MD Theses

Special Collections

1933

Sex hormone relationship between the pituitary and ovary with clinical classification and therapy

Harold A. Duey
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

THE SEX HORMONE RELATIONSHIP BETWEEN THE

PITUITARY AND OVARY WITH CLINICAL

CLASSIFICATION AND THERAPY.

Senior Thesis:
Harold A. Duey

University of Nebraska College of Medicine
Omaha, Nebraska

OUTLINE

Part I.

    A. History.

    B. Anatomy.

    C. Graafian follicle.

    D. Corpus Luteum.

    E. Hormones of anterior pituitary.

        (1). Prolan A.

        (2). Prolan B.

        (3). Lactation hormone.

        (4). Menstruation hormone.

    F. Summary.

Part II.

    A. History.

    B. Clinical Classification.

        (1). Fluhmann.

        (2). Frank.

        (3). Kurzrok.

    C. Therapy.

    D. Case histories.

PART I.

SEX HORMONE RELATIONSHIP BETWEEN THE PITUITARY AND OVARY

Possibly the earliest history of sexual differentiation with experimental background dates back to the Eunuchs of the Greek and Roman life in which it was noted on castration that male characters failed to develop as other male species. The sex differentiation had been destroyed. (21) The early history can be covered quickly. Von Baer in 1827 demonstrated the mechanism of ovulation, and for long after it was believed that the stimulation of this process accounts for those phenomena that are now known to be the result of internal secretion. (27).

The first suggestion of incretory properties in the ovaries was on of inference. In 1849, Berthold laid the corner stone of the Science of Endocrinology by showing that after castration of cockerels the typical appearences of castrates are prevented by reimplantation of the testicle. This would indicate that the testicle must produce a n internal secretion which acting through the medium of the blood preserves the integity of the genital organs. Much later towards the end of the nineteenth century similar experiments were done on the ovaries with similar conclusions. These earlier experiments proved beyond contention that theovary is an organ of internal secretion that governs the onset of puberty and maintains during sexual life the functions of the reproductive apparatus. (27)

Among the foundation stones of the special phase

of endocrinology, are placed such articles as that of
Beard, and Fraenkel, who called attention to the Corpus
Luteum as a gland of internal secretion; next to Halban,
who in 1905, basing his deduction purely on clinical
phenomena analyzed the effect of the hormone elaborated
by the placenta fully fifteen years before full experimen-
tal proof could be adduced. Leo Loeb's analysis of the
sensitizing and probably inhibiting action of the Corpus
Luteum (1905-1915) are of tremendous importance. Iscovesco
(1912-1915) laid foundation for purification methods of
the active substance. (21)

In 1922, Frank (20) pointed out the follicle fluid con-
tained the active substance. Stockard and Papanicolaou
(1917-1918) rediscovered the cyclical changes in the
rodent vagina (61), and thus paved the way for Allen and
Doisy's (1923) elaboration of a simple and easy qualitative
test for the recognition of the active substance. (5)
Since then, dates the speeding up of the work along these
lines. Many men since than have demonstrated the active
substance circulating in the blood as Frank and Goldberger
(23) in 1925. This has given additional confirmation
of humoral influences in the body. This led Frank and
Goldberger (24) to elaborate a clinical test to estimate
the ovarian activity in the living human female. Finally
it was demonstrated by Philip Smith (56) of the dominent
influence of the anterior lobe upon the genital system,
through its influence on the ovaries. It has actually afford-
ed proof of the long suspected and constantly referred to
interaction upon each other of the two glands of internal

(2)

secretion. (21)

Automatically the work falls into at least two main divisions, the first dealing with the history of the subject which has just been briefly reviewed. The chronology of achievement and the course of development can only be briefly referred to in this article.

The second part of this thesis will explore the clinial observations both as to classification of patients and therapeutic results. These have subsequently fallen under the headings of functional and organic classifications. (21)

It would be well to discuss briefly the anatomy of the ovaries and accessory organs of sexual reproduction. The ovary is a bean-shaped organ attached to the broad ligament by the hilum. The outer covering is the germinal epithelium, and from which the definitive ova are proliferated early in life (30,49) and possibly after puberty. The body of the ovary consists of a stroma of connective tissue in which the follicles are embedded, together with the products of follicular degeneration or maturation.(50)

The graafian follicle containing the ovum consists of two peripheral layers, the theca externa and the theca interna, surrounding the follicular epithelium which carries the ovum. In the more mature follicles an antrum appears which is filled with a viscous fluid, the liquor folliculi. The theca externa cells are fibroblastic and continue unchanged during the whole life of the follicle. After ovulation the theca externa produced trabeculae which carry

(3)

blood and lymph capillaries into the developing Corpus Luteum.(50)

Although ovulation is the predestined end of the Graafian follicle, the majority fail to complete the full life history owing to their extensive number, and undergo atresia at some stage of their growth. In the degenerative process the follicle is either entirely absorbed or metamorphased into interstitial tissue or a Corpus Luteum atreticum. (50)

After ovulation the shell of the ruptured follicle shrinks, and, owing to the previous rupture of the capill-aries, become filled with a greater or lesser amount of blood. From the follicular remains, the Corpus Luteum composed of large glandular cells containing the so-called lutein granules, develops with remarkable rapidity. The Corpus Luteum degenerates at the end of the menstrual cycle. If pregnancy ensues, after a certain time, which varies according to the species and the occurrence of lactation and preganancy, the Corpus Luteum retrogresses and finally is reabsorbed entirely or dwindles to a small Corpus Albicans. (50)

The essential features of ovarian activity are the maturation of the Graafian follicle and the discharge of the ovum. This periodic occurrence, together, with the intervening growth of the Corpora Lutea constitutes the ovarian cycle.

The accessory sex organs, namely, the Follopian tube down which the ova descends to the uterus and the vagina which connects the uterus with the valvular outlet. The mammary gland is also an accessory sexual organ. (21)

These accessory organs undergo definite changes during the period of what is called the menstrual cycle. The human cycle is divided into different stages, based on the condition of the uterine mucosa over a period of twenty-eight days normally. (a) Rest--The uterus is small pale, with very then mucosa and contains straight, simple glands, with wide interglandular spaces. (b) Interval--During this stage a slow growth of the mucosa takes place, without secretion. (c) Pregravid (premenstrual)--This stage is marked by turgescence hyperplasia of the glands, showing itself by toruosity of the gland contour and feathering of its epithelium. Intra-glandular secretion increases. The stroma undergoes well marked decidual changes. (d) Pregnancy--Its further development with nidation of the ovum, and the uterine and other changes incident to pregnancy, or menstruation are manifested.(21) See fig. I

In this paper it will be impossible to cover all the intensive investigations of many biologists, chemists, clinicians, etc., but an attempt will be made to show clearly the correlation of the ovary with the uterine cycle as shown by reproducing the ovarian stimuli in physiological experiments. The correlation of the sex hormone control of the anterior lobe of the pituitary gland over the ovary will also be demonstrated experimentally.

The synchronization found between development in the ovary and activity in the accessory reproductive organs immediately suggests that one controls the other, and it has become abundantly clear that the ovary is responsible for

the growth and cyclic changes of the uterus, vagina and mammary glands. Further more, evidence shows that the nervous system plays a very minor part in this correlation, which is maintained by means of internal secretions upon which this view has become chiefly placed.

So far in this discussion there has been no definition of the female sex hormone. Present knowledge permits giving only a very imperfect definition.

The definition given by Frank (21) states that: "The female sex hormone is of a simple composition (C-H-O). Chemically, it shows lack of affinities and activity, biologically on the contrary, its activity is exerted in a minute concentration. The activity is almost exclusively limited to Muller's ducts and the mammary glands. The effect produced by the female sex hormone foster, matures, and stimulates all feminine qualities and attributes as well as the organs needed for the perpetuation of the species."

It is a well established fact that the ovry is an organ of internal secretion. Lipschultz (38) states: "In all cases of castration an atrophy of the genital organs takes place and an atrophy of the vagina and especially of the uterus, menstruation ceases and there is characteristic fatty deposition."

Transplants in fowls done in 1762 and in 1849 shows that the sex characteristics are replaced by the normal sex characters. It was shown also that by removal of the transplants typical appearances of Capon reappear. (38)

Bucura states, "As regards to ovarian transplantation

in women there can be no doubt that the atrophy of the
uterus can be prevented by trasplantation; menstruation
occurs and even returns when it has formerly disappeared
in consequence of the removal of both ovaries.

