and many other sources. Its chemical structure shows it to be basically like the phenanthrene ring group of compounds, namely morphine, the bile salts, ergosterol, vitamin D, etc. This structure and its possible significance will be considered later in this paper.

A well known fact of chemotherapy, that an alcohol is more active than a ketone, resulted in an attempt to reduce the keto group of the crystalline estrone to
produce a secondary alcohol. Schwenk and Hildebrandt accomplished this in 1933. They obtained the substance now known as estradiol, the probable form in which the substance is first produced within the body. The introduction of this alcohol group on the 17th carbon atom increased the potency of the crystalline estrogenic substance about seven times. However, the effect of the product in the body was rather evanescent and so of comparatively little clinical value. For this reason workers tried to make a more lasting but still potent substance. Butenandt accomplished this by conjugating the alcohol with benzoic acid to produce a benzoate of estradiol which is absorbed much more slowly and whose effect is felt over a much longer period of time. This reduced the potency of the estradiol about one half but still it is much more potent than the original estrone. It is used quite extensively in clinical work now and is known commercially as progynon-B. The introduction of still another alcohol group was successfully accomplished but with disappointing results. This substance, estriol or theelol, with another OH group on the 16th carbon atom is a relatively impotent estrogen and of little clinical value.

In Kurzrok's recent book on the endocrines (Kurzrok, 1937) is listed rather completely the action of the estro-
Genital hormone. Eight separate functions of estrone as determined from the administration of the crystalline hormone are listed thus:

1. It stimulates the growth and development of the secondary sex characteristics of the female as well as the genital tract. This is best demonstrated by the effect of estrone on the prepubertal individuals, in primary amenorrheas, and in the castrated individual. (Werner and Collier, 1933)

2. The endometrium is stimulated to regeneration and hyperplasia. This occurs in the human during the postmenstrual phase of the normal menstrual cycle. It is in a sense only an extension of the first function we list here. (Marrinan and Parkes, 1930)

3. Estrone stimulates the growth of the mammary ducts. This seems to be a stimulation only to ductal growth in contrast to the action of the other ovarian hormone which stimulates lobular growth preparatory to lactation. The only apparent right to list this as a separate function lies in the fact that the secondary sex characteristics are developed as prepubertal traits while this is cyclic in character after the onset of the menses, occurring each month of the menstrual epoch. (Kurzrok, Wilson and Cassidy, 1935).

4. Estrone possesses an "antimasculine" effect upon the
male genital system. In large doses the hormone inhibits both the primary and the secondary sex characteristics. That is, this hormone is feminizing in action upon the male individual no matter if given before puberty or after. This is not permanent action. After cessation of administration of the hormone, the testes again resume their function. This effect of estrone is probably due to an inhibitory action on the hypophysis. (Spurrell and Ucko, 1938)

5. Estrone has an effect on uterine motility (denied by some authorities, especially Kurzrok, et al., 1936; Kurzrok, et al., 1937) best illustrated during the menstrual cycle or during pregnancy wherein uterine contractions tend to occur when the content of estrin is high and are absent or diminished when estrone is low in amount or when it is neutralized by the action of corpus luteum hormone. A method of contraception was conceived on this basis: Whitney and Burdick (1936) were able to show a definite slowing of the passage ova through the fallopian tubes following the administration of estrogenic substance into rabbits. Since the ova are quite short lived, it was thought that sufficient slowing in the passage of the ova would result in senescence and non-viability of the egg cell. This work has not been proven as yet, however. (Reynolds and Friedman, 1930; Reynolds, 1931; and Bourne
and Burn, 1928)

6. Baniechi showed in 1928 that estrone induces the formation of "pregnancy cells" in the anterior pituitary body. (Kurzrok, 1937)

7. Verzar and v. Arway demonstrated in 1931 that estrone has a stimulating effect on the basal metabolic rate, causing it to increase ten to twenty percent in the castrated female rat. It has no demonstrable effect on the B.M.R. of normal males and females, however. (Kurzrok, 1937) There is a possibility that the increased B.M.R. is due to a stimulation of the thyroid gland following the stimulation to the pituitary cells by the estrone.

The other ovarian menstrual hormone, the corpus luteum hormone progesterone or progestin, is produced by the cells derived from the remaining tissues of the Graffian follicle after its rupture at the time of ovulation. Whether the lutein cells are derived from the granulosa cells or from the theca interna is a moot question. The general consensus of opinion seems to feel that the granulosa cells are the source of the corpora cells. The distribution of this hormone is, in contrast to the estrogenic substances, rather limited. It is produced normally by the corpora only but during pregnancy by the placenta as well.
The corpus luteum hormone was isolated by three groups of workers almost simultaneously in separate laboratories in 1934. They were Slotta, Ruschig and Fels; Butenandt; and Wintersteiner and Allen (1934). Its structure was determined in 1934 by Butenandt, et al., by converting two physiologically inactive substances of known structures into the active corpus luteum hormone. These were stigmasterol, a sterol obtained from soy beans, and pregnanediol, a saturated divalent alcohol occurring in the urine of pregnancy. (Allen, 1935), (Allen and Reynolds, 1935), (Allen, et al, 1935)

The physiological action of the corpus luteum substance is listed by Kurzrok (1937) as five in number. Mackt (1938) limits it to only two significant functions for this hormone. Reynolds and Allen (1933) demonstrated in the rabbit and Knaus in 1936 that balloon recordings of uterine contractions showed definite inhibition under the influence of progesterone. This has been demonstrated to be an antagonistic action to the pitocin fraction of the posterior pituitary and to estrin from the ovary. Mackt also showed that progesterone exerts an inhibitory action on the uterine endometrial hyperplasia produced by the estrogenic substances. A number of investigators have demonstrated that this hor-
mone is an inhibitor of the estrous cycle and of ovulation. Makepeace (1939) claims that progestin inhibits the release of gonadotropin hormone from the pituitary. It is also a well known clinical fact that a corpus luteum cyst causes a patient to skip periods. The corpora are the essential inhibitors of the cycle during pregnancy. (Hisaw, 1929), (Hisaw, Fevold and Meyer, 1930)

The anterior pituitary gland evolves a large number of hormones. The number of hormones which this gland produces and their apparent regulatory influences on all of the other glands of internal secretion have led many individuals to dub this bit of tissue, the "master gland". It manufactures a hormone which influences the thyroid, one or more which regulate the ovaries, an adrenal factor, a pancreatic hormone and apparently several others. Those which are our concern are the gonadotropin, the thyrotropic and the adrenotropic principles. These latter two are of interest because the thyroid gland and the adrenal gland seem to influence the ovary in some manner, assumed by many authorities now to be a secondary affect mediated by way of the pituitary gland as a result of that gland's attempts to regulate the thyroid and the adrenal glands.

The substances produced by the anterior pituitary
which influence the ovaries are known collectively as the gonadotropic hormones. The number of reports on these hormones that have appeared in the past ten or twelve years is remarkable. The first fundamental observations were those of Smith and Engle and of Ascheim and Zondek in 1926, working separately. The hormones, probably proteins or closely associated to a protein molecule, have not been produced in a crystalline form as have the ovarian substances. Very similar hormones have been found in the placenta, in the urine of pregnancy, in castrate urine and in mare serum. These, since they can not be shown to be identical with the anterior pituitary substance, are called anterior pituitary-like substances (APL substances) or prolan. Perhaps the most distinctive difference that can be pointed out between the APL substances and the true gonadotropic substance is that, though both seem to have about the same influence on the ovary in the individual in whom the pituitary gland is intact, in those whose pituitary is absent or inactive, the APL substances are inactive or impotent. (Ross, 1937)

The gonadotropic hormones are found in no other gland of internal secretion except the hypophysis. During pregnancy some investigators believe that there is some other source of the gonadotropic hormones,
possibly the chorionic villi. Zondek has made several attempts to refute this conception. However, it is known that there is excreted during the pregnancy via the kidneys certain substances which are similar to but not identical with the anterior pituitary gonadotropic substances. Experimentally we find that these APL substances do not act on the ovaries of hypophysectomized animals as will anterior pituitary extracts.

