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ABERRATIONS OF THE MENSTRUAL CYCLE

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

by

CLARECNE S. HOEKSTRA

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The application of our recently acquired wealth of
knowledge on endocrime 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 mech-
anism of endocrine inter-play as we interpet it today is
liable to change within a short time for several reasons.
One of the outstanding weaknesses of our present concep-
tion of the endocrines is that only a few of the relation-
ships are known facts. The greater portion are in real-
ity assumptions based on clinical experience, a method
of investigation prone to fallacy because of the varia-
bility of factors whcih are difficult or impossibe 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 bldnd transfer-
ence of animal findings to human physidbgy is a common
fault of "laboratory technicians" and creates much fal-

lacious "knowledge". Though it is true that broad gen-
eralizations 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 hu-
man 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 endo-
crines in relation to the menstrual cycle and to ab-
normalities 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 Hippoc-
rates 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 ex-
perimental 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 ascendency 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 dihydrotheelin. 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 estra-
diol.
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 sub-
stances 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 phenan-
threne 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. Consider-
able 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 consid-
ered 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 intro-
duction 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 estra-
diol 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 pro-
gynon-B. The introduction of still another alcohol
group was successfully accomplished but with disappoint-
ing 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-

genic hormone. Eight seperate 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 estension of the first function we list here. (Marrian 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; Kurz-
rok, 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 seperate 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 occuring 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 (1932) 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. Macht 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 ovula-
tion. Makepeace (1939) claims that progestin inhibits
the release of gonadotropic hormone from the pituitary.
It is also a well known clinical fact that a corpus
luteum cyst causes a patient to skip periods. The corp-
ora 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 sev-
eral others. Those which are our concern are the gonad-
otropic, 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 glands 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 fundemental
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 crys-
talline 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 difficiency 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 interstial 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 interstial 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 interstial 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 simil-
arity 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 bio-
logical of his endocrine armementarium has been thyroid
substance or the thyroid hormone thyroxin. (Falk, 1937;
Litzenberg, 1937) Though hormonal control of the pro-
duction of the hormone thyroxin is dependent upon the
pituitary gland through its production of the regulating
thyrotropic substance, this gland has a powerful influ-
ence on the gonads. This is a secondary action mediat-
ed 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 oxi-
dation 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 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. ~~reaches~~. 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 ad-
renal tissue needs be present to satisfy the require-
ments 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 òf an adrenal tumor or a hyper-
plasia of the adrenal tissue. Other tumors give rise
to masculinization of the female, the virilism syndrome.
Addison's disease is frequently accompanied by a hypo-
lasia 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 oxytoxic principle,

a pressor and an anti-diuretic principle. The latter
two are usually combined as one in our present prep-
arations on the market because of the methods of fract-
ionating. It is known as pitressin. The oxytoxic por-
tion 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 investigat-
ors have shown that especially in rabbits, estrin sens-
itizes the uterus to the action of pitocin while pro-
gesterone 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 tonus and may produce cramps during the first half
of the cycle without significant changes in the tracings
from the inta-uterine balloon. It has been shown exp-
imentally 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 add-
itional factor, possibly, as suggested by Kurzrok (1937),
placental in origin.

The phenomenum of menstruation is perhaps the gyn-
ecologists chief concern for aberrations of this cycle
are the chief complaints of most of his patients. Long
ago this occurance 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 developes 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 dys-
functions 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, prob-
ably located in the floor of the third ventricle. Some
work has been done to indicate the production of anti-
bodies or antihormones in the body, antitheses of hor-
mones which act to balance hormonal action (Parkes and
Rowlands, 1936; Werner, 1938). This work is not gene
erally accepted as yet. Some say the apparent anti-
hormones are in reality but the production of a refract-
oriness as a result of impurities in the extracts used.
Crystalline preparations are said to fail to reproduce
the antihormone phenomenum 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 conced-
ed to be chiefly endocrine in nature. It is concern-
ed 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 evelving 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 follow-
ing description of the normal menses.