A great amount of work has been done to demonstrate the
organ of hormone secretion in the ovary. At first by
obliteration of parts of the ovary and noting the effects
and finally when it became possible to obtain viable
extracts from different parts of the ovary the extracts were
usedfor experimental work.

The Ovarian Sex Hormone (Folliculin)

Allen, Pratt, Bland and Newell state from their ex-
perimental work on this phase of the sex hormone of the
ovary, " Analysis of hormone content of isolated tissues
of human ovary have been made by injections of fresh foll-
icular fluid and by implantation of fresh Corpora Lutea,
of follicle walls, and of cortical stroma free from mac-
roscopic follicles. The use of graded amounts of ovarian
tissues has made possible roughly quantitative analysis.

"The test used as a criterion of hormone activity was
the full oestrous reaction of the ovariectomized rat as
reflected in the cell content of the vagina. Therefore
the hormone sought was that responsible for the genital grow-
th reactions of the periods of oestrus in lower mammals
and of the intermenstrum in primates.

"Therefore, recent Corpora Lutea tested corresponded to
unfertilized ova recovered from the uterine tubes. The stage

of development of these and other corpoa has been checked by histologic studies. High yields of this hormone have been obtained from recent corpoa removed from the thirteenth to seventeenth days of the menstrual cycle. There is a conderable decrease in amount by the twentieth to the twenty-second day. Corpoaof the first third of gestation contain considerable amounts. Two full term corpoa gave negative tests. This last result indicated definitely that toward the end of gestation the Corpus Luteum of women does not share responsibility for the large amounts of this hormone in the placenta, blood, and urine." (7)

"Liquor folliculi and pieces of follicle walls mostly (granulosa cells) contained considerable amounts of this hormone. In most cases the specimens tested were diagnosed as to normality or atresia by study (in section) of the follicle walls or the contained ova. In two cases of long continued bleeding large yields of hormone were obtained from cystic follicles. In one case of amenorrhoea, large amounts of fluid from cystic follicles returned negative tests.

Cortical stroma without macroscopic follicle, taken from ovaries containing follicles or corpora in which hormone was demonstrated, gave negative tests.

These results added to earlier data, demonstrate that as far as the secretion of the hormone is concerned, the human Corpus Luteum merely continues an acticity which is primarily follicular. This hormone content of the human Corpus Luteum is highest just after ovulation in the early stages of transition from follicle to Corpus Luteum and

decreases before the onset of the next menses. Normal
stroma tissue of the ovarian cortex shares little in
this function.

"Removal of parts of ovaries most active in secretion in
this hormone, either large follicles or recent CorporaLLutea,
when done during the intermenstrum, usually results in
the appearence of menstruation within the next forty-eight
hours. These observations substantiate earlier conclusions
from experimental work in monkeys that men truation is
degenerative in significance and primarily due to decrease
action of this ovarian hormone after it has induced a certain
amount of growth in the uterus." (7)

The Corpus Luteum Hormone   (Corporin)

Now comes the consideraton of the secretions of the
Corpus Luteum. The relationship between the Corpus Luteum
and Graafian follicle became definitely established when it
was shown that by abolation of the Corpus Luteum that in
early pregnancy one to two weeks the ova was absorbed; if
later an abortion resulted, it indicated definit ly that the
Corpus Luteum had a two fold function that of secreting
estrin and that of maintaining pregnancy and inhibiting
ovulation. The estrin secreting capacity of the Corpus
Luteum has just been shown. Further evidence showing this
relationship is presented in the experimental work of
Hisaw and Leonard. (37)

In a previous paper Hisaw and Leonard (34) pointed out
that the production of a progestational endometrium in
the uterus of a castrate rabbit required the combined action
of the follicular and Corpus Luteum hormones in which the

follicular hormones had to exert its influence first. This one-two relationship was previously demonstrated for the decidual reaction in the uterus of rats and guinea-pigs by Weichert (62) and for the Corpus Luteum hormone "relaxin" by Hisaw (32,33) and Fevold, Hisaw and Meyer. (18) This particular mode of action of the two ovarian hormones to produce the changes in the uterus has been upheld by Allen (9) and Parkes.(49) It was also shown in previous paper of Hisaw and Leonard (34) that the Corpus Luteum hormone "Corporin" (Hisaw)"Progestin"(Corner), responsible for the progestional changes could not maintain indefinitely the characteristic histological picture of early pregnancy in the uterus of castrate rabbits. Also it was demonstrated by injections of follicular hormone and Corporin that it was possible to prevent the progestional modifications of the uterus by sufficient quantities of the follicular hormone. In this paper Hisaw and Leonard present further data on the vestria-corporin relationship and discuss certain other physiological aspects which have developed from the experiments.

"Experimental: It was shown that when Corporin was injected in doses one to four rabbit units for each five days for a total of fifteen days and samples of the uterus being removed and sectioned every five days that, no matter how active the extract, it was impossible to prolong the modification beyond ten days and retrogressed to almost normal by the fifteenth day.

It was found when oestrin and corporin are injected simultaneously into castrate rabbits, the results to be

expected depends on the higher dosage of either hormone and the apparent antagonism is explained on the basis of the two hormones competing physiologically for the endometrium. The oestrus hormone can hold the action of injected corporin in abeyance for an extended period nine days at least after which if the dosage of oestrin is lowered and corporin treatment continued the effect of corporin becomes manifested.

It takes many more times the amount of oestrin to obliterate the characteristic modification in the endometrium of early pregnancy than it does to over power the effects of a rabbit unit of corpoin capable of producing a histological picture equally as good in a castrate animal.

Corpoin alone or with the addition of oestrin does not seem able to maintain the progestational modification indefinitely. This is not surprising if one considers the follicular hormone as a growth promoter and sensitizer of the uterus and corporin as a modifier of structures already formed by the follicular hormone.

If the amount of folliculin is physiologically greater than corpoin, the endometrium remains in the oestrous state; if the corporin is physiologically greater in amount than the follicular hormone, the glands undergo their modification as they would normally. " (37) See figure 1.

The Pituitary Ovarian Relationship

It has been shown that the cyclical changes in the uterus are definitely associated with concomitant changes in the ovary. The ovarian function depends largely upon the secretion of the anterior lobe of the Hypophysis as is

demonstrated by Smith 1926 (59), Smith and Engle 1927 (69).
Bleeding is recognized as the most important criteria of
menstruation. Corner (14) has found in Macaques that
menstruation may proceed, at least for a limited period,
without ovulation or the formation of a Corpus Luteum.
Maddux (41), and Morrell and associates (45) have shown
that when the follicular hormone (oestrin etc.) is injected
into spayed Macaques, bleeding from the uterus results
after the cessation of injections. Edgar Allen (2) found
that the transplantation of the anterior lobe of the
hypophysis in non-castrated immature macaques caused con-
siderable growth of the genital tract and marked growth of
the Graafian follicles. This led him to suppose that the
development of the genital tract and the effects of the
sex characteristics were secondary to changes in the ovary
for, as noted by him, these changes are similar to those
obtained in normal and castrated monkeys from injections of
ovarian hormone. The findings of Smith and Engle (60) that
anterior lobe implants were ineffective in castrated rats
also supported this supposition of Allen.

Hartman, Fivor, and Geiling (31) were able to cause
bleeding from the uterus in macaques by injection of
extracts of the anterior hypophysis. In a series of experi-
ments, they found evidence that the extract of the anterior
hypophysis caused bleeding in hypophysectomized macaques
while follicular hormone did not. This led them to postulate
the presence of a special anterior lobe hormone as the cause
of bleeding which is distinctly different from the follicle

stimulating hormone of Smith and Engle and the lutenizing
hormone of Evans and Simpson. (15)

Saiki (55),in experiments with monkeys has shown that
extracts of the anterior lobe do cause external bleeding
and other ovarian-pituitary relationships.

"The first two experiments involved simply the
administration of hypophysis extract to normal immature
monkeys. Showing that the injection of the hypophyseal
extract can cause external bleeding which in amount and
duration is similar to that found during normal menstruation.

"The next three experiments, injections were continued
longer to see whether bleeding might occur during the injection.
No bleeding till six days after discontinuing injections
whether injected eight of seventeen days.

"The next three experiments were designed to show
whether or not the bleeding may be induced at intervals
shorter than the normal menstrual cycle. These experiments
show that experimental-like bleeding can be produced two
or three times in the same monkey and at intervals shorter
than the normal cycle, by the injection of an extract of the
hypophysis.

