OVULATION, MENSTRUATION AND THE HORMONES *

GEORGE JOYCE HALL, M.D.

SACRAMENTO, CALIF.

IN considering the effect of the hormones on the uterus and ovaries, it seems advisable to summarize a few facts regarding the synchronous ovarian and uterine cycles and menstrual blood before considering the details of clinical results.

The graafian follicle begins to mature following menstruation and at maturity the follicle ruptures, extruding the ovum into the peritoneal cavity. This is apt to occur at about the fourteenth day following the onset of menstruation. The developing follicle and its successor, the corpus luteum, produce the female sex homone which is responsible for the rebuilding of the dismantled endometrium. The corpus luteum also produces simultaneously the nidatory hormone, progestin. The uterus is thus prepared for the reception of a fertilized ovum. The span of life of the unfertilized ovum is not definitely known. Allen and Pratt have shown that it is probably no longer than six days. If the ovum is not fertilized it probably dies on the twenty-eighth day and the corpus luteum degenerates and gradual involution takes place over the following four weeks.

If the ovum is fertilized, then the corpus luteum grows larger instead of degenerating, and the effect of progestin on the endometrium persists; the endometrium becomes the decidua and retains in a more definite way its premenstrual secretory function and appearance.

During the follicle growth characteristic changes occur in the endometrium and the typical secretory phase appears as a result of the corpus luteum hormone, progestin, during the last two weeks of the cycle.

It is authoritatively claimed that during the thirty to thirty-five years of sexual life of the average woman, only 360 to 420 follicles mature completely and rupture.

ATRESIA OF THE FOLLICLE AND RETENTION CYSTS

Some follicles develop to a degree and perish by the process of atresia; others develop and persist. Consequently the law of averages would show that 299 out of 300 primordial cells terminate in atretic bodies.

NORMAL ENDOMETRIAL CYCLE

The uterine mucosa has normally such definite stages of growth, development and disintegration during the twenty-eight day cycle that the clinician and pathologist must be thoroughly familiar with the microscopical findings. Six days after menstruation the glandular cells are high columnar with the stromal cells very close together. Thirteen days after menses the epithelial cells are still high columnar and show pseudo-stratification with an edematous stroma and cells far apart. About twenty-two days after menses the epithelial cells become low columnar cuboidal in type and the stroma cells are larger and closer together. Twenty-nine days after menstruation the epithelial cells show degeneration, and marked edema of stroma is evident.

MORPHOLOGY OF MENSTRUAL BLOOD

The morphology of the menstrual blood has a diagnostic value clinically, and in about 90 per cent of the cases true menstrual discharge can be identified. Therefore it becomes of value in determining the difference between normal uterine bleeding, abnormal uterine bleeding and bleeding from other vaginal sources.

Uterine desquamation seems to occur before the first day of menstrual bleeding, is greatest on the second day, and almost disappears on the fourth. Uterine stromal

* Read before the Sacramento Society for Medical Improvement, May 17, 1932.

cells appear in greater percentages on the second and third days and also are only rarely found on the fourth. Vaginal spindles seem to be present in almost all cases throughout, though the vaginal plaques become less each day. When uterine elements are found in the blood it is evidently of menstrual origin.

Geist of New York presents the following table:

PERCENTAGE VARIATION OF UTERINE VAGINAL ELEMENTS ON SUCCESSIVE MENSTRUAL DAYS

	1st Day Per Cent	2nd Day Per Cent	3rd Day Per Cent	4th Day Per Cent
Uterine epithelium	50	74	25	3
Uterine stroma	75	90	91	4
Vaginal spindles	95	95	82	100
Vaginal plaques	90	72	55	25

Most investigators, according to Graves, have come to the conclusion that "menstruation is not the homologue of proestrum, preparatory to ovulation, but on the contrary is a late result of ovulation and represents a disintegration of a structure that has been built up, but not required, for the reception of the fertilized egg," although Aschner believes that the flow represents an excretion following metabolic changes. Whether the uterine bleeding is a positive or negative factor, it is due to an active substance originating outside of the ovaries now proved to be in the anterior pituitary.

Corner's experiments with macacus rhesus monkeys have proved that menstruation can take place without ovulation, and it is considered by Graves and others including Allen that atresia can at times supply sufficient follicular hormone to bring on a premenstrual condition which is followed by menstrual flow.