Cole and Hart (1930) showed that the serum of pregnant mares during the midperiod of pregnancy contains large amounts of gonad stimulating substance which acts very similarly to the a. p. gonadotropic substances. Several cases are on record where the use of sera of pregnant women has been very effective where there seemed to be a deficiency of pituitary action (Hunt, 1938).

It is generally accepted that the basophile cells are the source of the gonadotropic hormones. Evans and his group (Evans, Korpi, Simpson, Pencharz, Wonder, 1936) separated by a process of salting out three distinct fractions of the gonadotropic group. These were an interstitial cell stimulating entity, a luteinizing fraction and a follicle stimulating part which prevents hypoplasia of this tissue and restores it after degeneration in hypophysectomized animals. This action is best seen in the testes where the cells of Leydig are regenerated in
a hypophysectomized animal in contrast to the near-by cells of the tubules which did not show response to this fraction. The same interstitial stimulation is seen in the ovary of these animals. The luteinizing fraction causes the formation of the lutein cells or the luteinizing of the walls of the Follicle but it is without effect on the interstitial cells of the gland. The follicle stimulating fraction causes a growth of the follicles without repair of the interstitial cells (the so-called "deficiency cells") or luteinization. Upon the male this fraction causes regeneration of the tubules after degeneration but does not effect the interstitial cells of the testes.

It is of interest to note the defference between the male and female hypophyses in view of their similiarity of gonadal influence. The anterior pituitary of the male secretes the same hormones as the female. The difference lies in the fact that the female gland produces the gonadotropic principle in a cyclic manner so that luteinization follows follicle formation. In contrast the male gland produces a constant supply of these hormones to the gonads. (Kurzrok, 1937). Pfeiffer (1936) showed that the same is true in the female with masculinized hypophyses, a constant estrus is the re- sult.
The thyroid gland and the thyrotropic hormone are of great interest to the gynecologist because it has been demonstrated clinically that perhaps the most readily available, the most economical and the most useful biological of his endocrine armamentarium has been thyroid substance or the thyroid hormone thyroxin. (Falk, 1937; Litzenberg, 1937) Though hormonal control of the production of the hormone thyroxin is dependent upon the pituitary gland through its production of the regulating thyrotropic substance, this gland has a powerful influence on the gonads. This is a secondary action mediated via the pituitary which emphasises again the central position of this "master gland". (Starr and Patton, 1935) The thyrotropic hormone's relation to the thyroid is almost parallel to the gonadotropic-gonadal relation. This similarity does not seem to be so strange when one considers that both hormones seem to be produced from the same type of cell if not from the same cell. The action of the hormone is to stimulate the thyroid to secrete thyroxin. This substance in turn is the regulator of the metabolism of the body; it is linked with the oxidation processes of all of the body cells. The selective relationship of the thyroid to the gonads is due to the polyhedral nature of the pituitary basophile cells, a stimulus to secrete thyrotropic substance may also be a
stimulus to produce other tropic substances: gonadotropic, adrenotropic, etc. The intimate nature of this relationship is suggested by Falk’s (1937) recommendation that all menstrual disorders should be recommended for basal metabolism studies as a routine procedure. Other men highly praise thyroid extracts as being very effacious as an ovarian stimulant even if the B.M.R. is normal or slightly increased. Care must be taken to avoid a thyroid reaction or to precipitate a toxic thyroid state. (Litzenberg, 1937)

Another closely related gland which is of note is the adrenal glands. Here again we see somewhat of a reiteration of the previous story, substituting the adrenals for the thyroid gland. The basophile cells again seem to be the elaborator of the adrenotropic principle. We know of two adrenal secretions and suspect at least one more or some mechanisms of these two which we do not understand today. The adrenals may be divided into two distinct parts, the medulla and the cortex, the former produces the hormone epinephrin or adrenalin and the latter the cortical hormone cortin. Epinephrin is a simple amine compound related to tyrosine and the cortical hormone is of unknown chemical structure. The activity of epinephrin has been established to be at the myoneural junctions of the sym-
pathetic nervous system. Of special interest to us is the fact that epinephrine causes contraction of the uterus during all phases of the menstrual cycle. The pregnant uterus also contracts under its influence. The cortical hormone seems to be the substance of the adrenal which is essential to life. It is the hormone used in Addison's disease or in individuals in whom the adrenals have been removed at operation. Incidentally it is worthy of note that only very small bits of adrenal tissue needs be present to satisfy the requirements of the body. Cortin may be used to prolong life almost indefinitely in these cases in contrast to the medullary hormone which is singularly ineffective. Aside from these two hormones we also find a definite inter-relationship between the gonads and the adrenals. Precocious puberty has been observed in both male and female in the presence of an adrenal tumor or a hyperplasia of the adrenal tissue. Other tumors give rise to masculinization of the female, the virilism syndrome. Addison's disease is frequently accompanied by a hypoplasia or atrophy of the ovaries. The mechanism of these syndromes, however, is still obscure and not well understood.

The posterior pituitary has been shown to secrete at least three hormones. They are an oxytocic principle,
a pressor and an anti-diuretic principle. The latter two are usually combined as one in our present preparations on the market because of the methods of fractionating. It is known as pitressin. The oxytocic portion is called pitocin or oxytocin. This fraction is our concern in gynecology because it causes contraction of the uterus under certain conditions. Its activity is dependent upon at least four factors; the species of the animal, the phase of the menstrual cycle, whether the uterus is pregnant or not, and the stage of the gestation. Experiments are somewhat contradictory to a certain extent as to what occurs. Several investigators have shown that especially in rabbits, estrin sensitizes the uterus to the action of pitocin while progesterone tends to render the uterus refractory to the action of this substance (Parkes, 1930). However, Kurzrok, Wiesbader, Mulinos and Watson (1938) made several studies of the action of pitressin, estradiol, and progesterone by the use of the intra-uterine bag and on human subjects. Significant conclusions from their studies are that the uterus shows spontaneous contractions during all phases of the menstrual cycle; that the uterus reacts to pituitrin in a positive manner during all phases of the cycle; progesterone produces uterine cramps during the postmenstrual phase of the
cycle but not during the premenstrual phase; and that estradiol occasionally produces a rise in amplitude and tone and may produce cramps during the first half of the cycle without significant changes in the tracings from the intra-uterine balloon. It has been shown experimentally and clinically that neither the hypophysis, the ovaries or a live fetus is essential to the onset and progress of labor. This suggests at least an additional factor, possibly, as suggested by Kurzrok (1937), placental in origin.

The phenomenon of menstruation is perhaps the gynecologists' chief concern for aberrations of this cycle are the chief complaints of most of his patients. Long ago this occurrence of cyclic bleeding was thought to be a characteristic solely of the human being. For the major part of the last century it was believed to be a characteristic only of the primates. Hartman (1937) made more careful studies and showed that bleeding begins with the Selachian fishes and occurs in the vertebrate scale upwards wherever the embryo develops within a brood chamber at the expense of the parent.

There is some debate among gynecologists as to just what constitutes true menstruation. Some believe that menstruation is cyclic bleeding (Allen, 1935). Another school define it as bleeding only from a premenstrual
endometrium. (Kurzrok, 1937; Wiesbader and Kurzrok, 1938; Ehrenfest, 1937) This point is stressed in order to distinguish the normal ovulatory cycle with bleeding from a premenstrual endometrium from anovulatory sterile cyclic bleeding from a postmenstrual endometrium. The control of menstruation seems to be almost entirely hormonal in character. The hormones directly involved are the pituitary and the ovary. However, the influence of other glands is evidenced by the clinical observation that many of the menstrual disorders are found in dysfunctions of the thyroid, the adrenals, and the pancreas. The problem of the menstrual cycle is further complicated by the work of Teel and Cushing (1930) and Hohlweg and Junkman in 1933 in which they tried to show that there probably was a central nervous system sex center, probably located in the floor of the third ventricle. Some work has been done to indicate the production of antibodies or antihormones in the body, antitheses of hormones which act to balance hormonal action (Parkes and Rowlands, 1936; Werner, 1938). This work is not generally accepted as yet. Some say the apparent antihormones are in reality but the production of a refractoriness as a result of impurities in the extracts used. Crystalline preparations are said to fail to reproduce the antihormone phenomenon described by those using
impure glandular extracts. (DuShane, et al, 1936) Aside from these factors there is also an auxillary mechanism present for the purpose of pregnancy and delivery of the child at term.