"Four experiments were preformed in which the hypophysis
extract was administered to spayed monkeys showing that
injections of hypophyseal extracts into castrated monkeys
caused no bleeding. Whereas the same extract when injected into
immature non-castrated monkeys did cause bleeding. It is
logical to suppose then that this bleeding is dependent upon
the presence of the ovary and that the uterine changes
follow the induction by the hypophyseal extract of some

alteration in the ovary.

"A series of experiments, to be added here, will sustain the idea that the bleeding occurs when the stimulating effect of the follicular hormone upon the endometrium is decreased after previously causing some change in it.

"In the first experiment of this series it was attempted to elicit bleeding by injection of the follicular hormone into a castrated immature macaque. In this experiment, just as in those of Allen and Morrell, external bleeding was produced into a castrated immature macaque by injecting follicular hormones. The bleeding occurred several days after cessation of the administration of the hormone.

"The fact that uterine bleeding could be produced by treatment with follicular hormone in this castrated immature animal demonstrates that failure to obtain the same results with hypophysis extracts in previous experiments on the same animal was not due to insensitiveness of the uterus.

"In the next experiment, an immature animal was given a small amount of hypophysis extract, insufficient to induce bleeding, but sufficient to cause some stimulation of the ovaries as evidenced by reddening of the sexual skin.

The animal was then spayed. From this experiment it is imaginable that the bleeding from the endometrium occurs when the stimulation of the follicular hormone is interrupted after it has caused certain changes in the endometrium. Also the experimental bleeding a few days after cessation of the injection of the anterior hypophysis hormone can be explained in the same way, since it is clear that the hormone

stimulates the ovary to produce follicular hormone.

" If this supposition be true, then if follows that the bleeding which would normally be induced by the hypophysis extract should be postponed by administration of follicular hormone immediately after cessation of the hypophysis injections. This was tried in four experiments and the results indicate strongly that the bleeding does not occur during the time the process caused by the follicular hormone is going on.

\On the basis of these experiments,it is tentatively assumed that the menstruation like bleeding of the endometrium occurs after a certain physiological state of the endometrium caused by the follicular hormone is altered when the hormone is reduced in amount or removed. The effect of the hypophysis extract is, under this interpretation, simply to stimulate production of the follicular hormone, which is then reduced in amount after cessation of the hypophyseal injection." See figure 1:$\mathrm{I\!I}$(55)

Zondek (64) drew similar conclusions following his experimental work .

Double Sex Hormone Action of Anterior Pituitary

Aschheim and Zondek claim the sex hormones of the anterior pituitary to be two hormones instead of one. (27) They state: " The administration of prolan in Zondek's experiments did not always have the same reaction. Sometimes it would produce normal ripening of the follicle with rupture and deposit of ova in the tubes and with this process the formation of a normal Corpus Luteum (Reaction I) often

however, the follicles would not rupture, the eggs would be retained and the entire cell apparatus of the follicle would become luteinized. If the potency of the extract in such a case were increased, the entire ovary would be converted into a single lutein body (i.e. lutein cyst, similar to those found associated with hydatidiform mole and chorion epithelioma, q.v.) in which case follicule-ripening could no longer be possible. Aschheim further showed that testing the urines of patients some showed Reaction I and others showed Reaction III.

"The logical conclusions from these observations that prolan contains two hormones was soon confirmed by Zondek, who was able to isolate from the whole substance a product which caused when injected into immature animals only follicle-ripening (Reaction I) with no luteinization (Reaction III). This product he named Prolan A, the remaining luteinizing hormone being entitled Prolan B." (27)

There are a great number of sources of the universal sex hormone (consisting of both Prolan A and B). It can be extracted from anterior pituitaries, placentas, ammiotic fluid, blood of pregnant animals, but the riches source of all is the urine of pregnant animals. Very early in pregnancy large amounts of the sex hormone are excreted in the urine. This is the basis of the Aschheim-Zondek test for pregnancy in women. The test consists in injecting into immature female mice a feww drops of urine twice daily for three days. The mice are killed on the fifth day of the test one-hundred hours after the first injection and the ovaries

(16)

are examined. Corpora Lutea and follicles filled with blood are definite signs of the presence of the sex hormone. This is presumptive evidence that the urine was excreted by pregnant women . (10) There are some other conditions such as chorioepithelioma which might give a false positive test and should be considered in the diagnosis. (40)

Many writers are of the opinion that the pituitary gland controls lactation. Some believe that this is the ovary; others believe it is direct.. Recently Corner (13) has obtained evidence which would indicate the Corpus Luteum is not essential for lactation but that one of the anterior hormones, acting alone is able to cause the secretion of mild. Nelson and Pfiffner (46) have found by experiments with guinea-pigs that the anterior-pituitary hormone can cause lactation without the aid of Corpus Luteum. They have drawn the conclusion that some ovarian hormone must act upon the mammary gland previously to enable the anterior pituitary hormone to produce lactation.

Parkes (52) found a hypophyseal extract which when injected in rabbit produced complete proliferation and lactation so he concluded that hypophyseal hormone acting through Corpoa Lutea caused the reaction.

Corner's (13) theory is generally accepted however as he has shown where complete proliferation and lactation can be produced by use of the alkaline extract of the. anterior pituitary. See fig.I.

The subject of cause of menstruation was thrown into confusion by Corner,(12), Edgar Allen (3), Hartman (30) and

others when they proved that the Corpus Luteum and oestrin
are not essential factors in production of menstruation.
Aside from Prolan A and Prolan B another factor has been
demonstrated in the anterior pituitary to be essential in the
production of menstruation.

Hartman, Fivor and Geiling (31) have discovered that
the bleeding of menstruation in monkeys can be initiated
by implantation of anterior pituitaries and by injections
of extracts of anterior pituirtaries or urine of pregnancy.
Uterine bleeding resulted from injections of ovarian follicular
hormone because of stimulation of the animals own pituitary
gland. Previous hypophysectomy prevented the uterine bleed-
ing except when replacement therapy was instituted by
implants or extracts which supplied the missing anterior
pituitary hormone. This brilliant piece of research supplies
positive evidence that menstrual bleeding is due to the
presence of an anterior pituitary hormone rather than due to
the absence of a Corpus Luteum hormone. See fig I

The question however arises as to what is menstruation.
Is this bleeding a result of true menstruation or is it a
true uterine hemmorrhage due to the action of the injected
hormone prepared by Hartman.

The various endocrine influences which have just been
discussed shows that the anterior pituitary lobe hormone ,
Prolan A, stimulates the ovary to produce follicles. The
follicle in turn elaborates the female sex hormone folliculin
which reaches the tubular tract by means of the blood stream.

The tubular tract after sufficient blood concentration has been reached then undergoes early premenstrual changes. Following ovulation another factor, Prolan B, the luteinizing hormone of the anterior pituitary becomes active and the Corporus Luteum in the site of the ruptured follicle. This transitory gland _{Corpus luteum} continues to produce female sex hormone as well as a special hormone, whose presence in the circulating blood has not been demonstrated , which enhances the local uterine changes necessary for nidation and early nutrition of the fertilized ovum. It also inhibits further ovulation. The chorionic epithelium, later developing in to the placenta, which has not been discussed in this article because it is only a gland of secretion during pregnancy. The placenta takes up the production of both the female sex hormone and the pre-pituitary hormone, Prolan B.