Novak believes the follicle to be responsible for the early slow hypertrophic changes in the endometrium up to the beginning of the secretory phase; and the premenstrual phase is associated with the development and maturation of the corpus luteum. Corner has definitely established the existence of a special corpus luteum hormone. Zondek and Ascheim designate the pituitary as the "regulator of menstrual rhythm." There are some who now consider the anterior pituitary to have five different hormones. Production of menstruation requires then the hormones of the follicle, corpus luteum and anterior pituitary.

OVULATION

Meyer, Ruge, Schroeder and Corner have all come to the conclusion that rupture of the graafian follicle occurs about fourteen to sixteen days after the onset of menstruation. And because the development of the corpus luteum is followed by changes in the endometrium there is doubtless a hormonal factor causing these premenstrual changes. The time relationship between ovulation and menstruation is rapidly becoming better understood but the true relationship between these two and conception is still a very difficult problem.

ENDOMETRIAL HYPERPLASIA

In the endometrial hyperplasias the actively growing gland cells are heaped together in a pseudo-stratified manner showing numerous mitotic figures and the stromal cells are small but closer together than those thirteen or fourteen days after menses in a normal patient.

In a case of endometrial hyperplasia there is such a predominance of these retention cysts that the follicular hormone effect causes a persistent growth of the endometrium with the irregular hypertrophy so often seen by the pathologist, or macroscopically by the surgeon and in the hysterogram by the roentgenologist. In the absence of the lutein hormone, progestin, the secretory phase of the endometrium does not occur. There is some discussion and difference of opinion regarding the etiology of the persistent bleeding, and the histopathological condition of the endometrium. The dysplasia of the

endometrium results in localized thrombosis and necrosis with consequent hemorrhage. The persistent ovarian follicle at times, instead of becoming atretic, develops into a cystic condition, and whether the endometrial hyperplasia is the effect of this cystic fluid hormone or the anterior pituitary, or both, on the endometrium is being rapidly determined by a number of investigators.

Cystic fluid removed from an ovary with no corpus luteum and injected into a female laboratory animal is followed by the same uterine changes of endometrial hyperplasia in the animal as were exhibited in the patient. These patients are evidently suffering from a lack of corpus luteum hormone. This one fact is surely the keynote in the clinical treatment of such cases.

ISOLATION OF OVARIAN HORMONES

The effort to isolate the ovarian hormones has been persistently going on for a number of years, mainly because ovarian gland extract therapy has been unsatisfactory. The isolation of the follicular hormone in a crystalline form, a colorless white crystal, was accomplished by Allen and Doisy in 1928, and a few months later it was also isolated by Butenandt of Germany. This is a triple unsaturated oxyketone with the formula $C_{18}H_{22}O_2$. Theelol has the formula $C_{18}H_{24}O_3$ and is about one-fifth as potent as that of $C_{18}H_{22}O_2$.

This has stimulated an active interest again in clinical therapy relative to the disorders of menstruation. But, because many were still unsatisfied, a continued research has developed many other factors including the role of the anterior pituitary.

Follicular hormone is found in very large quantities in the placenta, the blood and urine of pregnant woman. It is from this latter source that most of the products now available are obtained. It takes in the neighborhood of 1000 gal. of urine to obtain 1 gm. of follicular hormone, which is about 8,000,000 mouse units.

The fact that the corpus luteum develops a hormone has been well established, the final scientific proofs being presented by Corner in 1929. The dual secretion of the ovary also has now been well established. The hormone of the follicle and that of the corpus luteum are positively antagonistic, as has been demonstrated in many ways experimentally and is easily proved clinically.

CLINICAL EXPERIENCE

The laboratory research must be followed by an effort clinically to evaluate the practical use of the various hormone preparations in an effort to relieve the distress and discomfort of those whose endocrine systems do not seem to be properly geared, or whose gears are not properly meshing, or, as most investigators prefer to consider it, whose body chemistry is disturbed by an unbalanced percentage of the various hormones. During the past two years our work has been with the use of the follicular hormone and the luteinizing anterior pituitary; we have treated our cases with these products exclusively, not in a spirit of over-enthusiasm but in order to determine the effect statistically of each preparation.

Because so many of the symptoms of menstrual disorders are of the subjective character we have found much more satisfaction in drawing conclusions in the treatment of private patients than of the clinic types who are financially and socially handicapped.

We have worked with cases of amenorrhea, menorrhagia, metrorrhagia, dysmenorrhea, oligomenorrhea, and the conditions attendant to the menopause.

