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

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THE SEX HORMONE RELATIONSHIP BETWEEN THE  
PITUITARY AND OVARY WITH CLINICAL  
CLASSIFICATION AND THERAPY.

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OUTLINE

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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 appearances 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 integrity 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 the ovary 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 experimental 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 contained 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 then 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 dominant influence of the anterior lobe upon the genital system, through its influence on the ovaries. It has actually afforded proof of the long suspected and constantly referred to interaction upon each other of the two glands of internal

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 clinical 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

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 metamorphosed 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 capillaries, 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 <sup>the</sup> end of the menstrual cycle. If pregnancy ensues, after a certain time, which varies according to the species and the occurrence of lactation and pregnancy, 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 Fallopian tube down which the ova descends to the uterus and the vagina which connects the uterus with the vulvular 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 thin 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 tortuosity 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. 1

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 fosters, 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 ovary 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 <sup>trans</sup>plantation; 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 used for experimental work.

#### The Ovarian Sex Hormone (Folliculin)

Allen, Pratt, Bland and Newell state from their experimental 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 follicular fluid and by implantation of fresh Corpora Lutea, of follicle walls, and of cortical stroma free from macroscopic 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 growth 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 corpora has been checked by histologic studies. High yields of this hormone have been obtained from recent corpora removed from the thirteenth to seventeenth days of the menstrual cycle. There is a considerable decrease in amount by the twentieth to the twenty-second day. Corpora of the first third of gestation contain considerable amounts. Two full term corpora 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 activity 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 Corpora Lutea, when done during the intermenstrum, usually results in the appearance of menstruation within the next forty-eight hours. These observations substantiate earlier conclusions from experimental work in monkeys that menstruation 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 consideration 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 ablation of the Corpus Luteum that in early pregnancy one to two weeks the ova was absorbed; if later an abortion resulted, it indicated definitely 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 progesterational 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"(Gorner), 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 oestrous 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 overpower the effects of a rabbit unit of corporin capable of producing a histological picture equally as good in a castrate animal.

Corporin 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 corporin, 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 <sup>that</sup> 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 considerable 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, Fiver, 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 experiments, 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 or 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 performed 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 it 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:II(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 follicle-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, amniotic fluid, blood of pregnant animals, but the richest 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 few 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

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 milk. 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 Corpora 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. 1.

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 pituitaries 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 bleeding 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 1

The question however arises as to what is menstruation. Is this bleeding a result of true menstruation or is it a true <sup>uterine</sup> ~~urine~~ hemorrhage 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 Corpus Luteum in the site of the ruptured follicle. This transitory gland <sup>Corpus luteum</sup> 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.