It is also claimed that there are other hormones of the anterior pituitary . They are the lactation hormone and the uterine bleeding hormone which have been shown to have a direct effect without the intermediary ovary. See figure 1.
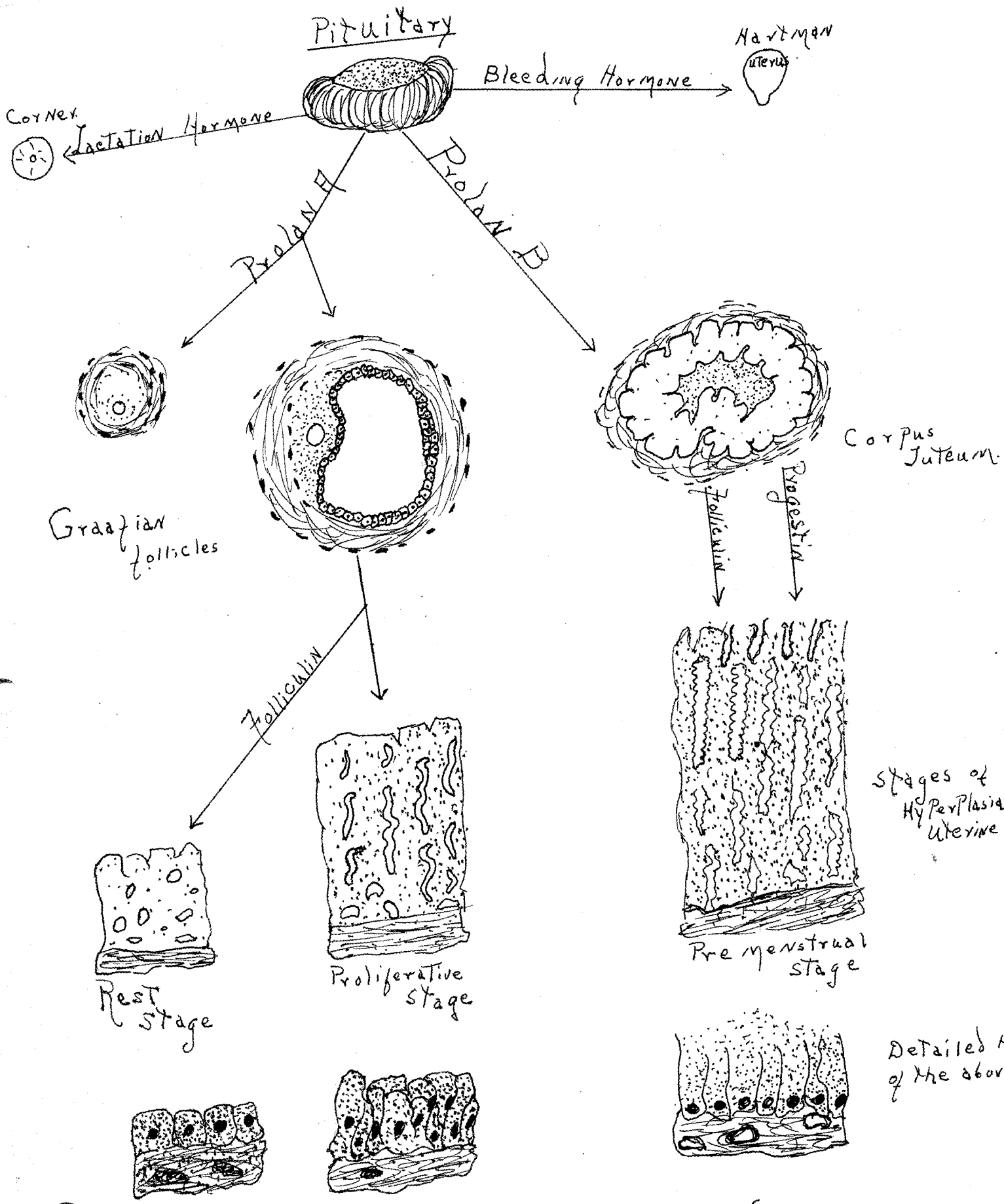
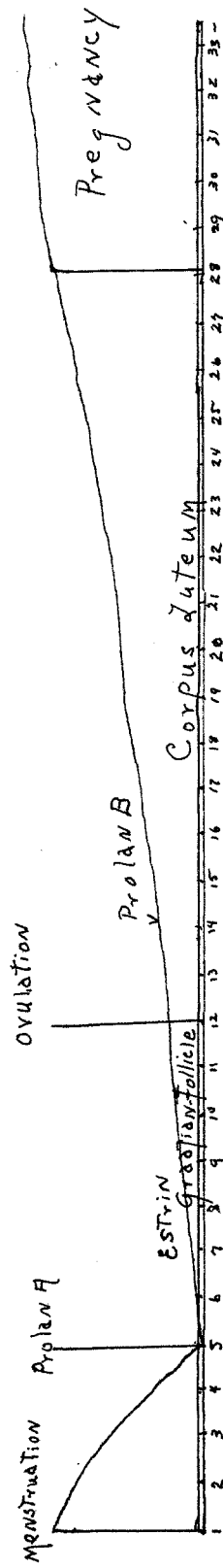Diagram of Action of the sex Hormones.

Figure I

Diagram showing Relation in Time of Uterus and Ovary during Sex Cycle

Figure II

PART II.

Clinical Classification and Therapy

Today in analyzing the role of the female sex
hormone especially, with regard to therapy there is found a
complicated situation. However if one understands the phy-
siology of the hormones involved, this having been reviewed
in this paper, the situation becomes less intricate.

A rapid review of the development of suitable extracts
for therapy shows that until 1912, attempts to extract the
follicular hormone, estrin, were unsuccessful because of the
use of solvents and the lack of a test object to determine
the potency of these extracts. At that time Iscovesco (43)
realized the inadequacy of aqueous extracts and therefore
employed lipoid solvents (ether, alcohol, etc.). He also
found that experimental hyperplasia of the animal breasts
as result of female sex hormone injections is inadequate
for test purposes. He therfore employed the increase
growth of the uterus of the virgin rabbit treated with this
product as evidence of its potency. This involved the
sacrifice of each test animal

Stockard and Papanicolaous (43) discovery of the
succession of changes in cell types in the vagina of the
guinea-pig during the sexual cycle and the observations of
Long and Evans (39) that these cyclical changes totally
cease after double ovariectomy were the foundations on which
Allen and Doisy (5) later built the international test for
determining quantitatively the activity of ovarian and
placental lipoid extracts. Essentially this test consists

in reproducing estrus in the spayed rat. A unit of the female sex hormone (estrin) is the minimum quantity which, when given in three divided doses, at four hour intervals, will produce estrus in the castrated rat. This effect must be obtained in at least four out of five test animals. A rat unit is equivalent to five mouse units. (43)

The chief difficulty of present day therap lies first in the correct diagnosis of the individual case and second a suitable properly prepared hormone that will produce therapeutic results. Reports of various men with any sizeable list of patients in this field if limited. More and more however, re recognizing its value and especially in the past two years are reporting success in their treatment.

The attempt at classification of these patients has been made by Fluhmann (19) in non-pregnant individuals. The fundamental studies demonstrating the ovary stimulating properties of substances derived from the anterior lobe of the hypophysis has furnished the basis of an important laboratory test. This was first used by Aschheim and Zondek (19) for the examination of urine and developed as a "pregnancy test" as was stated before. Studies conducted for the past three years in the Stanford Gynecological Laboratory has shown that application of this test procedure to the examination of the blood of women in non-pregnant conditions may yield results of important clinical significance.

Fluhman (19) has utilized this test in an attempt at clasification of these patients. "The test consists in the

induction of changes in the ovaries of immature mice by the
injection of 5.0 c.c. of blood serum from the patient. The
finding of mature Graafian follicles (Reaction I or APR I)
in the test animals is considered as positive for the presence
of the 'follicle ripening' hormone of the anterior hypophysis
(APH-A) while luteinized cysts or structures made up of
lutein cells surrounding an ovum, (APR-III) denote the pres-
ence of the 'luteinization' factor (APH-B). The present
report is based on the results of the test preformed in
two-hundred and eighty non-pregnant women in whom no gross
lesions of the pelvic organs could be demonstrated, and
included one-hundred and eight cases used in the previous
papers." (19)

It was found essential to discover whether patients who
show disturbances in their sexual sphere are free from
other demonstrable endocrine diseases, such as the well
understood classical syndrome Froehlick's Dystrophia Adiposa-
Genitalis, thyroid over activity or underactivity, for in
these conditions genital disturbances are usually secondary.
The secondarily genital deviations are purposely left out in
the paper in order to simplify the already sufficiently
complicated problems encountered. (22)

"It would seem particularly desirable to develop a.
clinical classification based on the results of the test
described. It may be of use as a starting point for further
similar studies or in determining the indications for 'ovary-
stimulating' or 'ovary-substituting' therapeutic preparations.
This study represents such an attempt, and in doing so it
has been found impracticable to undertake a classification

based on endocrinological diagnosis which seeks to determine the exact etiology of pelvis dysfunction. It was therefore necessary to resort to an interpretation of certain symptoms, and as a result it is possible to offer a grouping in terms of ovarian function as determined by the history of the menstrual cycle. (19)

" From this standpoint it is found that there are four main groups of patients. In the first two (normal ovarian function, hypohormonal function or condition) the test has been found negative but in the two categories (afunctional conditions of the ovaries; hyperhormonal conditions) it has been positive in a large proportion of the cases." (19)

Frank(22) uses 40 c.c. of patients blood in testing the blood cycles and has a much higher precentage of positives as compared to Fluhman√(19). The use of more blood is probably a more exacting condition of the hormonal cycle in the blood of these patients.