Amenorrhea. Primary amenorrhea cases have exhibited an improvement in general but the establishment of regular menstruation has not been obtained. At times one becomes enthusiastic only to find that in another month or two black disappointment is encountered. The definite tonic effect on the individual with the administration of follicular hormone is nevertheless obvious in every case. In secondary amenorrhea our results were

quite gratifying, and in the primary irregularities administration of the follicular hormone has been universally satisfactory.

There are, in my opinion, patients with relative deficiency of follicular hormone due to a loss of so much of the normal amount formed in the ovaries due to "kidney permeability" that they are apt to develop a secondary amenorrhea. Massive doses of follicular hormone are required to bring about the desired results in such cases, but the response is much more rapid than in those whose ovarian function is impaired. Patients who have had varying degrees of partial castration are very grateful when given the proper individual doses of follicular hormone with the required regularity.

Functional menorrhagia and metrorrhagia of early years of menstrual life show clinically an endometrial hyperplasia and, in some cases, excess of female sex hormone in blood and urine. These cases, in which there is a relative or real excess of follicular hormone and very little if any corpus luteum hormone, progestin, obviously are not proper cases in which to administer follicular sex hormone. But the luteinizing pre-pituitary hormone does give excellent results in these young girls just as well as in the hyperplasias of older women nearing the menopause. Apparently in these hyperplasias in which bleeding is more or less slow this "prepituitary B" will prevent the necessity of roentgen ray or radium therapy or surgery. But in the severe hemorrhages it does not seem to have sufficiently rapid effect.

G. V. S. Smith and O. W. Smith have delved into the functions of progestin, the hormone of the corpus luteum, in the menstrual cycle and in pregnancy. Among other findings they observed that it also has an inhibitory action on the function of follicle hormone, the continued and unantagonized action of which is responsible for functional uterine bleeding. As potent products of progestin are not available for therapeutic use, the prepituitary B hormone obtained from pregnancy urine is employed to evoke luteinization and consequent production of progestin to control the harmful effect of the follicular hormone on the endometrium.

Alvarez classifies a certain group of people as "constitutional inadequates." These naturally have a poor background, a poor foundation. There are those who do not develop genitally to maturity and others who are just on the threshold and manifest their "inadequacy" by only two or three menstrual pads monthly. Some have a few of the angioneurotic symptoms frequently found in menopausal women. Most clinicians report a comparative failure in these patients by the use of follicular hormone. In our experience both of these groups have shown most pleasing improvement under treatment with this product. In fact these cases seem to offer the most gratifying results and it seems to me to be really constructive therapy. Just how long they may be "carried over" is problematical. But one naturally hopes for a satisfactory "prolan A" preparation that will stimulate the ovaries of these patients to renewed function.

The series of tests recently described by R. T. Frank and now easily performed in small laboratories include:

1. Female sex hormone test of the blood.
2. Female sex hormone test of the urine.
3. Prepituitary maturity factor test of the blood.
4. Prepituitary maturity factor test of the urine.

The prepituitary tests are primarily simplified methods of the work done originally by Aschheim and Zondek. Just as soon as these become laboratory methods the clinician will have less of the "trial and error" methods to follow in his administration of the ovarian and prepituitary hormones. At such a time there will be fewer "negative" results clinically and a greater percentage of satisfactory reports in each series.

Dysmenorrhea. It has been reported that in many cases of dysmenorrhea the administration of the follicular hormone

seemed helpful, and in a small percentage of cases apparently curative. Rather surprising results are obtained in the severe cramps of young girls, or at least in the majority of them. The belief that many of these are due to a lack of sufficient vascularization of the uterus naturally has prompted us to use various methods of causing pelvic congestion. We were satisfied many months ago that the follicle hormone not only does that but increases the congestion of all of the female genital organs, so we felt thoroughly justified in the use of that hormone in such patients, and now believe sincerely in its efficiency in such types of dysmenorrhea. In some of my cases, what has seemed an overdose apparently increased the cramps. It would require a full discussion of dysmenorrhea to determine logically the place of the hormones in this distressing phase of the early years of menstruation in some women. Most of these patients are permanently cured of dysmenorrhea by pregnancy and normal delivery. The hormonal changes during pregnancy cannot be determined by a clinician. Such work must be continued by Fluhman, Novak, Corner, Zondek and hundreds of others who are doing the real research work now.

The physician does not enjoy the empirical use of any form of therapy. It therefore becomes necessary for the clinician to learn the whys and wherefores. As far as I know there are many questions of prime importance still unanswered. The follicular hormone is commercially obtained from the urine of pregnant women. It is obvious then that there is not only a larger amount of follicular hormone developed in the body during pregnancy, but there is a very large amount excreted, not needed, possibly wasted as far as that individual is concerned. Is it possible that this is all formed in the ovaries, or is the placenta not only a place where the follicular hormone is stored in large quantities but also the source of the hormone? Doubtless Collip can answer this question after his experience with emmenin.