The normal menstrual cycle is generally conceded to be chiefly endocrine in nature. It is concerned with the development of the egg in the ovary, its extrusion from the ovary, its transportation to the uterus and fertilization and pregnancy or subsequent nidation at the end of the cycle as a part of the menstrual flow if fertilization does not occur. The rhythmical stimulus necessary for menstrual activity comes either from Hohlweg and Junkman's sex center, from the pituitary or from some gland evolving a "bleeding hormone" (Hartman and Firor, 1937). Since the pituitary hypothesis is our most generally accepted one, we will use it as the starting point in the following description of the normal menses.

A rather complete diagramatic portrayal of the endocrine inter-relationship during the normal menstrual cycle was published in a paper by Kurzrok, Wilson and Cassidy (1935) and is presented below slightly modified for reference in this discussion. Broken lines indicate inhibitory action and solid lines stimulating action. Question marks indicate unproven hormonal action.
Both the follicle stimulating hormone and the luteinizing factor of the pituitary gland are necessary for a complete cycle and normal menstruation. The hormones act in rotation but overlap some at the midpoint of the cycle or at about the time of ovulation. Considerable evidence points to a status of equilibrium between these two hormones at which time ovulation tends to occur (Lase, Smelser and Kurzrok, 1938). There is a quantitative relationship existing between these two hormones, as well. (Marrian and Parkes, 1930; Kaufman, 1932; Parkes, 1938; Szarka and Kurtz, 1938) If the
follicle stimulating hormone is present in an inadequate amount, an immature follicle which is incapable of normal luteinization results. Inadequate luteinization results in an inadequacy of the lutein hormone and in consequence a postmenstrual rather than a premenstrual endometrium at the time of the menses. This is the cyclic anovulatory sterile cycle which some authorities say is not a true menstruation (Wiesbader and Kurzrok, 1938). The other extreme, an excess of the luteinizing hormone results, due to the continued action of the lutein principle on the endometrium, in further stimulating the endometrium to hyperplasia of the glandular type and the inhibition of any bleeding. The corpus luteum hormone renders the endometrium and the ovary refractory to the follicle stimulating hormone and so no new follicle develops and no second menstrual cycle begins. The balance between these two hormones is a rather delicately maintained one.

The course of the pituitary and ovarian activity during the cycle is a very precise one. The ovary, first under the stimulation of the follicle stimulating hormone of the anterior pituitary and later (after ovulation) under the influence of the corpus luteum fraction from the anterior pituitary forms first the follicle
and then the corpus luteum, each in turn producing their own hormones. Estrone, produced by the follicle, has a stimulating effect on the endometrium to cause it to regenerate postmenstrually, an effect on the uterine musculature to render it susceptible to the action of pitocin, and upon the mammary glands causing a growth of the ducts of the gland. An inhibitory influence is also exerted on the pituitary (through the sex center?) whereby its presence in large amounts tends to restrict the production of the gonadotropic hormone. The action of estrone is maintained throughout the cycle to a greater or lesser degree since it is produced throughout the cycle, after the rupture of the follicle, by the corpus luteum. Its action is neutralized some by the corpus luteum hormone, however. The predominate hormone of the second half of the cycle is progesterone. This hormone stimulates the uterine glands to their secretory phase and renders the uterine musculature refractory to hormonal stimulation. This hormone also stimulates the mammary lobules to proliferation. The relative amounts of these two hormones required to produce these changes in the castrated individual has been worked out by Kaufman in 1932 (Kurzrok, 1937) to be 40,000 rat units of estrone and 35 to 50 rabbit units of progesterone. These amounts have also
been checked by using them in the case of primary amenorrhea and have been found to produce the desired results. (Kurzrok, Wilson and Cassidy, 1935)

These amounts are not only sufficient to bring about the menses themselves but also the full psychic and physical changes involved in a normal menstrual cycle as well. This amount is not adequate to bring about the development of all of the secondary sex characteristics, however. With but little doubtful evidence to support their claims, some investigators have hypothetitized a "bleeding hormone or factor" which causes cyclic flow. The source of this hormone is in disagreement. Some point to the ovary, others to the uterus and others to the pituitary.

The endometrium at various stages of the cycle is characteristic. Under the influence of estrone we see a regeneration and hyperplasia, a simple growth of the epithelium from the bases of residual fundi of the glands left after the nidation with the past menses. There is also an increase in the amount of submucoa as well. This endometrium is the postmenstrual hyperplastic type. The glands are typically straight tubules lined with cuboidal epithelium and not showing secretory activity. Under the influence of progestrone, the glands are stimulated to further growth and
to secretion, becoming markedly tortuous and filled with secretion, the typical premenstrual endometrium. Near the end of the cycle, due to some unknown stimulus, the endometrium begins to slough and menstruation occurs. An anovulatory cycle possesses only a postmenstrual endometrium at the time of the menses due to a lack of the progesterone stimulating phase of the cycle.

The effect of the sex hormones at various periods of the life cycle is a very interesting sidelight of the activity of the hormones. Probably the earliest differentiating processes of early cell life, the motivating force is not endocrine in nature. The segmentation and differentiation proceed according to some foreordained pattern possibly due to some "germ plasm force", an unknown quality and quantity. The whole process is as regular and regimented as the dress parade of crack drill troops; beautifully precise throughout. The development of the accessory sex organs, the uterus and the breasts most notably, are apparently not on the basis of endocrinology though they show a very early sensitivity to endocrine influence. It has been noted by a number of clinicians that the uterus is larger at birth than it is shortly afterwards. The withdrawal of the influence of the maternally derived hormones may also bring about a single pseudomenstrual bleeding a week
or so after birth, the so-called "non-menstrual genital hemorrhage of the newborn". The mammary activity of both sexes at birth and while at breast has been an observation of long standing and a very good illustration of the sensitivity of the infantile tissues to the sex hormones. This activity of the breasts is most pronounced during the second week postpartum, varying in quantity from a few drops to fifteen to twenty cubic centimeters. It is known more commonly as "witch's milk". The pituitary hormone prolactin has not been demonstrated in the infant but the APL substances and estrogenic substances are found in the urine and blood of infants during the first few days of life. (Soule, 1938)

Little is known of the importance of the ovary during the prepubertal years. We do know that the follicles mature to a certain stage of development and that at least some estrone is produced for a long time, even several years before the actual onset of puberty. This apparently parallels a similar awakening of the pituitary gonadotropic hormone activity in the basophile cells of the anterior pituitary gland. The various sex and secondary sex organs are selectively sensitive to the various hormones. This is demonstrated by the occurrence of precocious puberty and menstruation in children with granulosa
cell carcinoma and vaginal epithelial hyperplasia like that of puberty following the therapeutic administration of the estrogenic substances in the treatment of infantile gonorrheal vaginitis. (Lewis, 1933; TeLinde, 1938; Novak, 1938) Granulosa cell tumors are developed from rests of redundant granulosa tissue left over in the early development of the oophorogenic apparatus of the ovary. In the same manner the arrhenoblastoma, masculinizing tumors manifest themselves by their endocrine activity. They may develop from the persistent remnants of the masculine scaffolding which precedes chronologically the formation of the Mullerian apparatus.