Fluhman's (19) first group is the "normal ovarian function". This group is the control series and includes forty-five woman who gave a history of normal menses and the pelvic examination is each case revealed no extensive disease beyond possibly a mild injection of the cervix, an uncomplicated retroversion, a Bartholin's gland cyst, etc. The blood examination represents all stages of the menstrual cycle, and in each instance a negative reaction was found.

Frank (21) reports the results of blood test on more than five hundred women also the urine was tested in a great number of the women by the simple vaginal test as previously

(23)

described by Allen and Doisy (5). In normal women a low
hormone blood level exists until about the seventh day be-
fore the onset of the next menses. The rise produces a
three plus or four plus in test mouse. The threshold
mechanism, which keeps the blood level low during the inter-
menstrual, and permits the sudden rise, has not been fully
clarified. The governing mechanism of excretion through
the urine and feces has not been determined.

The second classification of Fluhmann (19) is the
"Hypo-hormonal conditions". "In this group, also charact-
erized by a test negative for anterior pituitary hormone in
the blood are found five different clinical manifestations.
(a) Irregular delayed menses, the interval between periods
varying from five weeks to several months in length, and in
most cases with a scanty flow; (b) Totally irregular menses,
the interval being sometimes shortened and sometimes length-
ened; (c) Regular menstrual cycle, but with a scanty flow
(oligomenorrhea); (d) Amenorrhea of short duration (six weeks to
six months); (e) Amenorrhea of over six months duration."

Frank's (22) classification is quite similar with the
hypo-hormonal conditions. His first is amenorrhea with a
definite blood level, but low so "Sub-Threshold". These
patients at more or less regular intervals show an accumu-
lation of the hormone in the blood which however rarely reabh-
es above two plus considered about the lower limit by Frank.
The urine curve corresponds with the blood curve. The second
group failed to demonstrate accumulation of the hormone over
long periods. The urine on the other hand shows an exess of

(24)

hormone over a long period of observation. He concludes that this must be due to an abnormal permeability of the kidney. In other words a low renal hormone threshold level. This contrasts Sharply with some "premenstrual tensions"in which the renal threshold is abnormally high. (22) The last group of amenorrheas he discusses has neither blood or urine hormone cycle. Clinically these patients are indistinguish - able from the threshold blood cycle patients. The prognosis is poor in these patients.

The third classification of Fluhmann (19) is the afunct- ional condition. The patients of this group are character- ized by a total deficiency of ovarian function, this is confirmed by Mazer and Hoffman (42). "The number of positive tests obtained in women after operative extirpation of the ovaries increases rapidly in the first few weeks following operation so that after three months seventy-six per cent of the patients give a follicular stimulating test, and this reaction has also been found as long as fourteen years post-castration or fifteen years after the menopause.

"The inclusion of women following operative extirpation of the ovaries, radiation castration and following the climacteris as examples of total ovarian deficiency cannot be questioned, but the advisability of placing a number of patients with amenorrhea is the category of twenty-six women with periods of amenorrhea of over six months duration ten gave a strong positive test, and clinically it was found that obesity was associated with the condition in six of ten cases, whereas in the sixteen patients with a negative test

obesity was noted only in four. The interpretation that the existence of a positive test here represents a total absence of an obarian function is open to question and must be subjected to further investigation. It is possible also that the presence of the hormone in the blood may be merely a phase of the disease and subsequently disappear. The prognosis in these cases must be considered as unfavorable but not helpless, as at least two of the patients of this group presponded to treatment."

Frank (22) says, "In the sterile group the majority of menstruating women either show a subthreshold blood cycle such as was described under the amenorrheas, or negative blood condition with urinary cycle present. These cases in which sterility if combined with amenorrhea are explained by the hormone changes accompanying the amenorrhea. In sterile types also, the grouping and prognosis depends almost exclusively on hormonal observations."

The last classification of Fluhmann (19) is the Hyper-hormonal group. "The findings in this group are not as definite as in the preceding since positive tests have been obtained in a small number of cases and in some instances it has been necessary to repeat the examination two or three times before the presence of the anterior pituitary sex hormone could be demonstrated in the blood. It includes a number of younger women with too grequent and profuse menses, approximately one-third of the women of the menopausal age with menstrual irregularties (also chiefly poly-menorrhea), as well as three isolated observations on patients with normal or profuse menses associated with marked dysmenorrhea."

The hyper-ovarian functioning conditions found by Frank (22) has a rather high hormone blood level. "'Puberty bleeding', more than a dozen of these adolescents have now been followed for from three to six years. Both the clinical and the hormonal picture in every member of this group is alike. The abnormal bleedings may be either the menorrhagia or metorrhagia type and eventually lead to grave exsanguination. In contrast to the abnormal functional bleeding of mature women, the blood hormone level for female sex hormone appears constantly high, so that an over-loading of the circulation is demonstrated. Coincidentally the bleeding mucosa shows marked cystic endometrial hyperplasia. The urine excretion of these girls also demonstrates the marked over production of the hormone as an undue amount is excreted constantly, often without typical cyclic variation."

Preclimacteric bleeding of purely functional character likewise shows a high hormone blood level, but usually some cyclic variation is noted. Nervous and vascular symptoms in this group is characterized by both a high and a low blodd level." (22)

Kurzrok (35) divides the menopause cases into two groups similar to Frank(22). One group shows follicular hormone in the urine, and the other group does not. One-hundred cases of menopause were thus studied. The hormone was determined by the method of Kurzrok and Ratner (36). Follicular hormone is a benefit only in the group in which no hormone is to be found in the urine. The therapeutic results are very good when the cases are treated according to this grouping.

Dysmenorrhea which was mentioned by Fluhmann (19) is discussed by Novak (47) in which he attempts to explain the cause on an endocrine basis. "Many theories have been offered to explain the etiology of primary dysmenorrhea, and many plans of treatment suggested. None have seemed adequate, although the importance of psychogenic, constitutional and other such factors in the causation of many cases is undoubted. The immediate cause of pain on the basis of the physiologic studies reported in this paper, is almost surely a disturbance of the normal motility factors of the uterine muscles. In general, female sex hormone or theelin is an excitant and progestin an inhibitor of this motility. Preparations of the urine of pregnant women, presumably because of their prolan content likewise are strongly inhibitory.

"The inhibitory influence of progestin on uterine motility is removed a day or two before the menstrual onset, and the withdrawal of this restraining factor produces dysmenorrhea in some women, possibly those with such predisposing factors as constitutional sub-normality or psychoneuroses. In other cases it would seem that there is an actual inbalance between theelin aNd progestin, either quantitative or chronological or both," (47)

It has been shown that the Corpus Luteum is essential for excretion of estrin in women and is being utilized as a clinical test for presence of Corpus Luteum activity as quoted by Smith and Smith (60). "We have also tested a great many urines of patients who were receiving oestrin in one form or another for the treatment of sterility or

amenorrhea. In practically all the urines there was no trace of oestrin although the women were taking as much as 200 to 400 R. U. daily by month."(60)

"The clue to this situation was suggested when we discovered the progestin (prepared according to the method of Corner and Allen) (14), causes the excretion of injected oestrin in rabbits." (59)

Thus it would seem that Corpus Luteum is essential to oestrin secretion in urine as was shown by their results which are her summarized. "Oestrin has been given orally to women whose urines were followed for its excretion over a period of one to two months. Eight cases are reported, including four amenorrheic patients, three sterile, and one normal control. The results would indicate that in women as in rabbits oestrin is excreted only when the organism has been exposed to the action of Corpus Luteum. It appears possible by this means to differentiate between a persistent Corpus Luteum, irregular appearence of total basence of Corpus Luteum, and cyclic activity of the Corpus Luteum."(60)

THERAPY

The attempt at classification of the disorders of the ovary and pituitary sex hormone relationship has been presented. The therapeutic value which may be obtained from the use of extracts in the various cases will be shown.

The administration of female sex hormone has no effect on the ovaries; on the contrary, large doses were shown to inhibit ovarian function. (4) As a preliminary to specific

(29)

treatment of the gland primarily responsible for the amenorrhea and the associated sterility, it is essential to employ female sex hormone to vascularize and increase the size of the uterus and thereby render it more responsive to reactivated ovarian impulse. (43)

Clinical data concerning the effcacy of female sex hormone in treatment of amenorrhea are somewhat contradictory. Thus, Fellner, reported, by Mazer and Ziserman (43) favorable results in 205-of a series of 296 cases of amenorrhea treated with female sex hormone. Mc Clendon (44) induced menstruation by the administration of 15,000 mouse units of female sex hormone in a women who had not menstruated for five years. Streck (43) reports favorable results by the oral administration of 500 to 4500 rat units of female sex hormone (Progynon). He emphasizes that the results are better in those women in whom genital hypoplasia was not too far advanced. Batesweiler reports (43) either temporary or permanent improvement in menstrual periodicity in eight of nine cases of amenorrhea. Zondek employed pituitary sex hormone in the treatment of amenorrhea. (43) Rubin (54) sounds a pessimistic note on the other hand regarding the effcacy of female sex hormone in treatment of menstrual disorders.