Menopause. During the menopause, when there is a gradual reduction of ovarian function, theoretically one might expect relief of many of the subjective symptoms complained of by the judicious administration of both ovarian hormones. Actually in practice almost all of the commercial preparations seem to have some beneficial action. Obviously there would be no justification for the administration of the prepituitary hormone in the frank menopause. Naturally the effort of the physician is to relieve the angioneurotic symptoms during these distressing months. Replacement therapy with the follicular hormone administered in various ways to a large number of patients justifies our belief in the efficacy of the product. They seem better generally and claim to be greatly improved. The follicular sex hormone preparation has apparently made them feel better than others.

Uterine Bleeding. The anterior pituitary lobe undergoes marked hypertrophy during gestation, and Novak places this as the cause of the acromegaloid changes seen at times in late pregnancies.

According to Schroeder the cause of bleeding in the hyperplasias is due to small areas of necrosis, thrombosis or necrobiosis. But it is generally considered to be some change in the permeability of the blood vessels. The endometrial lesion itself cannot account for it because the same histological picture may be found with amenorrhea.

HORMONAL THERAPY: DOSAGE AND MODE OF ADMINISTRATION

In the administration of the follicular hormone one should know the amounts needed, the minimum and maximum doses and how to offset the effects of incorrect amounts in the individual. How much is absorbed when it is given intramuscularly and orally? What percentage, if any, is changed chemically? Is there a saturation point varying in different individuals dependent upon their physiological needs? Is there a deleterious effect on the indi-

vidual by what might be termed an overdose? Why is one patient given complete relief with 150 R.U. intramuscularly while another whose subjective symptoms seem parallel is not relieved by a dose short of 900 to 1000 R.U. intramuscularly, if there is no need of individualizing treatment? What happens to the hormone, not excreted, after it leaves the blood stream? Is it stored up for a certain period of time, and if so, where? How soon is the effect of an individual dose noted by the patient and how long after the last of a series does the effect seem to be noted? It may be stated here that some of the most frequently subjective changes due to the administration of follicular sex hormone are relaxation from nervousness, disappearance of phobias, return of mental calm, relief of various headaches and cerebellar pressures, increase in ambition and enthusiasm and capacity for physical work or exercise. Fatigue is relieved and the face and eyes become brighter. A general increase in libido is noted by the majority of patients. We are arriving at the conclusion that follicular hormone has not only a replacement value but that it is a definite stimulant as well. And this may account for the fact that some report a sensation of well-being for about ten days after the last dose of a series followed by a gradual return of their predominating symptoms. The most frequent statement of results made by those who have been languid (or nervous) semi-invalids for months, is that they felt so good that they "got up and cleaned house."

Dosage of (follicular sex hormone progynon) ranges from 25 to 300 R.U. by hypodermic each month up to 600 R.U. by mouth daily for three weeks. I now have several patients taking 600 R.U. orally each day for three weeks out of every four. This gives them in the neighborhood of 12,000 R.U. monthly. Many have stated and some still believe that 50 or 100 R.U. per dose is insufficient to give clinical results, but it is the clinicians who will determine that. The majority of our cases are doing well on a total of 150 to 300 R.U. intramuscularly or from 300 to 3000 R.U. orally each month.

During the last six months we have used only two products in our clinical experiments, namely the follicular hormone (in the form of ampoules, or tablets of 30, 200 and 600 R.U. each) and the luteinizing hormone of the anterior pituitary as used by Novak. The dose of the early product of luteinizing prepituitary hormone seemed to be 50 to 100 R.U. daily. In our experience 50 R.U. were all that could be given in daily doses intramuscularly without causing a general reaction, but the later product permits the safe use of 200 R.U. daily.

For many years I have employed commercial preparations of ovarian tissue with uncertain results, but during the past two years the follicular hormone, which I have mentioned, has given me the best results clinically. Of course, the action of the luteinizing prepituitary hormone is remarkable in the type of cases reported by Novak. Naturally, I am extremely grateful to Drs. Stragnell and Sharpe for the generous quantities of material they have furnished me for clinical use.