In conclusion we may say that, though the primary sex differentiation is due to the initial germ impulse, the process from there on out is due to endocrine activity. The gonads under the influence of the pituitary bear the chief burden of unfolding the secondary sex characteristics as well as developing the genitals themselves. Though we know little quantitatively of the inter-play of these two factors, the knowledge of their activity has allowed the gynecologists to explain more logically and physiologically the varying degrees of sexual reversal seen in human beings and lower animals. This is in contrast to and a step above prior times when explanations were only on an anatomical basis which was
applicable only to the well developed cases with marked structural changes. Now we can appreciate the less well developed cases of sexual reversals; appreciate that an individual with testes may be dormant femininely feminine and the contrary as well. On a purely endocrine basis we may now explain the virilism syndrome of the adrenal cortex (androgenic tissue ?); tumors of the pituitary, the so-called Cushing Syndrome; and tumors of the ovary, the arrenoblastomas.

Little is known of the prepubertal function of the ovaries. The basis of our knowledge is based for the most part on the negative evidence furnished by castrations. These cases are rather rare in the female in contrast to the male. The only effect noted in humans to date has been a failure of appearance of the menses together with a disproportionately skeletal growth like that seen in early male castration that produces our eunuchs.

Long before the first menstruations, maturation of the follicles and the production of estrone are noted by histological sections and hormonal determinations done on the blood. The usual sequence is first an incomplete maturation and then graduated degrees through partial to complete maturation without ovulation but possibly with periodic bleeding and finally full maturation with ovul-
ation followed by formation of the corpus luteum and the beginning of the ovulatory type of monthly flow, the true menstrual period. There is little doubt but what many girls ovulate with the first menses and some even before as adjudged from the reports of pregnancy immediately after the onset of the menses or before the first periodic flow in a few cases. All evidence, however, points to this as an exception rather than the rule. Biopsies of the endometrium of the uteri of girls who are just beginning to have a monthly flow show a postmenstrual type rather than premenstrual, indicating an anovulatory cycle with no formation of a corpus luteum. This indicates, as we stated previously, the periodic bleeding which so many authorities do not wish to call true menstrual flow. The flow may be quite normal in amount and regular in rhythm but more often there are irregularities of either the amount of flow or the time interval of the flow so that clinically these cases frequently present themselves as instances of functional bleeding of mild or severe grade as the case may be. Further evidence lies in the physiological sterility of most childbrides as those in India. Studies made in the Berlin Frauenklinik by Mikilicz and Krausch a few years ago on a large number of young primigravidas from a standpoint of their cohabitational history in relation
to their fecundity show a surprising amount of sterility for as long as several years in many cases in spite of an active sex life from puberty.

We see the same fundamental "tapering off" at the other end of the sex period of women, the menopause. Here it has been demonstrated by endometrial biopsy a tendency to a hyper-estrinization due to failure of ovulation to occur. Functional hemorrhage, for that matter, has been shown to occur at almost any age after puberty because an anovulatory cycle is a rather frequent occurrence through the lives of most women. This is usually unaccompanied by any abnormality of bleeding or other symptoms so that the individual is unaware of which cycles are anovulatory and which are not. It has been stated by some that the interval following an anovulatory cycle tends to be a long one in contrast to the anovulatory cycle which tends frequently to be shorter. Kurzrok, Lase, and Smelser (1937) noted in lactating individuals, too, a predominance of anovulatory cycles for a variable period of time. The record in several patients showed more than six successive anovulatory cycles in individuals producing milk. This is said to hold true in from 55% to 60% of the cycles during lactation. Such men as the above three, Lahn and Riddell (1936), Dresl (1935), Kurzrok and Wilson (1936) and others have used this as a basis for
attempting to set up a physiological method of hormonal contraception. Their work is still in the experimental stage.

Though we believe that the endocrine motivation for ovulation is probably the pituitary, the association with lactation also points to a possible inhibitory factor in the secreting breast or, more remotely, an accelerating factor in the quiescent breast. The inhibitory factor was demonstrated experimentally in mice and rats by Drese (1935) and later confirmed by Riddle (1936). They showed that prolactin, the pituitary hormone stimulating lactation, is capable of producing a temporary suppression of the ovarian cycle activity. Clinically we see three schools of thought as to the cause of failure of the follicle to perform as it usually does. Some treat these anovulatory sterility and hyperestrinization cases as being due to a lack of the follicle ripening factor (the anterior pituitary follicular hormone). Others consider the luteinizing factor of the anterior pituitary to be the deciding endocrine. Hisaw and his coworkers (1935) believe in a balance of these two factors. These investigators have, by varying the proportion of these two gonadotropic elements, been able to induce ovulation in non-ovulating monkeys. The therapeutic value of this work is of course suggestive only because quantities are not only species variable but also somewhat var-
iable form one individual to another. The accepted therapy at the present time is the use of one or the other of the gonadotropic substances at or near the calculated time of ovulation with subsequent satisfactory results shown by the presence of a premenstrual endometrium upon curettage. Some of these "satisfactory" results may be false positives in that not all menstrual cycles in the same woman need be anovulatory and perhaps the cycle under treatment was a normal rather than abnormal cycle. (Novak, 1937) For a period of time near the time of the menopause, the tapering off of the gonads make such therapy a very variable quantity and of doubtful value. Some cases possess sufficient of the hormones that only a very small amount needs to be supplied artificially to produce the desired results. Other cases where the menopause is more advanced, larger doses are needed to produce the same result and tide the patient over until an endocrine realignment has been made.

The following discussion of gynecological problems from an endocrine standpoint will be on the basis of symptomatology; the cause and treatment of the patients presenting symptom such as an amenorrhea, dysmenorrhea, menorrhagia, etc. Diagnosis and treatment are based on the basic endocrine pattern heretofore outlined.
Perhaps the most common of the female complaints in relation to the menstrual cycle with which the gynecologist must deal is the problem of amenorrhea. It may be defined as the absence of menstruation either after the menes have once begun (secondary amenorrhea) or a failure of the menes to begin (primary amenorrhea). The endocrine basis of menstruation limits this symptom to a malfunction of one of three glands or a combination of any of these. These glands are the ovary, the thyroid and the pituitary. (Frank, Goldberger, Salmone and Fel­skin, 1937; Falk, 1937)

The normal amenorrhea of the menopause and the prepubertal periods is most certainly due to a lack of ovarian activity. It is no doubt an expression of the beginning and the completion of the life span of that gland. Premature ovarian failure is essentially an early menopause characterized by an amenorrhea, disappearance of estrin in the blood and a persistence of the pituitary gonadotropic hormones. At times we also see concomitant vasomotor and subjective menopausal signs. Curettage reveals an atrophic uterine endometrium. This amenorrhea is usually intractable to treatment; one might say that it represents a short lived ovary. A possible relief especially in the young individuals from the vasomotor and other subjective symptoms lies in ovarian
transplantation. Kurzrok, Wilson and Cassidy (1935) in a study of primary and secondary amenorrhea treated with large doses of estrogenic substance, found estrogenic substance to be most effective in secondary amenorrhea where they were able to bring about regular cyclical bleeding after the administration of massive doses of estrogenic substance (up to 200,000 R.U.). Their study also confirmed Kaufman's findings that 40,000 R.U. of estrogenic substance was necessary to bring about all of the phenomena of the menstrual cycle, organic and psychic. In this group of primary amenorrhea we have the type which is without evidence of pituitary or thyroid disorder and in which the only clinical conclusion is that of hypogonadal function. Perhaps some of these are capable of normal activity if only the other associated endocrine stimulation were sufficient. That is, sufficient pituitary stimulation would result in ovarian activity. Primary amenorrhea of this type usually show a hypoplasia of the genitalia and an absence of or an underdevelopment of the secondary sex characteristics. Therapy in these cases is frequently of little ultimate therapeutic gain. In some cases thyroid administered will increase the gonadotropic secretion to the threshold necessary for ovarian activity. Cessation of treatment is usually followed by a cessation of the bleeding and a regression of
the other characteristics that were brought about by the treatment. Since there is no ultimate gain, and since it is not a life saving measure, many authorities do not consider such treatment worth while. Kurzrok (1937), however, believes that such treatment is desirable because it is a step in the right direction. That is, it is an attempt to restore the body to its normal state of functioning and it does make these patients more comfortable, perhaps more psychically than physically. Kurzrok speaks hopefully of the possible preparation in the near future of more potent glandular preparations and preparations which will be absorbed slowly over a period of time. Thus, these patients would be much like our diabetics at this time. The mild cases of hypogonadism of short duration are frequently permanently cured with the use of thyroid. (Litzenberg, 1937)

That the pituitary may be the cause of an amenorrhea is readily demonstrated by the fact that Frolick's Syndrome (dystrophia adiposogenitalis) contains as a component an amenorrhea. However, not all pituitary amenorrhea are of this adiposogenital dystrophic type. As a rule, hypofunction of the pituitary gland does usually produce an amenorrhea, especially in those who have never menstruated. These primary amenorrheas most commonly show a concomitant growth disturbance of the skeletal system.
Since the pituitary is the whole driving force behind the genital tract, hypofunction of this gland will manifest itself very frequently as varying degrees of genital inadequacies. There is usually an absence of the secondary sex characteristics or at least a retardation; there is a persistent absence of estrin in the urine because the pituitary is not stimulating the ovary to follicular formation; and there is a lack of or a diminished amount of gonadotropic principle excreted in the urine. Administration of estrone or of gonadotropic substance (not APL substances) to these patients will bring about temporary relief but, like the completely nonfunctioning ovary, it is not permanent. (Kurzrok, 1937) In cases of secondary amenorrhea attributable to pituitary hypofunction its response to therapeutics is more promising than the complete types. In all cases of amenorrhea, pregnancy or recent abortion must be ruled out. Perhaps the Friedman test is the clinician's most accurate laboratory method for this. Estrone, thyroid substance or the gonadotropic principle administered to these individuals frequently will stimulate the pituitary basophile cells to activity and, since the ovaries are normal, cyclic ova production will again be resumed. In the use of the APL substances and of the gonadotropic hormones, Ross (1937) deplores their indiscriminant use and advises against it. If these substances are given, avoid the commonly made
error of not giving enough of these substances. Ross
blames many of the clinically poor results from these
hormones to inadequate dosage.

One of the usual components of a hypothyroidism
(myxedema) is an amenorrhea. This is no doubt due to
the fact that the thyroid gland is not secreting the
necessary amount of thyroid substance either because
of a deficiency of thyrotropic principle from the ant-
erior pituitary or a lack of response on the part of
the thyroid to normal thyrotropic stimulation. The in-
adequacy of the thyroid is reflected via the basophile
cells of the adenopituitary as a hypofunction of the
ovary, secondarily, and an amenorrhea. An apparent
antithesis to this is seen in cases of hyperthyroidism.
Here, too, we frequently see an amenorrhea. This may
be rationalized, however, when one considers the forces
of compensation that we find in the human body. Generally
speaking, small amounts of hormonal secretions injected
into the individual are stimulating in nature while large
amounts tend to act as substitutive sources and so depress
the activity of the gland cells. (DaCosta and Carlson,
1933) Whether this is a direct suppressive action on the
gland or not is not known. Rather it is felt that it is
probably a reflex control of the gland mediated via the
"master gland", the pituitary. That is, as in hyperthy-
roidism, the large amounts of the hormone thyroxin produced tends to suppress the basophile cells of the pituitary in an attempt to reduce the amount of thyrotropic principle formed and so reduce the activity of the thyroid. As the basophile cells slow down on the formation of the thyrotropic substance, the gonadotropic substances produced by the same cells is also diminished resulting in a deficient stimulus to the ovary and an apparent amenorrhea. This amenorrhea may be either of the primary or secondary type, usually the latter since most cases of hyperthyroidism occur postpubertally. Treatment is of course along the lines of restoring the normal endocrine balance, most easily done here by correcting the thyroid function. Thyroid substance or thyroxin is used for hypothyroid states. It must be remembered that the hypothyroid state does not need to be a full blown myxedema and that it may not even show a significant change in the B.M.R. readings. (Haines and Mussey, 1935) Hyperthyroidism which does not yield to medical treatment of course comes under the surgeon's care for an extirpation of most of the gland. (Kurzrok, 1937; Falk, 1937)

The etiology of dysmenorrhea, our next consideration, is said to lie in the development of the uterus (Israël, 1936). The development of the uterus in turn is under the control of the hormones and the central nervous system. Additional factors are seen in the nervous makeup
of the individual and the constitutional type. The thin
dynamic and "high strung" person seems to be more prone
to discomfort at the time of the menses. The emotional
background is also seen as a factor in the frequently
seen too literal interpretation of the "sick period"
by the woman. Young women are frequently taught that
the period of menstrual flow is a normal sick time for
females and that at that time she is supposed to be ill,
weak, fatigued and very susceptible to all sorts of ail-
ments.

Primary dysmenorrhea is our concern from the view-
point of endocrinology because almost all secondary
dysmenorrheas, those that have their inception after
the normal onset of the menses, is on an anatomical
basis and is seen most often following childbirth trauma.
Novak and Reynolds (1932) consider the cause of dysmen-
orrea to lie in an imbalance in the estrin-progesterone
ratio; they believe that an increase in theelin (estrin)
and diminished amount of progesterone is the cause of the
pain. Moir (1934) carries their concept a step further.
By a system of balloons in the uterine cavity, he profess-
es to have shown that the sensation of greatest discomfort
coincided with the peak of a uterine contraction. Also
each peak is marked by a disappearance of the uterine art-
erial pulsations causing an area of ischemia and pain much
like that that we see in angina pectoris and intermittent claudication of a part. Kennedy (1932) believes that dysmenorrhea is associated with degeneration in the Frankenhauser's ganglion due to an estrin deficiency. Therapeutics in the latter concept is of course the administration of estrin. In the first hypothesis, since the estrin is believed to be in excess and the hormone present in diminished amounts is progesterone, this hormone is the logical therapeutic agent. Both of these schools of thought are combined by those who stick to the middle path and say it can be either or a little of both. These use whole ovarian substance or the gonadotropic hormones from the pituitary gland. All three schools claim about the same proportion of cures or relief of the symptom. (Novak and Reynolds, 1932; Novak, 1933; Campbell and Hiswa, 1936; Elden and Wilson, 1936; Kotz and Parker, 1937) Lachner, Krohn and Soskin (1937) have done an extensive study of the problem of dysmenorrhea. Using an intrauterine bag, they claim to have shown that estrogenic substances augment uterine contractions and progesterone inhibits (Krohn, Lachner and Soskin, 1937). Kurzrok (1937) emphatically denies that this occurs and criticises these men's work on the basis that the intrauterine bag stimulates the uterus to contract to a degree
that renders their conclusions inaccurate. However, these three workers have applied the endocrines in their cases, not by rule of the thumb but rather on the basis of their physical findings with rather good therapeutic results. They divide their dysmenorrheic patients into two types. In the first are those who indicate the presence of an excess of estrin by virtue of having a large well developed uterus with moderate to long contractions, as revealed upon bimanual pelvic examination and the intrauterine bag. These patients were relieved by the use of progesterone. In those individuals in which they found a small hypoplastic uterus which shows little or no contractility are treated with estrin with good results. It has been observed clinically for a long time that pregnancy frequently has a salutatory effect on primary dysmenorrhea, probably because of the "shock" to the endocrines as they adjust for the pregnancy and then readjust afterwards for the nongravid state.

The symptom of excessive bleeding, either at the usual time of the menses or between the periods may be due to an organic or a functional condition. In the former, the endocrines are of no avail as far as therapy is concerned for the condition shows anatomical changes irreversible under the influence of any of the endocrines. The
only part these substances play in the lesion is perhaps prior to their development; an etiological factor which we will consider later. This functional type of bleeding frequently responds to endocrine therapy because it is usually due to an ovarian hypofunction, (Wilson and Kurzrok, 1936; Burch et al., 1937). It has been shown a number of times by various authorities that the endometrium reflects proportionally the severity of the hypofunction of the ovary. Therefore biopsy is indicated in these cases not only as an index of the degree of ovarian failure but also to differentiate it from an organic lesion.

Menorrhagia or metrorrhagia may be seen at almost any age. In the adolescent irregular bleeding is probably due to an endocrine immaturity; a failure up to that time of the establishment of a normal endocrine balance. These individuals almost invariably correct themselves spontaneously but may need aid perhaps more psychologically than physically. These profuse bleedings of the adolescent are usually caused by a hyperthelolinism with a typical hyperplastic anovulatory endometrium. Administration of progesterone for a number of days, usually about five, prior to the time of the expected period will frequently precipitate the ovary back to its normal rhythm of function. Shute (1936) makes the statement that an in-
sufficiency of the anterior pituitary is probably the cause of most of the disorders of the other endocrines and may even lead to a secondary hypogonadism in the male and the female. Burch, et al (1937) have had rather good results with the use of progesterone in cases in which the ovaries have started activity.

The middle age group is by far the biggest clinical group with the excessive bleeding syndrome (Falk, 1937). Perhaps the most striking form of functional menorrhagia is that in which we find a glandular cystic endometrial hyperplasia, the so-called "swiss cheese" endometrium. Shroeder in 1912 was the first to emphasize the correlation between endometrial hyperplasia and the ovarian changes characterized by an absence of corpora and the presence of follicular cysts. It has since been demonstrated experimentally that partial destruction of the ovary may cause an alternation in the estrous cycle so as to produce prolonged stages of estrus and glandular cystic hyperplasia of the endometrium. The same thing has been observed in partially hypophysectomized animals as well. Payne (1937) analyzed a series of 534 cases and attempted to demonstrate that a failure of correlation between endometrial hyperplasia and functional bleeding existed. Criticism of his paper by several men emphasized the lack of standardization of the term endometrial
hyperplasia. A loose application of the term has led some workers to consider all growth of the endometrium, even that of the normal ovarian cycle, an endometrial hyperplasia. Burch, et al (1937) brought out that the evidence is almost conclusively an indictment of the hypofunctioning ovary as the immediate cause of the functional menorrhagia and metrorrhagia. The degree of hypoactivity is reflected almost quantitatively in the uterine endometrium. Cases of functional bleeding which show rather mild symptoms and in which we can demonstrate a more or less normal endometrium is indicative of a first degree ovarian failure; severe bleeding with a characteristic glandular cystic endometrium indicates a second degree hypo-ovarianism; and bleeding or the opposite, an amenorrhea, is found in cases with an atrophic endometrium as a result of a third degree (complete) ovarian failure.

In almost all cases of functional bleeding we see evidence of other endocrine disturbances as well, no matter the degree of ovarian failure. The glands which are usually involved are the triad, thyroid, pituitary and ovary. The sum and substance of the whole matter is that metrorrhagia and menorrhagia are but manifestations of an ovarian hypofunction, which may be in itself primary or secondary to disease or dysfunction of the pituitary, the
thyroid, or to some constitutional disease affecting one or more of the endocrine glands. The microscopic examination of the endometrium is our yardstick of the severity of disturbance of the ovarian function.

The principles of treatment as advocated by Kurzrok; Burch, et al; and others may be listed as four in number. First and foremost is a correct diagnosis. Then it is necessary that we treat the specific endocrine lesion. Best results in the past have been had with hypothyroidism, or with the administration of thyroid substance even where the B.M.R. is normal (Falk, 1937; Litzenberg, 1937). The third cardinal point is the eradication of any contributory factors of ill health. The final resort is surgery. Before using this means, one must be certain that the surgery eliminates the primary pathological condition if the patient is to be cured.

The consideration of the climacteric is an important one. This period marks the end of the sexual epoch in woman that was initiated at puberty. In fact, it is probably the referral of the process which we find marking the change from adolescence to sexual maturity. Kurzrok (1937) states that it seems to be a cessation of the pituitary-ovary-uterine relationship. The etiology is therefore dependent on one or a combination of these three
structures. Ultimately, of course there is always an ovarian failure.

The menopause is popularly conceived to be an abrupt process marked by an amenorrhea. This is an error. It is in reality a very gradual process beginning perhaps about the middle of or the latter part of the fourth decade of life as a slight diminution in the flow and perhaps without a conscious manifestation to the individual. The whole process proceeds to the actual cessation of the menses. However, the number of cases on record of pregnancy after the onset of the menopausal amenorrhea indicates that the amenorrhea is no absolute criterion of ovarian inactivity. In short, the menopause consists of an internal unconscious mechanism which is manifest somewhere in its course as an amenorrhea. Other presenting symptoms seen in varying degrees are neurovascular symptoms, observed in almost all patients to a greater or lesser degree as hot flushes, sweats, palpitation, sleeplessness, numbness or tingling of the extremities and sensory neuroses especially of the throat; pelvic atrophies, perhaps most frequently an associated pruritus vulvae; and disturbances in other glands of internal secretion. About one third of the patients show weight increase of twenty pounds or more. About 10% have joint symptoms. Languor and fatigue are
are common complaints. There is frequently a thyroid dysfunction at this time with a tendency to hyper-
rather than a hypothyroidal state, usually. Novak
(1938) claims that the vasomotor symptoms are the only
ones that can clearly be attributable to hormone mal-
adjustment. The other symptoms may possibly be pro-
duced secondarily as a result of this imbalance.
(Wiesbader and Kurzrok, 1938; Donald, 1938)

When the endocrine glands are pictured as a bal-
anced group, it is readily seen that the loss of one of
the group may upset the balance to a greater or
lesser degree and necessitates a compensatory read-
justment of these glands to a new state of balance.
Watson, Smith and Kurzrok (1938) and Kurzrok and Smith
(1938) seem to have demonstrated that the ovarian fail-
ure is due to inherent qualities which render the ovary
refractory to the gonadotropic substance from the pit-
uitary. This loss of responsiveness is gradual in onset,
culminating usually at about the forty-fifth year in a
completely non-functioning ovary. This functional limit-
atation of the ovary has been demonstrated clinically to
exist not only at this end of the sex epoch but also
at the other end. Here, too, it is a graduated process
of ovarian refractoriness progressing, however, from an
insensitivity to the normally sensitive ovary of the
menstrual cycle; the menopause in reverse, so as to speak.
The point of least response to stimulation at this end of the cycle is at about the age of six months. Greatest sensitivity to the gonadotropic substances is said to be during the third decade of life. Moricard (1936) as a result of a number of attempts to graft ovaries from young girls to elderly individuals with a large number of failures to "take", believes that there must be some additional factor. He suggests a general senile diathesis or perhaps a lack of adaptability in the more elderly individual.

In about 85% of the women, the symptoms are not severe enough to force them to consult a physician. The symptoms of the biggest portion of the remaining 15% which are seen as patients by the profession are rather self limited and usually respond readily to some mild form of therapy. Since the process is one of ovarian failure, the logical course of therapy is the administration of estrin or whole ovarian substance (Macleod, 1938). Kurzrok (1937) recommends a combination of the two. He claims that the symptoms are usually relieved very promptly or are at least helped. Best results were seen in his cases in those individuals who have a complete menopause, i.e. complete cessation of the menses. Pratt and Thomas (1937) bring out in their paper the marked psychogenic factor in this syndrome. In a series of cases which they
considered well controlled, they received almost an equally good result with a placebo as with the administration of the endocrines or sedation. Contemporary comment on their paper tended to indicate a majority of opinion that, though a marked psychogenic factor is probably present, better results are seen in those patients that receive ovarian substance rather than sedation or placebo, other things being equal. The administration of the hormones are only for relief of the distressing symptoms and a tapering off should be followed as much as possible. Novak (1938) in a recent paper states that the results from estrogenic therapy for the menopausal symptoms are very variable, rarely brilliant but usually satisfactory.

The only tumors of the ovary which have endocrinological importance are but two in number. Both of these are relatively uncommon but their characteristic endocrinological symptomatology justifies their being included here. Since these two tumors are best classified by the character of the endocrine product excreted, they are termed estrin producing tumors and masculinizing tumors or arrhenoblastomata (Novak and Long, 1933; Novak and Gray, 1936).

Arrhenoblastomata (Novak, 1938) develop from undifferentiated sex cells near the hilum of the ovary,
remnants of the male cells which were present when the ovary was an undifferentiated gonad in the embryo. Thus, when these tumors suddenly begin to grow, they usually produce male characteristics. That is, we have the virilism syndrome: the breasts atrophy, the clitoris enlarges, and the hair distribution is of the masculine type. This is very interesting in view of the fact that, though androgenic preparations inhibit the anterior pituitary, estrin has a much greater inhibitory power and these tumors frequently develop in the face of both of these hormones. (Nelson and Gallagher, 1936; Wolfe and Hamilton, 1937) This syndrome (Falk, 1937; Varangot, 1938) is present in three types of tumors: arrhenoblastomata of the ovary, the so-called Cush ing syndrome described for tumors of the anterior pituitary, and tumors of the adrenal cortex. The Cush ing syndrome is the result of an overproduction of one of the pituitary hormones, probably adrenotropic which stimulates the androgenic tissue to increased activity and thereby cause the masculinization of the individual. The accompanying glycosuria, obesity, etc. of the Cush ing syndrome is no doubt the result of involvement of the intra-medullary connections or possibly to stimulation to production of other hormones by the pituitary. The male sex hormone that may be active in the arrhenoblast-
omata can arise from the tumor cells, from the medulla of the ovary which has potential masculinizing powers, or form a referred stimulation of androgenic tissue in the adrenals via the pituitary or perhaps even directly. It must be stated, however, that no one has been able to demonstrate in the presence of an arrenoblastoma an excess of the male sex hormone. Hormonal studies on these patients are of doubtful value since both the male and female hormones are commonly found in the urine of both sexes (Novak, 1938). Therapy is destruction of the tumor either by excision or with roentgen ray.

The estrin producing ovarian tumors are either granulosa cell tumors or theca cell tumors. The first is composed of typical granulosa cells while the latter has a connective tissue-like or theca-like character. Geist and Gaines (1938) speak of the presence of doubly refractive fat in large amounts in these tumors as characteristic. Though pathologically different, these tumors are clinically identical because they both evolve the estrogenic hormones which are responsible for the clinical picture. The granulosa type is by far the more common. These islands of embryonic cells may start to grow and function at any age, causing symptoms of hyperestrinization. About ten percent are found in individuals before puberty, forty-two percent during active sex life,
and about forty-eight percent post-menopausal. The theca cell type is more prone to occur after puberty and the menopause than the true granulosa cell type, Falk (1937). The origin of the stimulus to grow is not known, but it is generally considered to be of endocrinological origin, more probably the pituitary. Both of these tumors produce large amounts of theelin (estrin) and clinically present a picture due to this hormone production. The symptoms are dependent somewhat on the age of the patient at the time that the tumor begins to function. In young girls, the secondary sex characteristics appear and the uterus enlarges and they begin to menstruate. In the childbearing age the symptoms are masked by the normal menstrual activity and the only evidence of an abnormality is an excessive menstrual flow. The diagnosis of a granulosa cell tumor during the active sex life of the individual is very frequently missed on this account. After the menopause, the symptoms are again the presence of unaccountable bleeding. Carcinomatous degeneration of the uterus must be ruled out in all cases of bleeding. (Meeker and Localio, 1938) Removal of the tumors by excision or by roentgen ray results in a prompt regression of the sex characteristics developed as a result of the tumor. This tumor is a relative benign neoplasm though some reports have
been made of malignant activity of this type of growth. (Norris; 1938)

One of the most startling and efficacious uses for one of the ovarian secretions has been established during the past five or six years. That is the use of estrogenic preparations in the treatment of vaginitis, gonorrheal vaginitis in children and senile or infectious vaginitis of adults past the menopause. Lewis (1933) was the first to use estrogenic substances in the treatment of vaginitis. He used the hormone on little girls having gonorrheal vaginitis with resulting startling changes in the epithelium of the vagina, change in the character of the vaginal secretions and prompt alleviation of the condition.

Gonorrheal vaginitis is one of the most common affections of little girls, especially during infancy and the first five years of life. Although seldom serious, the disease is tedious and a source of great anxiety and unwarranted mortification to the parents. It may also serve as a source of secondary infections, especially the eyes. It seems to be self-limited in character and seldom if ever leaves any permanent after effects. Recovery is almost always complete before the age of puberty: the disease is seldom if ever carried over into the period of puberty. This condition is important not because of any serious nature of the disease
but rather because of its high incidence in institutions where the increase in morbidity is significant.

In 1933, Lewis published his article which revolutionized the treatment of this condition. He conceived the idea that, since gonorrheal vaginitis is not seen after puberty, the infection must in some manner be altered by the changes that occur with puberty. It was common knowledge at that time that the prepubertal vaginal mucosa is but four to ten cells in thickness in contrast to the pubertal vaginal lining which is twenty to thirty cells thick. Lewis, in his paper, credits Edgar Allen as the immediate stimulus for his idea for the treatment of this specific vaginitis. Allen had demonstrated in his laboratory that one of the effects of estrogenic substances in the monkey was an increase in the thickness of the vaginal mucosa from a few cells to many cells and a differentiation into two distinct zones after about 21 days. Lewis did not mention the work of Loeb and Kountz (1928) in which they recorded the results of experiments on guinea pigs with estrogenic substances. Lewis and Weinstein (1936) reported several years later that the use of the estrogens in this therapy brought about a change in the pH of the vaginal tract from a neutral to strongly acid secretion like that seen in the adult menstruating woman.
Before puberty and after the cessation of activity of the ovary, the vaginal mucosa is a delicate few-celled mucous membrane with a neutral to faintly acid reaction. During these years it is an easy prey to invasion by pathogenic bacteria, especially the gonococci. This organism and others are unable to live in a pH of less than 6. In patients treated with estrogenic substance the pH drops to 5 or less, approaching that seen during the normal activity of the ovary in the female. On this basis the treatment of the senile and prepubertal types of vaginitis is founded.

Lewis (1933) attempted to reproduce the findings of Allen in the human being. His report of eight cases treated with estrogenic substance given hypodermically in which six complete cures were obtained and two cases clinically cured but returning later with an apparent reinfection rather than a recurrence of the previous infection is our first record of this type of treatment for gonorrheal vaginitis in children. TeLinde and Brauer (1935) were the first workers to use suppositories rather than hypodermic injection of the estrogen with brilliant results. Pratt and Thomas (1937) found the suppositories to be vastly superior to the hypodermic injection of the substance. TeLinde (1938) in a survey of 175 cases found oral administration very ineffective,
hypodermic injection effective in most cases but that local application of the estrogen by means of suppositories to be the most universally effective of all methods. Treatment is continued ideally for six to eight weeks. The characteristic vaginal change is secured in 13 to 15 days and smears are almost invariably negative within an average of 17 to 19 days. Dosages are from 50 to 100 rat units per day, twice to four times a week (Falk, 1938). TeLinde's series (1938) showed no case that failed to respond to this therapy. Expense of the treatment is a drawback. It costs an average from eight to ten dollars for the necessary amount of estrogenic substance. As a result other methods of treatment are being developed along other than endocrinological lines.

Until even more recently the treatment of senile or postmenopausal vaginitis has been very ineffective. After cessation of the estrogenic influence of the ovary, the vaginal mucosa as depicted above, reverts back to the thin structure of the prepubertal period of life. The secretuibs are no longer acid and the mucosa becomes easily infected. When infected, the patients complain of burning, itching or pain in the vagina and coitus is practically impossible. Davis (1935) reported remarkable success in treating these cases with amniotin (an estrogen) subcutaneously. In the majority of cases he adm
istered 100 rat units of amniotin three times each week for about six weeks. Symptomatic relief was obtained within 10 days. Jacoby and Rabbiner confirmed Davis' findings in 1936. It has been found that vaginal suppositories in this type of vaginitis are not as satisfactory as the hypodermic administration.

Another side of the polygonal subject of the sex hormones has been their chemical structure and the close similarity that exists between them and the sterols, the male sex hormone and especially the carcinogenic hydrogenated phenanthrene ring compounds. Since about 1930 much literature has been published on these substances. Most progress is in the isolation of the crystalline substance, discovery of their structural formulae and their synthetic production.

The estrogenic hormone was the first known of the ovarian hormones and was thought for a time to be the sole hormone of menstruation. Considerable argument was rampant from 1926 to 1928 as to whether there was another hormone of menstruation. The crystalline estrone was isolated in 1929 from the urine of pregnant women. Since then, estrone has been isolated from many sources, animal, plant and inanimate. Its chemical structure shows it to be basically like the phenanthrene ring group of compounds, namely morphine, the bile salts,
ergosterol, vitamin D, etc.

![Phenanthrene group](image1)

![Estrone](image2)

The corpus luteum hormone was discovered in 1934 and its chemical structure worked out in the same year by Butenandt. He derived his pure product from stigmasterol and pregnenediol. His formula is given here:

![Corpus luteum hormone (progesterone)](image3)

Perhaps of more interest to the general profession at this time is not so much the exact whereabouts of the double bonds or the position of the keto- or alcohol group but rather the similarity which we see in the structural formulae of these hormones and the carcinogenic substances of the tar series. Yamagiwa and Ichikowa described the experimental production of cancer in rabbits with tar in 1915. Kennaway, Cook, Mager and others showed repeatedly that the carcinogenic compounds contained a hydrogenated phenanthrene ring. (Novak, 1937)
The presence of this ring in both these carcinogenic substances and the estrogenic substances; the fact that certain members of the coal tar series have been definitely established as being estrogenic; the extensive proliferation of the endometrium during the postmenstrual phase under the influence of estrin, a process so comparable to carcinoma in rapidity and extent of growth; certain experiments which seem to indicate a probability that estrogenic substances may, under certain conditions become carcinogenic; all lend credulity to the idea that the estrogens are possibly potentially carcinogenic.

Novak and Yui, in an article on endometrial hyperplasias (1936), considered this point fairly thoroughly. Novak (1937) in an article a year later again emphasized the close correlation of structure. He comments on the frequency in which estrin is found in the urine of women long after the menopause and even after surgical castration. His conclusion that, since the placenta will during pregnancy produce large amounts of estrin, other organs could do likewise. One must remember, however, the origin of the estrin producing portion of the placenta may be the residual granulosa cells that accompany the ovum to the uterus where it implants, a factor not present in any of the other organs in the body. Novak and Yui, in their study of 864 cases of hyperplasia of the
endometrium and 104 cases of adenocarcinoma of the
tfundus of the uterus, correlated what seemed to be
sufficient evidence for Novak (1937) to state that,
"the inference would seem justified then that a
postmenstrual endometrium subjected to a persistent
estrogenic stimulation is predisposed to carcinoma."
In the breast, repeated injections of estrin have
apparently produced cancer in a surprising number of
laboratory animals and, once started the malignant
process continues even after the hormone is withdrawn.
A cancer-like picture has been produced in the cervices
of mice by Perry (1936) and Loeb, et al (1936) using
estrogenic substances.

In direct contrast, Roberts (1936) stressed the
factor of heredity rather than the sex hormones in the
etiology of cancer. He tends to minimize the role of
the hormones in the cause of cancer. Macklin a number
of years ago (1933) analyzed a number of cases of ento-
dermal tumors and found that such tumors were twice as
common in the male as in the female. She grudgingly
admits the possibility of the sex hormones being a fact-
or but tends to depreciate the likelihood. She feels
that heredity plays a much greater role. She says, "the
explanation of this increased incidence in the male
appears to rest upon factors inherent in the male con-
stitution; factors which are genetic (sex linked) in their basis and not merely dependent upon hormonal influences arising from male gonadal tissue."

None-the-less, this close chemical relationship admits the possibility of the formation of carcinogenic substances from the sterol compounds by some abnormality of metabolism. Cook (1933) pointed out that such a transformation would involve only reduction, dehydration and dehydrogenation, processes which readily occur in the animal body normally. This is indeed a very promising lead for those in cancer research. Many are now working on such phases of the cancer issue at this time and it is not improbable that new developments may be forthcoming soon either in refutation or support of the theory.

SUMMARY

1. The endocrine system is normally in a state of imperfect balance, the control of which seems to center for the most part in the anterior pituitary gland. There may be a central nervous system control, however.

2. Estrone is the ovarian hormone of the first half of the cycle and progesterone of the last half of the menstrual cycle.

3. The various tropic secretions of the adenopituitary are very closely related and may be produced from the
same cell (basophile).

4. Indications for the use of estrone and progesterone during the menstrual cycle are rather definite. The amounts required to produce all of the phenomena of the menstrual cycle has also been worked out.

5. Substitutive therapy, though expensive and noncurative, is a step in the right direction especially for young individuals in that it rehabilitates the individual not only physically but mentally; it makes their lives more comfortable and liveable thereby.

6. Generally speaking, large doses of the endocrines tend to depress that gland while small doses are stimulating. This may be due to a direct effect, and effect mediated through the pituitary gland, or to the formation of antihormones.

7. In considering the cause of any malfunction of menstruation, we must consider at least three glands, the ovary, the adenopituitary and the thyroid gland.

8. Primary amenorrhea and the menopause are essentially expressions of the same disturbance, a hypo-ovarianism. The ovarian activity in the amenorrhea may be due secondarily to pituitary or thyroid pathology or it may be like that of the menopause, an ovarian failure or hypofunction.

9. Whole ovarian substance and the estrogens are our most effacious treatment for alleviation of the menopausal symp-
10. Dysmenorrhea of functional nature may be due to either a hyper-estrenization or to too much progestrone. Treatment is an effort to supply the necessary antagonist to buffer the hormone that is present in excess.

11. Excessive bleeding must be correctly diagnosed, most preferably by biopsy. A careful examination of the endocrine system is essential, especially the thyroid and the ovary. Treatment depends upon the cause of the symptom.

12. Arrhenoblastomata (masculinizing tumors) and granulosa cell tumors (estrin producing tumors) are the only two ovarian tumors of endocrinological importance. Treatment for both is surgical or irradiation.

CONCLUSIONS

1. The subject of endocrinology is a young one which is still open to much investigation and revision before we can expect stability.

2. Glands of internal secretion may reflect their abnormal function by influencing the pituitary's control of some other gland.

3. It must be remembered that the endocrine system is an imperfectly balanced set of glands. Deviations in one
gland may manifest itself frequently as upsets in the endocrine balance rather than ust too much or too little of that one glandular secretion.

4. Thyroid substance or thyroxin is our cheapest, most available and most generally efficacious endocrine product.

5. The treatment of menstrual aberrations should be on the basis of etiological factors.

6. The carcinogenic relationship of the ovarian hormones is an unsolved problem so far. Evidence so far seems to indicate a probable indictment of the sex hormones.

7. The past two decades have seen discoveries in the field of endocrinology which have been startling in their scope and kaleidoscopic in their rapidity. All has not been said about these substances. We can expect more discoveries and revisions in the next few years.
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