"Follicle cytosis and resultant endometrial hyperplasia are usually due to inadequate stimulation of the ovarian follicle by the anterior pituitary gland. This condition requires treatment of the gland primarily responsible for the follicle cytosis, either by injections of a potent pro-

duct of anterior pituitary sex hormone or by low dosage
irridation of the hypophysis." (43)

Occassionally, follicle cytosis is consequent to an
antecedent pelvic infection with resultant thickening of th e
ovarian tunic which mechanically inhibits ovulation and the
formation of a Corpus Luteum. In these cases prolonged
diathermy treatment often effects a permanent cure. Occassion-
ally, operative measures, as outlined by Reynolds and
MaComber (53) are necessary.

The treatment of amenorrhea as quoted by Novak (47),
is as follows: "In the treatment of amenorrhea, the most
logical plan would be the hypodermic injection of folliculin
followed by similar injections of progestin. Since the
latter is not available for human use, its place may perhaps,
for the time being, be taken by anterior pituitary luteiniz-
ing hormone. This plan of treatment produces, so far as we
know, no permanent stimulating effect on the ovary."

Campbell and Collip (11) report on the use of emmenin
and second anterior pituitary like principle of the human
placent . In oligomenorrhea, the majority of the subjects
of this type of secondary amenorrhea appear to respond very
staisfactorily to treatment, whereas, subjects of primary
amenorrhea and of secondary amenorrhea for some years dur-
ation appear not to be amenable to this therapy. The dosage
used in this group of cases has been twenty-five grams of
placenta three times daily until results have been obtained
or treatment has been discontinued. The average time of
twenty-three days elapsed before menstruation occurred in a

group of forty cases.

The treatment of functional bleeding as menorrhagias and metrorrhagias is essentially that of Corpus Luteum stimulation. As the female sex hormone has no effect on the ovaries its employment in these cases only aggravates the localized necrosis in the hyperplastic endometrium and result in more profuse bleeding. In women under forty years of age, dysfunctional uterine bleeding is usually due to the lack of pituitary stimulation of the ovary, insufficient to carry the ovarian follicle through the entire cycle. The logical treatment, therefore is the administration of anterior pituitary sex hormone (Prolan, Follutein) which has a tendency to complete the ovarian cycle (Luteinization) and thereby normalize the structure of the endometrium. (43)

The dysfunctional uterine bleeding of the menopause while presenting the same pathology should be viewed from a different angle. In this class of women there seems to be present a compensatory hyperfunction of the anterior pituitary lobe in an attempt to stimulate the declining ovaries. This has been clinically shown that an excess of anterior pituitary sex hormone exsists in a considerable number of menopausal women. The administration of anterior pituitary sex hormone in these patients is theoretically unsound and clinically valueless. (43)

Novak and Hurd (43) have obtained excellent results in a large series of cases. Many of them young women in whom the only alternate would have been surgery of radiotherapy. The treatment consists of the intramuscular injection of a luteinizing hormone prepared from the urine of pregnant women.

Campbell and Collip (11) report on the use of the anterior

pituitary like principle in menorrhagias and metorrhagias as quoted. "Dosage: A stable preparation of this hormone containing forty day rat units per c. c. has been administered subcutaneously in from one to two c. c. daily or bi-daily."

"Results: In a series of forty cases of menorrhagias and metorrhagias the excessive bleeding (uterine) has as a rule been controlled. In most instances normal preriods have been instituted thereafter, but these have not been the same regularity as in cases of other types treated with emmenin."

Treatment of dysmenorrhea on strictly endocrine basis is highly satisfactory. In the absence of inflammatory or other organic conditions of the pelvic organs, dysmenorrhea is purely an outward expression of an arrest of genital development due to endocrine distrubance. The investigations of Schultz (43) show that these women have a preponderance of connective tissue over muscle tissue in the uterus in the ratio of two to one--a condition normally found in the prepubertal child. He believes that the failure of the myometrium to empty the uterine veins results in venous stasis and pressure stimulation of the uterine nerves.

"There is no agent at our disposal more capable of producing growth and vascularity of the uterus then the female sex hormone. When administered in adequate dosage together with small doses of thyroid extract over a long period, functional dysmenorrhea can usually be relieved. In some, we were forced to resort to cervical dilatation for the relief of severe dysmenorrhea." (43)

Campbell and Collip (11) report on the use of emmenin in dysmenorrhea."'Emmenin: Dosage five c. c. doses have been admin-

istered orally one to three times a day before meal. Each
c. c. of the preparation used represented five day rat units.
It was practically oestrin free and also free of the second
principle anterior pituitary like hormone."

"Results: Over two hundred seclected subjects in whom
pelvic diseases had been eliminated as an etiological factor
have been eliminated as an etiological factor and treated.
The following impression has been formed.   In dysmenorrhea
excellent results in over 90 percent of the cases that have
been observed." (11)

In the treatment of menopause cases one must consider
that the endocrine pathogenesis is of a pluriglandular
nature, if that term might be used. Variations of clinical
manifestations occuring in the climacterium are undoubted-
ly an expression of the combined effects produced by
different stages of activity on the part of the glands of
internal secretion. The hypersensitivity of the sympathetic
nervous system as evidences by the vasomotor symptoms, may
reasonably be attributed to the lack of the female sex hormone.
Although the symptoms strongly resemble the syndrome of
hyperthyroidism, there is usually no evidence of an increase
basal exchange. The administration of female sex hormone
in these cases is the most rational and clinically the most
effective method of controlling the vasomotor symptoms. Even
the non-standardized product is termed by Graves (26) a
"near-specific" in the treatment of hot flashes and vaso-
motor disturbances of the menopause. (43)

Glismann (25) believes there is a deficiency of the
Corpus Luteum hormone in the first trimester of pregnancy.

During this period the organism is under excessive strain in adjusting itself to its new economy; and this means in the last analysis, endocrine adjustment. Since the luteal body is the new factor in this adjustment, it is not unreasonable to suppose that is the dominating factor in this condition.

"For sometime it has been our practice to use injections of lipo-lutein for this condition with what we feel are very gratifying results. In our small series of some twenty cases, nausea and vomiting have been practically, completely, controlled within twenty-four hours, in most cases never to return except as an occasional slight nausea in the morning. In a few cases a second or third dose is required at intervals of one to two weeks." (25)

The effcacy of the oral administration of a single large dose of the hormone is followed by its rapid elimination in the urine and other channels before concentration in the uterine mucosa was possible. On the other hand, when a larger quantity is administered in divided doses over a period of twenty-four hours only traces of the hormone can be recovered from the forty-eight hour output of urine. (47)

"In our practice, the prolonged administration of progynon tablets at intervals of four hours has been the most convenient and effective method of increasing the vascularity and growth of the uterus preparatory to treatment directed to the particular gland responsible for the existing condition." (47)

"The administration of the hormon by means of vaginal pessaries is also unsatisfactory because they can usually

be employed only before retiring. Furthermore, the
gelatine mass almost always escapes from the vagina." (47)

CASE HISTORY REPORTS

The following are a few select cases from a series
reported by Hamblen . (28) The patients were selected
on the same basis as those classified by Frank (22) and
Fluhmann (19).

Scheme of Treatment as reported by Hamblen (28) is
as follows: "With the exception of several patients to
whom vaginal pessaries incorporating the active hormone were
supplied, the hormones were administered intramuscularly.
When it was possible, a single hormone was used. In the major-
ity of patients the hormones were administered daily in doses
of 100 R. U. for two weeks with rest intervals of two weeks.
Administration in this manner was repeated until results
justified discontinuation. If it was possible, the hormones
were administered during the intermenstrual phase of the
cycle. Sedatives were not dispensed for the relief of the
subjective symptoms or combined in any way with these
treatments. The only measures adjuvant to the endocrinal
therapy were the correction of dietetic and hygienic errors.
Local Reactions: There were no untoward reactions at the
sites of injections. In a few instances patients receiving
the anterior pituitary luteinizing hormone complained of
slight local pain, twenty-four to forty-eight hours after a
certain injection; investigation usually revealed that the
injection had been made too superficially.