During the last two years we have treated over 200 patients, mostly falling into the menopausal and secondary amenorrhea groups. Some of the most interesting cases are the so-called "neurotics." In almost every instance one can obtain a history of a greatly reduced menstrual flow. The results of the hormone therapy in these cases are only short of miraculous. You may perhaps suspect that the effect is purely psychological, but I am sincere in my claim that a large number of women of twenty-five to thirty-five become neurotic or hysterical because their ovaries are not properly functioning. So that a monthly replacement of ovarian hormones will correct their troubles until such time as the prolan A and prolan B are both available commercially. These younger women, I believe, can have their ovarian system stimulated to function properly. But those of forty-five to fifty-eight years old are

in need only of the required monthly replacement doses to permit them to enter gracefully the period past the so-called "change of life." Obviously the pre-pituitary hormones are not indicated in the latter.

Scanty menses in young women and at the climacteric are accompanied by angioneurotic dyscrasias, obesity, susceptibility to infections, etc., and one-third of hypomenorrheic patients show arthritic, rheumatic or neuralgic conditions. Pains in this latter group are worse before and better after menstruation. Relief is obtained by treatment with ovarian hormone.

Under the care of Molle, 2½ to 3 pound premature infants improved in development by the daily use of follicular hormone.

So-called "menstrual migraine" in some cases is reduced in severity by the administration of corpus luteum injections daily for ten days pre-menstrual. These patients include those who have an actual reduction of corpus luteum hormone or a relative increase of follicular hormone.

Basal headaches occurring during the menopause are promptly relieved by correct doses of follicular sex hormone.

Theoretically, the luteinizing pre-pituitary hormone should be of value in threatened abortion, and helpful in preventing premature delivery as large doses of follicular hormone are considered abortifacient.

In the use of these newer chemicals the over-enthusiastic clinician is apt to make claims that the test of time and a larger series of cases prove to have been unwarranted. But over a period of two years we have watched a sufficiently large group to be able to justify our claims that the follicular hormone in the form of progynon, and Novak's luteinizing pre-pituitary are very helpful agents in the treatment of many menstrual disturbances.

REFERENCES OF DR. THOMPSON*

5. Clery, A. B. Fracture of the scaphoid with dorsal dislocation of the distal fragment of that bone and of the distal carpal row. *Irish J. M. Sc.*, 8: 372–373, 1926.
6. Cotton, F. J. Wrist fractures: disability following restorative operations. *Trans. Am. Surg. Assn.*, 40: 289, 1922.
7. Destot, E. Fractures du semilunaire. *Lyon chir.*, 19: 178–186, 1922.
8. Fisher, A. G. T. Injuries and diseases of the articulations. *Lancet*, 2: 541, 1923.
9. Grace, R. V. Fracture of carpal scaphoid. *Ann. Surg.*, 89: 752, 1929.
10. Ito, L. K. The nutrition of articular cartilage and its method of repair. *Brit. J. Surg.*, 12: 31–42, 1924–25.
11. Johnson, R. W. A study of the healing processes in injuries to the carpal scaphoid. *J. Bone & Joint Surg.*, 25: 482–497, 1927.
12. Manon, M. Les fractures du trapeze dans les traumatisme du poignet. *Rev. d'Orth.* s. 3, 2: 127–140, 1924.
13. Menard, L. Fractures ancienne partiellement consolidée du scaphoide du poignet gauche. *Paris méd.*, 1: 115, 1927.
14. Nathan, P. W. The pathology and treatment of fractures of the spongy bones. *Am. J. M. Sc.*, 161: 585–595, 1921.
15. Peltesohn, S. Uber Bruche des Os Triquetrum nebst Bemerkungen zur Unfallbegutachtung. *Med. Klin.*, 28: 78–80, 1932.
16. Phillips, K. T. A fracture of the carpal cuneiform. *New England J. M.*, 204: 322, 1931.
17. Piney, A. The anatomy of the bone marrow. *Brit. M. J.*, 2: 792–795, 1922.
18. Speed, K. *a.* The fate of the fractured carpal navicular. *Ann. Surg.*, 80: 532–535, 1924.
    b. Fractures. *Journal-Lancet*, 47: 265–269, 1927.
    c. Fractures of carpal navicular. *J. Bone & Joint Surg.*, 7: 682–695, 1925.
    d. The pathology of carpal bone fractures. *Trans. West. Surg. Assn.*, 31: 61, 1921–1922.
    e. Traumatic Injuries of the Carpus, Including Colles' Fracture. N. Y., Appleton, 1925.
19. Todd, T. W. The role of cancellous tissue in healing bones. *Ann. Surg.*, 72: 452–465, 1920.

*Continued from p. 226.