A rather complete diagramatic portrayal of the
endocrine inter-relationship during the normal menstrúal
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.
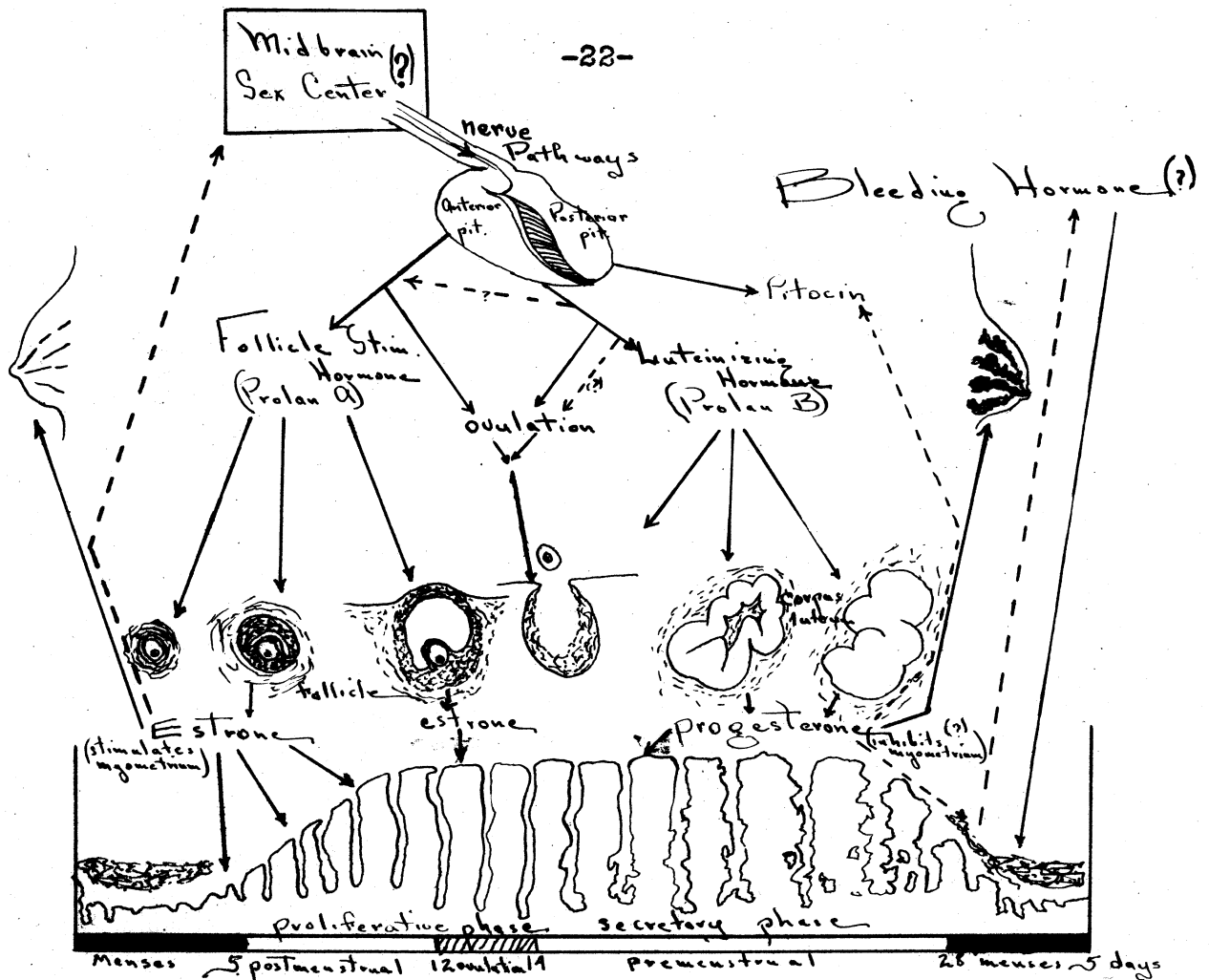
Both the follicle stimulating hormone and the luteinizing factor of the pituitary gland are necessary for a complete cycle and normal menstruation. The hormones act in rotation but overlap some at the midpoint of the cycle or at about the time of ovulation. Considerable evidence points to a status of equilibrium between these two hormones at which time ovulation tends to occur (Lass, Smelser and Kurzrok, 1938). There is a quantitative relationship existing between these two hormones, as well. (Marrian and Parkes, 1930; Kaufman, 1933; Parkes, 1932; Szárka 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 developes 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 susceptable to the ac-
tion of pitocin, and upon the mammary glands causing
a growth of the ducts of the gland. An inhibitory in-
fluence 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 through-
out 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 prolif-
eration. The relative amounts of these two hormones
required to produce these changes in the castrated indiv-
idual 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 de-
sired 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 charact-
eristics, 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 submucosa
as well. This endometrium is the postmenstrual hyper-
plastic type. The glands are typically straight tub-
ules lined with cuboidal epithelium and not showing
secretory activity. Under the influence of progest-
erone, 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 stim-
ulus, the endometrium begins to slough and menstrua-
tion 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 seg-
mentation and diferentiation 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 through-
out. The development of the accessory sex organs, the
uterus and the breasts most noteably, 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 occurance 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 develope 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 dormantly 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 castra-
tions. 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 disproportionant 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, how-
ever, 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 post-
menstrual type rather than premenstrual, indicating an
anovulatory cycle with no formation of a corpus luteum.
This indicates, as we stated previouly, 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 rhythum but more often there are
irregularities of either the amount of flow or the time
interval of the flow so that clinically these cases freq-
uently 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 steril-
ity for as long as several years in many cases in spite
of an active sex life from puberty.