Case Reports (1): Negative and normal physical and

laboratory findings are for the most part omitted in these reports. Patients with symptoms referable to the <u>climacteric</u>: Mrs. B. S., aged forty, para 8-2-5, was admitted to the hospital complaining of an almost constant frontal headache of approximately six months duration. During this time there had been a marked decrease in menstrual flow, associated with extreme nervousness, flashes, emotional instability, and increased severity of the hadaches. Blood pressure at the time of admission was 210/160; urinalysis gave normal findings. Blood urea was 66 mgm. per 100c.c. Physical examination revealed a moderate enlargement of the heart with good regularity and no murmurs; eyes and sinuses were normal. Radiography of the sella turcica revealed a slight hypoplasia. She was given a one-fourth grain hypodermic injection of morphine at the time of admission for the immediate relef of an almost unbearable headache. Subsequent treatment consisted of a diet of moderately restricted protein and the administration of anterior pituitary luteinizing hormone, 200 R. U. daily for ten days. During this time patient was confined to bed in hospital. After two days of this treatment there occurred the first free and normal menstrual cycle the patient had had in six months without the usual symptoms and no headache. At the time of discharge from the hospital, her blood pressure was 150/96 and blood urea 38 mgm per 100 c.c. She is to receive further treatment.

Case Report (2) Patient with symptoms referable to artificial menopause: I. R., age twenty-four, Para 0-0-0, was referred to our dispensary for treatment of symptoms foll-

owing a hysterectomy and bilateral salpingo-oophorectomy
in another hospital in July 1930. The patient complained of
loss of appetite and wight, insommia, failure to regain
strength and nervousness. Physical examination and labora-
tory tests revealed no abnormalities. She was given theelin,
100 R. U. daily for two weeks. She reported at the end of
the treatment a complete relief of subjective symptoms.
She recently returned to the clinic after a month's rest from
treatment and during this interval had had no return of symptoms.

Case Report (3): Patient with secondary amenorrhea.
Mrs. P. B., aged 29, Para 1-1-0, was referred to the gyne-
cological clinic with symptoms of marked menstrual irregul-
arity, nervousness, emotional instability and frequent front-
al headaches. She gave a history of menstrual irregularity
of approximately five years duration. She had experienced
varying periods of amenorrhea, one of two years, and had
not menstruated for two months when she came under our care.
Physical examination revealed an obese white woman with
typical pituitary distribution of fat. The basal metabolic
rate was minus eighteen per cent. The laboratory findings
were normal. The eyes, ears, nose and throat showed no
abnormalities. She was given anterior pituitary luteinizing
hormone in doses of 100 R. U. daily for two weeks. She was
also given thyroid substance indosage of one grain daily. A
scant flow of two days duration resulted during this treatment.
She has subsequently received two series of hormonal inject-
ions with the usual rest interval. Subjective symptoms have
disappeared. There have been no further menstruation. She

has lost ten pounds in weight. She is still under treatment.

Case Report (4): Patient with idiopathic menorrhagia. Mrs. D. B., aged nineteen was admitted to the hospital complaining of marked menstrual irregularity characterized by intervals of amenorrhea followed by periods of menorrhagia. At the time of admission the patient had had a scant flow for two and one-half months. She had experienced menstrual irregularity since her menarche and had had radium therapy twice elsewhere. General physical examination, laboratory and xray studies were negative. The basal metabolic rate was normal. The patient was given a thorough curettage; microscopic study of the scrapings showed evidence of chromic endometritis with slight fibrosis. She was then given the following treatment: rest in bed; theelin in doses of 100 R. U. daily for twelve days; and colcium lactate, 120 grs. daily. After the fourth day of this treatment the bleeding ceased. A communication from this patient six months after discharge from the hospital reports that for the first three months her menstrual periods were quite irregular and scanty, but that her last three menstrual periods have been regular and lasted four to five days." (28)

Sevringhous and Evans report clinical observations of the use of amniotin in a case of menopausal distress: "Mrs. D., aged fifty-eight years, complained of nervousness insomnia, hot flashes eight to ten times daily, and pelvic pain. Physical examination showed nothing unusual. Some menopausal symptoms had been present for eight years. The

use of ten units of amniotin daily gave immediate relief.

On the evening of the second day, six hours after the inject-

ion, there was an unusually severe flash accompanied by

peculiar abdominal symptoms and urinary urgency for six

hours. Reduction of the dose to five units daily was foll-

owed by the return of an occasional flash. Insomnia was

relieved at once. Transfer to the use of the pessaries

containing about eight units each, inserted on alternate

nites, again gave complete relief. Use of the pessaries on

every third night was not quite adequate to prevent hot

flashes. After several weeks relief from hot flashes re-

quired the use of ten unit pessaries daily, and still later

the return to the use of fifteen to thirty units hypoder-

mically. Ten units hypodermically were no more effective

at this time than when given by vaginal route." (56)

Case Report (6): Glimann reports a case of vomiting

in the first trimeister of pregnancy. "Mrs. S. J. S., twen-

ty-five years of age, Para 2. The first pregnancy resulted

in an uncomplicated miscarriage at three months in July 1928.

Her family history was negative. Her personal history shows

a 'nervous-breakdown' at the age of eighteen years. However

she seems to be very weâl stablized and free from the usual

nervous traits. Last eriod the 29th of Sept., 1929. On

November 29th she came to the office complaining of excess-

ive nausea and vomiting, onset two weeks previous, with

severity increasing, so that for the past four or five days

she has been unable to retain any food. She looked sick.

Gave one ampule of lipo-lutein subcutaneously. The next day

40

she returned, her appearence entirely changed and stated
that she felt fine, but that she 'was afraid she was going
to vomit once when she ate some very rich turkey hash'.
Nausea and vomiting has never returned even though she had
a very severe cold early in February." (25)

BIBLIOGRAPHY.

BIBLIOGRAPHY

1. Allen, E. 1927 Menstrual Cycle of the Monkey, Effect
    of Removal of Ovaries and Placental
    Extracts. Contributions of Embryology
    Carnegie Inst. Wash. 19: 1-45.

2. Allen, E. 1928 Precocious Sexual Development from
    Anterior Hypophysis Implants in a Monkey.
    Anat. Rec. 39: 315-323.

3. Allen, E. 1928 Effect of Ovariectomy upon Menstruation
    in Monkeys. Amer. Jour. Physiol. 85:
    471-475.

4. Allen, E. 1928 Reaction of Immature Monkeys (Macacus
    Rheus) to Injections of Ovarian Hormone.
    Jour. Morphol. 46: 479-482.

5. Allen, E. and Doisy, E. A. 1923 An Ovarian Hormone.
    Preliminary Report on Its Localization,
    Extraction and Partial Purification
    and Action in Test Animals. Jour. Amer.
    Med. Assn. 81: 819-822.

6. Allen, E. and Doisy, E. A. 1924 The Induction of a
    Sexually Mature condition in Immature
    Females by Injection of the Ovarian Foll-
    icular Hormone. Amer. Jour. Physiol.
    69: 574-577.

7. Allen, E., J. P. Pratt, L. J. Bland and Q. U. Newell. 1930
    Hormone content of the Human Ovarian
    Tissue. Amer. Jour. Physiol. 92: 127-143.

8. Allen, W. M. 1929 Physiology of the Corpus Luteum.
    Amer. Jour. Physiol. 92: 612-618.

9. Allen, W. M. 1932 Physiology of the Corpus Luteum.
    Amer. Jour. Physiol. 100: 650-663.

10. Bugbee, E. P., A. E. Simond, and H. W. Grimes 1931 1931
    Anterior Pituitary Hormones. Endocrin-
    ology 15: 41-54.

11. Campbell, A. D. and J. B. Collip 1930-31 Notes on the
    Clinical use of Certain Placental Extracts.
    The Brit. Med. Jour. 2: 1081-1083.

12. Corner, G. W. 1927 Relation between Menstruation and Ovul-
    ation in the Monkey. Jour. Amer. Med.
    Assn. 89: 1838-1840.

13. Corner, G. W. 1930 The Hormonal Control of Lactation. L
    Non-effect of Corpus Luteum. II Positive
    Action of Extracts of the Hypophysis.

(42)

Amer. Jour. Physiol. 95: 43-55.

14. Corner, G. W. and W. M. Allen 1929 Physiology of the Corpus Luteum. Amer. Jour. Physiol. 88: 326-339.

15. Evans, H. M. and M. E. Simpson 1928 Antagonism of the Growth and the Sex Hormone of Anterior Hypophysis. Jour. Amer. Med. Assn. 91: 1337-1338.