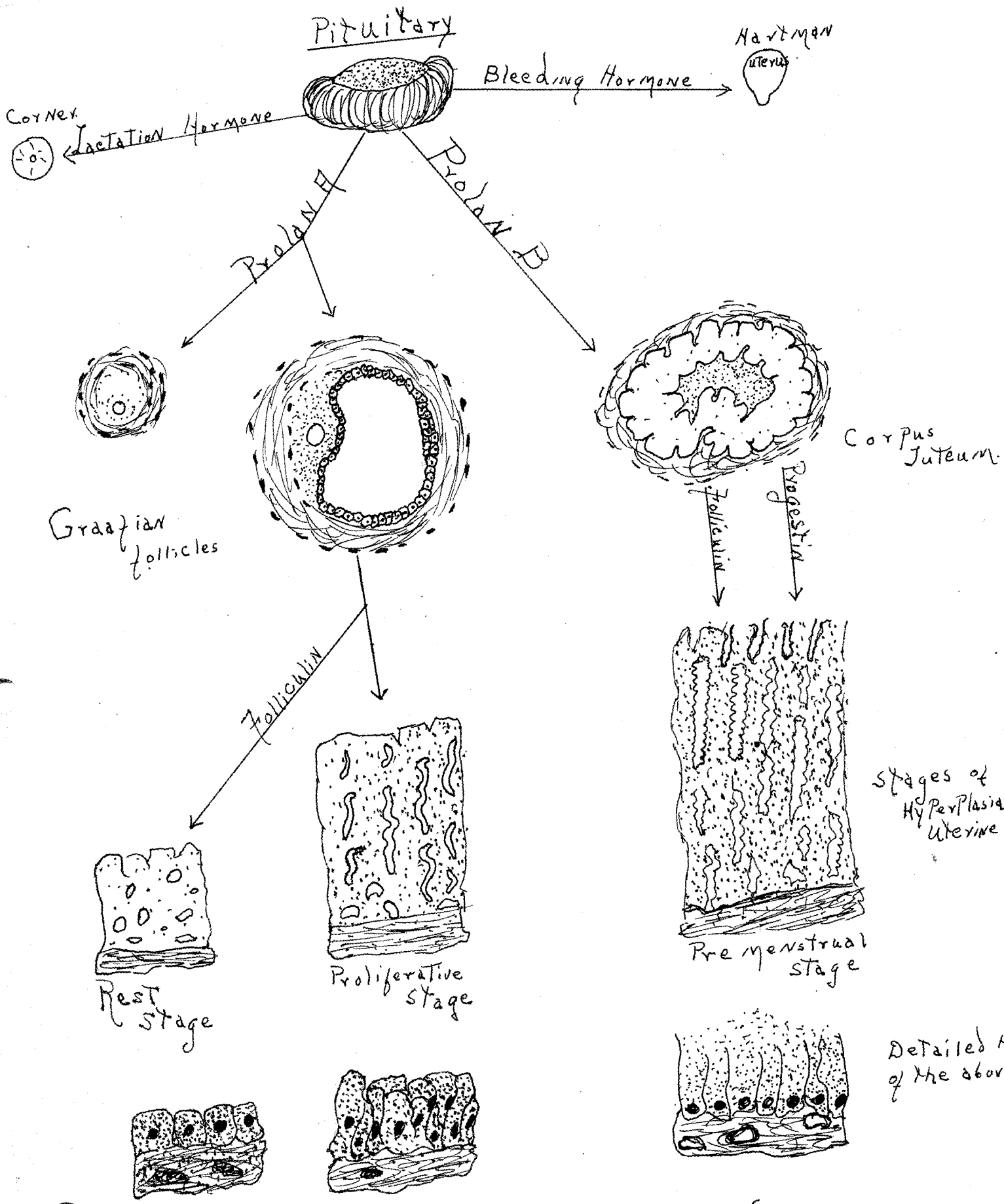


Diagram of Action of the sex Hormones. Figure I



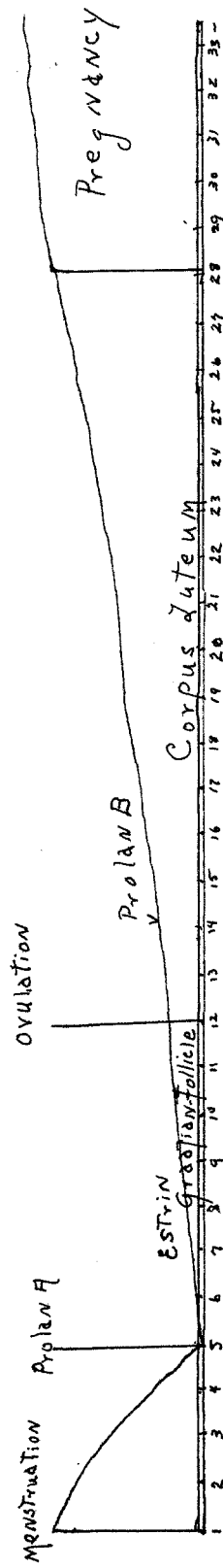


Diagram showing Relation in Time of uterus and Ovary during sex cycle

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 physiology 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 lipid 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 therefore 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 lipid 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 therapy 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 is limited. More and more however, are 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 presence of the 'luteinization' factor (APH-B). The present report is based on the results of the test performed 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 Froehlich'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 percentage 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 in 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

described by Allen and Doisy (5). In normal women a low hormone blood level exists until about the seventh day before 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 intermenstrual, 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 characterized 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 lengthened; (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 accumulation of the hormone in the blood which however rarely reaches 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 excess of

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 indistinguishable from the threshold blood cycle patients. The prognosis is poor in these patients.

The third classification of Fluhmann (19) is the afunctional condition. The patients of this group are characterized 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 in 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 ovarian 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 responded 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 frequent and profuse menses, approximately one-third of the women of the menopausal age with menstrual irregularities (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 blood 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 progesterin an inhibitor of this motility. Preparations of the urine of pregnant women, presumably because of their prolactin content likewise are strongly inhibitory.

"The inhibitory influence of progesterin 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 imbalance between theelin and progesterin, 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

amenorrhoea. 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."(50)

"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 here 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 amenorrhoeic 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 appearance of total absence 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

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 efficacy 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 woman 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 <sup>not</sup> too far advanced. Batesweiler<sup>reports</sup> (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 efficacy of female sex hormone in treatment of menstrual disorders.

"Follicle cytolysis 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 cytolysis, either by injections of a potent pro-

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

Occasionally, follicle cytolysis is consequent to an antecedent pelvic infection with resultant thickening of the ovarian tunic which mechanically inhibits ovulation and the formation of a Corpus Luteum. In these cases prolonged diathermy treatment often effects a permanent cure. Occasionally, 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 luteinizing 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 placenta. In oligomenorrhea, the majority of the subjects of this type of secondary amenorrhea appear to respond very satisfactorily to treatment, whereas, subjects of primary amenorrhea and of secondary amenorrhea for some years duration 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 exists 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 or 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 periods 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 disturbance. 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 than 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 selected 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 occurring in the climacterium are undoubtedly 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 evidenced 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 vasomotor 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 efficacy 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 hormone 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 majority 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 climacteric: 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 headaches. 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 relief 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 weight, insomnia, failure to regain strength and nervousness. Physical examination and laboratory 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 gynecological clinic with symptoms of marked menstrual irregularity, nervousness, emotional instability and frequent frontal 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 in dosage of one grain daily. A scant flow of two days duration resulted during this treatment. She has subsequently received two series of hormonal injections 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 chronic 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 injection, 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 followed 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 nights, 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 required the use of ten unit pessaries daily, and still later the return to the use of fifteen to thirty units hypodermically. Ten units hypodermically were no more effective at this time than when given by vaginal route." (56)

Case Report (6): Glikmann reports a case of vomiting in the first trimester of pregnancy. "Mrs. S. J. S., twenty-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 well stabilized and free from the usual nervous traits. Last period the 29th of Sept., 1929. On November 29th she came to the office complaining of excessive 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

she returned, her appearance 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)



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