We see the same fundemental "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
occurance through the lives of most women. This is usual-
ly 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,
Lass, 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 Riddle (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 Dresl (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 satis-
factory results shown by the presence of a premenstrual
endometrium upon curettage. Some of these "satisfact-
ory" 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 per-
iod of time near the time of the menopause, the taper-
ing 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 ad-
vanced, larger doses are needed to produce the same
result and tide the patient over until an endocrine re-
adjustment 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 gyn-
ecologist must deal is the problem of amennorrhea. It
may be defined as the absence of menstruation either
after the menses have once begun (secondary amenorrhea)
or a failure of the menses 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 Fel-
skin, 1937; Falk, 1937)

The normal amenorrhea of the menopause and the pre-
pubertal periods is most certainly due to a lack of ovar-
ian activity. It is no doubt an expression of the begin-
ning and the completion of the life span of that gland.
Premature ovarian failure is essentially an early meno-
pause 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 amenorr-
hea is usually intractiable 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 300,000 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 psych-
ic. 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, suffic-
ient pituitary stimulation would result in ovarian act-
ivity. Primary amenorrhea of this type usually show a
hypoplasia of the genitalia and an absence of or an under-
development of the secondary sex characteristics. Therapy
in these cases is frequently of little ultimate therapeu-
tic gain. In some cases thyroid administered will increase
the gonadotropic secretion to the threshold necessary for
ovarian activity. Cessation of treatment is usually fol-
lowed 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 desir-
able 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 amenorr-
hea is readily demonstrated by the fact that Frolick's
Syndrome (dystrophia adiposogenitalis) contains as a
component an amenorrhea. However, not all pituitary amen-
orrhea 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 in-
adequacies. There is usually an absence of the second-
ary sex characteristics or at least a retardation; there
is a persistant 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. Admin-
istration of estrone or of gonadotropic substance (not
APL substances) to these patients will bring about temp-
orary relief but, like the completely nonfunctioning
ovary, it is not permanent. (Kurzrok, 1937) In cases of
secondary amenorrhea attributable to pituitary hypofunc-
tion its response to therapeuses is more promising than
the complete types. In all cases of amenorrhea, preg-
nancy 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 gonad-
otropic principle administered to these individuals freq-
uently 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.
It these substances are given, avoid the commonly made

error of not giving enough of these substanses. 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 pro-
duced tends to suppress the basophile cells of the pit-
uitary 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 pro-
duced by the same cells is also diminished resulting in
a deficient stimulus to the ovary and an apparent amen-
orrhea. 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 hypo-
thyroid states. It must be remembered that the hypothy-
roid 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) Hyperthyreid-
ism 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 (Israel,
1936). The development of the uterus in turn is under
the control of the hormones and the central nervous sys-
tem. 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 interpetation of the the "sick period" by the woman. Young women are frequently taught that the period of menstrual flow is a normal sick time for females ant that at that time she is supposed to be ill, weak, fatigued and very susceptible to all sorts of ailments.

Primary dysmenorrhea is our concern from the viewpoint 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 dysmenorrhea 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 professes 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 arterial pulsations causing an area of ischemia and pain much

like that that we see in angina pectoris and inter-
mittent claudication of a part. Kennedy (1932) be-
lieves that dysmenorrhea is associated with degener-
ation 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 believe to be in excess
and the hormone present in diminished amounts is pro-
gesterone, 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 ovar-
ian 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
Hisaw, 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 intra-
uterine 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 treat-
ed 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 of between the periods may be
due to an organic or a functional condition. In the form-
er, the endocrines are of no avail as far as therapy is
concerned for the conditon shows anatomical changes irrev-
ersable under the influence of any of the endocrines. The

only part these substances play in the lesion is per-
haps prior to their development; an etiological factor
which we will consider later. The functional type of
bleeding frequently responds to endocrine therapy be-
cause 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 proportionatly the severity
of the hypofunction of the ovary. Therefore biopsy is
indicated in these cases not only as an index of the de-
gree of ovaian 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 prob-
ably 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 psychologic-
ally than physically. These profuse bleedings of the ad-
olescent are usually caused by a hypertheelinism with a
typical hyperplastic anovulatory endometrium. Admin-
istration of progesterone for a number of days, usually
about five, prior to the time of the expected period will
frequently percipitate 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 distruction 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 enometrial
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 de-
onstrate a more or less normal endometrium is indiative
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 (comp-
lete) ovarian failure.

In almost all cases of functional bleeding we see
evidence of other endocrine disturbance 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 Kurz-rok; 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 that 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 climateric 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 reversal of the process which we find marking the change from adolescence to sexual maturity. Kurz-rok (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 en
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 indiv-
idual. The whole process proceeds to the actual cess-
ation 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 meno-
pause consists of an internal unconscious mechanism
which is manifest somewhere in its course as an amenorr-
hea. Other presenting symptoms seen in varying degrees
are neurovascular symptoms, observed in almost all pa-
tients 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-
ation 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. Great-
est 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 administra-
tion 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 prompt-
ly or are at least helped. Best results were seen in his
cases in those individuals who have a complete menopause,
ie. 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 recieved almost an
equally good result with a placebo as with the admin-
istration of the endocrines er 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 recieve 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 possibàe. 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 endocrin-
ological importance are but two in number. Both of
these are relatively uncommon but their chracteristic
endocrinological symptomatology justifies their being
included here. Since these two tumors are best class-
ified by the character of the endocrine product excreted,
they are termed estrin producing tumors and masculiniz-
ing tumors or arrhenoblastomata (Novak and Long, 1933;
Novak and Gray, 1936).

Arrhenoblastomata (Novak, 1938) develope from un-
differentiated 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 develope 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 Cushing
syndrome described for tumors of the anterior pituitary,
and tumors of the adrenal cortex. The Cushing syndrome
is the result of an overproduction of one of the pitui-
tary hormones, probably adrenotropic which stimulates
the androgenic tissue to increased activity and there-
by cause the masculinization of the individual. The
accompaning glycosuria, obesity, etc. of the Cushing
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 distruction 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 hyper-estrinization. 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 anaccountable 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 neoplasms though some reports have

been made of malignant activity of this type of growth.
(Norris, 1938)

One of the most startling and effacious 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 epi-
thelium of the vagina, change in the character of the
vaginal secretions and prompt alleviation of the condi-
tion.

Gonorrheal vaginitis is one of the most common
affections of little girls, expecially during infancy
and the first five years of life. Athough seldom ser-
ious, 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 selflimited 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 v
over into the period of puberty. This condition is im-
portant 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 revolu-
tionized 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 tha the prepubertal vag-
inal 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 Brawner (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 suppos-
itories 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 casts as an average from et
eight to ten dollars for the necessary amount of estro-
genic 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 e
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 estrog-
en) subcutaneously. In the majority of cases he admin-

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.
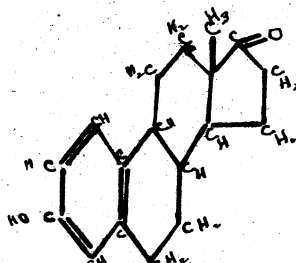
Another side of the polygonal subject of the sex hormones has been their chemical structure and the close similarity that exists between them and the sterols, the male sex hormone and especially the carcinogenic hydrogenated phenanthrene ring compounds. Since about 1930 much literature has been published 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 arguement 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,
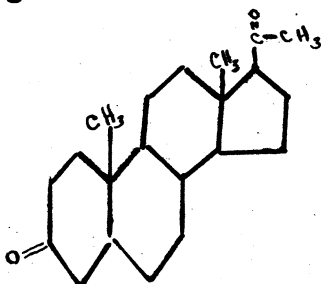
ergosterol, vitamine D, etc.
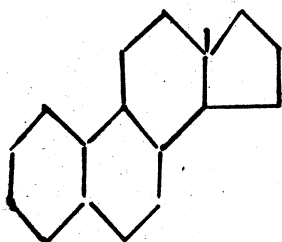
Phenanthrene group   Estrone

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 stig-
masterol and pregnanediol. His formula is given here:

Corpus luteum hormone
(progesterone)

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 carcino-
genic substances of the tar series. Yamagiwa and Ich-
ikowa described the experimental production of cancer
in rabbits with tar in 1915. Kennaway, Cook, Hager 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 definit-
ely established as being estrogenic; the extensive pro-
liferation of the endometrium during the postmenstrual
phase under the influence of estrin, a process so comp-
arable 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 hyper-
plasias (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 fpund in the urine of women
long after the menopause and even after surgical castra-
tion. His conclusion that, since the placenta will dur-
ing pregnancy produce large amounts of estrin, other org-
ans 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 pres-
ent 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
fundus 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 sufjected 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 minimizes 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 carcinogen-
ous substances from the sterol compounds by some ab-
normality of metabolism. Cook (1933) pointed out that
such a transformation would involve only reduction,
dehydration and dehydrogenation, processes which read-
ily 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 develop-
ments may be forthcoming soon either in refutation or
support of the theory.

SUMMARY

1. The endocrine system is normally in a state of imper-
fect 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 men-
strual 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 anti-hormones.

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 tht 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-

toms.

10. Dysmenorrhea of functional nature may be due to either a hyper-estrinization or to too much progesterone. 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 abnoral 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 effacious 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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