16. Evans, H. M. and M. E. Simpson 1928-29 Hyperplasia of Mammary apparatus in Precocious Maturity induced by Anterior Hypophyseal Hormones. Proc. Royal Soc. Series B. London 104: 189-190.

17. Evans, H. M. and M. E. Simpson 1929 Hyperplasia of Mammary Apparatus in Precocious Maturity induced by Anterior Hypophyseal Hormones. Proc. Soc. Exper. Biol. and Med. 26: 598.

18. Fevold, H. L., F. L. Hisaw, and R. K. Meyer 1930 The Relaxative Hormone of the Corpus Luteum. Its Purification and Concentration. Jour. Amer Chem. Soc. 52: 3340-3348.

19. Fluhmann, C. F. 1931 Anterior Pituitary Hormones in Blood of Women preliminary Clinical Classification of Results on Non-pregnant Individuals. Endocrinology 15: 177-183.

20. Frank, R. T. 1922 The Ovary and the Endocrinologist. Jour. Amer. Med. Assn. 78: 181-184.

21. Frank, R. T. 1929 The Female Sex Hormone. C. C. Thomas.

22. Frank, R. T. 1931 The Role of the Female Sex Hormone. Jour. Amer. Med. Assn. 97: 1852-1857.

23. Frank, R. T. and M. A. Goldberger 1926 The Female Sex Hormone.IV Its Occurrence in the Circulating and Menstrual Blood of the Human Female. Preliminary Report. Jour. Amer. Med. Assn. 86: 1686-1687.

24. Frank, R. T. and M. A. Goldberger 1928 The Female Sex Hormone. VI Demonstration of the Female Sex Hormone in the Human Blood. Technic: Clinical Applicability. Jour. Amer. Med. Assn. 90: 106-110.

25. Glismann, M. B. 1930 Clinical Observations on the Use of a Lipoidal Extract of Corpus Luteum; Lipo-Lutein. Jour. Okla. Med. Assn. 23: 387-392.

26. Graves, W. P.   1927 Ovarian Therapy. Jour. Amer. Med. Assn. 89: 1308.

27. Graves,W. A.   1931 Female Sex Hormone. W. B. Saunders Co.

28. Hamblen, E. C. 1931 Clinical Experience with Follicular and Hypophyseal Hormones. Endocrinology 15: 184-193.

29. Hartman C. G.   1926 Post Pubertal Oogenesis in the Opossum. Anat. Rec. 32: 276.

30. Hartman C. G.   1930 The Corpus Luteum and the Menstrual Cycle. Amer. Jour. Obst. and Gynec. 19: 511-519.

31. Hartman C. G., W. M. Fivor, and E. M. K. Geiling 1930 The Anterior Lobe and Menstruation. Amer. Jour. Physiol. 95: 662-669.

32. Hisaw, F. L.   1926 Experimental Relaxation of Pubic Ligment of Quinea-Pig. Proc. Exper. Biol. Med. 23: 661-663.

33. Hisaw, F. L.   1929 The Corpus Luteum. Physiol. Zool. 2: 59-79.

34. Hisaw, F. L. and S. L. Leonard, 1930 Relation of the Follicular and Corpus Luteum Hormones in the Production of Progestional Proliferation in Rabbits Uterus. Amer. Jr. Physiol. 92: 574-582.

35. Kurzrok, R.   1932 Follicular Hormone in the Urine as an Index of Therapy in the Menopause. Endocrinology 16: 366-368.

36. Kurzrok, R. and S. Ratner, 1932 The Relation of Amenorrhea Accompanied by Genital Hypoplasia to the Follicular Hormone in the Urine. Amer. Jour. Obst. and Gynec. 23: 689-694.

37. Leonard, S. L., F. L. Hisaw, and Fevold, H. 1932 Further Studies of the Follicular-Corpus Luteum Hormone Relationship in Rabbit. Amer. Jour. Physiol. 100: 111-121.

38. Lipschultz, 1924 Internal Secretions of the Sex Glands. C. C. Thomas.

39. Long, J. A. and H. M. Evans, 1922 The Estrus Cycle in the Rat and its Associated Phenomena. Mem. Univ. Calif. 6: 98.

40. Mack, H. C. 1930 The Aschheim Zondek Reaction for Pregnancy. Surg. Gynec. Obst. 51: 476-488.

41. Maddux, W. P. 1930 Experimental Induced Intermenstrual Bleeding in Ovariectomized Monkeys. Proc. Soc. Exp. Biol. Med. 27: 873-874.

42. Mazer, C. O. and J. Hoffman, 1931 Three Hormone Tests for Early Pregnancy. Jour. Amer. Med. Assn. 96: 19-22.

43. Mazer, C. O. and A. J. Ziserman, 1929 Present Status of Female Sex Hormone Therapy. Med. Jour. and Rec. 135: 35-38.

44. Mc Clendon, J. F., G. Burr and Wildebrush, F. F. 1929 Induction of Menstruation in Women by Use of Ovarian Hormone. Proc. Soc, Exper. Biol and Med. 26: 43-50.

45. Morrell, F. A., H. H. Powers, J. R. Varley and De Frates, J. 1930 The Administration of Amniotin to Monkeys Results of Oral Administration. Endocrinology 14: 174-178.

46. Nelson, W. O. and J. J. Pfiffner, 1930 An Experimental Study of the Factors Concerned in Mammary Growth and in Milk Secretion. Proc. Soc. Exper. Biol. and Med. 28: 1-21.

47. Novak, E. 1931 Bearing of Recent Work on Anterior Pituitary Hormones upo Gynecological Problems With Special Reference to Disorders of Menstruation. Endocrinology 15: 273-280.

48. Novak, E. and R. M. Reynolds, 1932 The Cause of Primary Dysemnorrhea. Jour. Amr. Med. Assn. 99:1466-1471.

49. Papanicolaon, G. N. 1924 Ovagenesis During Sexual Maturity as Eluciadated by Experimental Methods. Proc. Soc. Exper. Biol. and Med. 21: 393-396.

50. Parkes, A. S. 1925 Physiology of Ovarian Hormones. Proc. Royal Soc. Series B. 97: 188-190.

51. Parkes, A. S. 1929 The Internal Secretion of the Ovary. Longmans, Green and Co.

52. Parkes, A. S. and C. W. Bellerby, 1927 Studies on Internal Secretions of the Ovary. The Effect of the Injection of Oestrin during Lactation. Jour. Physiol. 62: 301.

53. Reynolds, E. and D. Macomber, 1924 Fertility and Sterility in Human Marriages. W. B. Saunders Co.

54. Rubin, I. C., 1929 Ovarian Hypofunction, Habitually Delayed and Scanty Menstruation in Relation to Sterility and Lowered Fertility. Amer. Jour. Obst. and Gynec. 18: 603-608.

55. Saiki, S., 1932 Relation of the Hypophysis and Ovary. Amer. Jour. Physiol. 100: 8-20.

56. Sevringhous, E. L. and J. S., Evans, 1931 Clinical Observations on the Use of an Ovarian Hormone--Amniotin. Amer. Jour. of Med. Science. 178: 638-644.

57. Smith, P. E. 1927 Genital System Responses to Daily Pituitary Transplants. Proc, Soc. Exper. Biol. and Med. 24: 337-338.

58. Smith, P. E. 1926 Hastening Development of Female Genital System by Daily Homoplastic Pituitary Transplants. Proc. Soc. Exper. Biol. Med. 24: 131-132.

59. Smith, G., Van S. and Ow. Smith, 1929 Physiology of Corpus Luteum. Amer. Jour. Physiol. 98: 578-584.

60. Smith, G., Van S. and O. W. Smith, 1932 The Excretion of Oestrin by Women. Amer. Jour. Phys. 100: 553-558.

61. Smith, P. E. and E. T. Engle, 1927 Experimental Evidence Regarding the Role of the Anterior Pituitary in the Development and Regulation of the Genital System. Amer. Jour. Anat. 40: 159-217.

62. Stockard, C. N. and G. N. Papanicolaon, 1917 The Existence of a Typical Estrous Cycle in the Guinea-pig, With a Study of its Histological and Physiological Changes. Amer. Jour. and Anat. 22: 225-284.

63. Weichert, C. K. 1928 Production of Placentoma in Normal and Ovariectomized Guinea-pigs and Albino Rats. Exper. Biol. Med. 25: 490-491.

64. Zondek, Bernhard , 1932 The Relation of the Anterior Lobe of the Hypophysis to Genital Function. Amer. Jour. of Obst. and Gynec. 23: