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Introduction

So active has been the study of the female reproductive cycle in recent years, and so extensive has the literature become, that the medical student of today can scarcely appreciate that almost up to the beginning of this century very little was known as to the physiology of the sex cycle. It is no exaggeration to say that more has been learned in regard to this subject within the past 35 years than had been learned in as many centuries preceding. Perhaps the beginning of the modern viewpoint dates back to the work of Krauer (29) who in 1899 developed the hormone theory of menstruation.

The indispensability of the ovaries to the sex cycle was demonstrated easily enough by the abolition of the cycle following castration. The persistence or reestablishment of the cycle following transplantation, or implantation of the ovaries in castrated animals further confirmed this fact and at the same time proved that the influence of the ovaries was not exerted thru their nerve connections, as some believed, but that it was dependent upon some substance which was given off into the blood stream.
Despite all of the brilliant and exhaustive work which has already been done, the final chapter in our knowledge of the activity of the ovarian constituents is yet to be written. This is especially true of its relation to the other glands of internal secretion.

The purpose of this paper will be to discuss and review in a general way the ovarian constituents, exclusive of its external product—the ovum, their activity, relation to other parts of the body, and, association with such things as metabolism, menstruation etc. In as much as various terms have been applied to the product of the follicle, such substance will be referred to in this paper as folliculin. Also, following Willard M. Allen's (6) suggestion the name progestin will be used to designate the specific hormone of the corpus luteum. In a like manner, Fluhmann (19) suggests that the term Prolan A be applied to the anterior pituitary hormone which stimulates Graffian follicles and Prolan B to the hormone which stimulates the corpus luteum.
The ovary is a most intricate organ in regard to its functions. On the one hand the genital gland provides ova for reproduction and on the other hand, by means of its internal secretions, this organ insures that the general metabolism shall be adjusted to the reproductory requirements. This is not only directly but indirectly thru the other organs of internal secretion. The ovary is supposed, too, to influence the sex characteristics. Its importance was stressed by W. Blair Bell (9) in an address delivered to the Reading Pathological Society in which he remarked, "Sex glands generate the most potent forces in life--they not only fill the cradle, but also guides the hand that rocks it and rules the world".

Bell considers that there are two aspects of the relation of the female gonads to the sex-characters, namely, the influence of the ovary on the sex-characters, and, the importance of the ovary in determining the sex of an individual. Concerning the first aspect of the subject, it has been commonly held that the gonads constitute the primary sex characteristic, and the secretions arising from the gonad in question--male or female as the case may be, governs the secondary characteristics.
It is well known that each person is partly masculine and partly feminine—that in each is to be found especially in regard to the genital ducts, relics of the opposite sex, and that early in foetal life it is not possible to identify the trend of sex development. At about the end of the fifth week of foetal life it is possible to tell if the gonad is to be an ovary or a testis. The development of the Gartnerian and Mullarian ducts often giving the first indication of sex determination. By the time the nature of the gonad is declared, the fate of the ducts is sealed. If the gonads be male in type the Mullerian ducts degenerate while Gartners ducts develop and visa versa. Bell(9) therefore contends that normally the sex development of the ducts is not primarily dependent on the nature of the gonad, but rather, the character of the sex pervades all of the tissues of the foetus including the sex gland itself. That is, the primary sex characteristic is the predominance of maleness or femaleness in the fertilized ovum. He also points out that this predominating potentiallity also effects the supra-renal, thyroid and pituitary glands. This would favor
the belief that all the secreting glands control the
sex-functions, sex-characteristics and sex-metabolism
from the beginning and all owe their directive tend-
cencies to the predominating sex potentiallity in the
zygote.

We are now in possession of so much indisputable
evidence which demonstrates that the reproductive
functions, apart from the production of ova are as
much dependent for their integrity on the organs of
internal secretion other than the gonads as is the
very structure of the genitalis themselves. Likewise
the secondary sex characteristics are more dependent
upon the pituitary, thyroid and suprarenal than they
are on the gonads themselves. It is apparent that all
of the organs of internal secretion appear to hold the
balance of maleness or femaleness as laid down in the
fertilized ovum. In proof of this statement attention
may be directed to the large number of cases wherein
the secondary sex characteristics of one sex have been
changed to those of the opposite sex, even in adult
life.) For example, we may have hypopituitarism orig-
inating before adolescence or originating after. If
before, there results adiposity with skeletal and
sexual infantilism in childhood. If after, there results
adiposity with sexual infantilism of the reversive type. In addition, the ovary does not function until puberty while the other glands are ever active(13). Thus the gonad is not solely responsible for the secondary sex characteristics.

The genital functions of the ovary are concerned in reproduction directly and indirectly. By directly is meant the regulation of the genital cycle with the provision of ova and their implantation in the uterus. By indirectly is meant the relation of the genital function to the general metabolism and the regulators thereof.

The cyclical regularity of genital activity and reproductive capacity is a remarkable phenomenon. Before considering the normal function it is important to remember that the uterus and mammary gland inevitably atrophy if the ovaries are removed, and changes occur in the other ductless glands with consequent alterations in the general metabolism(8). Also that ovarian tissues tend slowly to undergo premature atrophy after the removal of a previously functional uterus and this is in all probability not due to traumatic causes(9).
It is only in recent years that definite evidence of an ovarian cycle has been obtained in connection with the important phenomenon of ovulation. Loeb has shown that the corpus luteum which is formed after the rupture of the follicle and liberation of the ovum, prevents during its maturity further ovulation, and, that removal of an active corpus luteum accelerates subsequent ripening and rupture of another Graffian follicle. It appears probable therefore that the ovary is self regulating. Yet there are certain facts which array themselves against such a supposition, although it cannot be denied that the ovarian secretions are essential to the well being of genital function. Other organs of internal secretion are equally concerned. There is no more striking demonstration of this than the rapid atrophy of the genital glands that follows certain destructive lesions in the pituitary.

The menstrual cycle is concerned in keeping the uterus and general metabolism ready for the great opportunity of supporting a foetus. Nutrition is demanded and first conveyed to the foetus by way of the blood stream and later through the medium of the mother's milk. It comes about therefore that the mammae must be kept potentially functional, and, indeed,
at menstruation there is invariably to be recognized by the women some increased degree of sensitiveness in the glands. Further association between the ovary and the mammae is shown by the development of the breasts at puberty when the ovary becomes active, and the atrophy of the mammae when the ovary becomes inactive or is removed.

The changes which follow oophorectomy in adults are well known. Alterations are to be seen in most of the other organs of internal secretion and of course this is to be expected. In the presence of normal genital function all of the ductless glands are engaged in controlling the general metabolism to conform to the reproductive needs—which no longer exist after the removal of the ovaries. The natural menopause in women is usually a gradual process and no doubt so in order that the rest of the body may be adjusted to the metabolic changes. Hence, sudden cessation of ovarian function may lead to very obvious and distressing symptoms. In women, however, in whom the nervous system and mind is highly sensitive, considerable alterations of the physical and mental processes may be manifest and the larger the balance of femininity a woman possesses
the greater appears to be the upheaval caused by the sudden obliteration of the ovarian function. If now the point of view is reversed it is evident that the ovaries are important to the normal women--apart from the benefits to her of gestation--owing to the place they occupy in regard to metabolism and the continued normality of the other organs of internal secretion on which her own physical and mental welfare depends. The thyroid gland appears liable to undergo pathological changes of a pronounced character after disappearance of ovarian secretion (9). The sympathetic control too, always somewhat unstable in women, becomes more variable owing to the changes which take place in the calcium metabolism.

At this time it seems advisable to review the steps by which our present knowledge of the specific hormones of the ovary were developed and also, their relation to the hypophysis. The beginning of the study dates back to the work of Knauer, Loeb, Fraenkel and others, wherein the indispensability of the ovaries to the sex cycle was demonstrated. The extremely important studies of Fraenkel pointed to the importance, in rabbits at least, of the corpus luteum in the pro-
duction of the cycle and in implantation of the ovum in the uterine mucosa. Perhaps the next advance of major importance came about through the work of Stock-ard and Papaniculaou(13) in which they discovered the vaginal smear method for the chronological study of the cycle in lower animals. The anatomists and physiologists were especially stimulated at that time and since then have contributed the bulk of the newer knowledge on the subject.

The next salient advance was the demonstration, by Frank, and, Allen and Doisy(3) of the physiological activity of the ovarian follicle hormone and of its dominating importance in the female sex cycle, of the lower animals at least. Allen and Doisy(7) demonstrate that lipid extracts of ovarian follicles quite completely substitute for certain phases of the internal secretion of the ovary—the hormone producing striking growth in the female genital organs of rats and mice. Robert T. Frank(10) summarized his work as follows:

1. The primary development of the female genital organs, which include the mammary gland, depends upon the action of the hormone elaborated by the growing follicle.
2. The corpus luteum hormone produces a periodic accentuation of this effect and prolongs the growth stimulus during the early part of pregnancy.

3. The follicle hormone causes the pre-menstrual uterine changes. If no pregnancy occurs, as soon as the corpus luteum becomes functionless, the hypertrophic uterine mucosa breaks down and menstruation results.

4. Periodicity of menstruation is due to inhibitory action of corpus luteum upon development of follicles.

At about this same time Zondek and Aschheim (36) working in Germany found ovarian substance provoked the cycle within a few days but only the wall of the mature or nearly mature follicle or their liquid content is active. A year later Zondek and Aschheim (37) after further study reported that in the post menstrual phase, the retrogressing corpus luteum contains no hormone. The wall of the maturing follicle, the follicular fluid and the fully developed corpus luteum contain the hormone. It is also present in the corpus luteum of pregnancy. They apparently make no distinction between two separate and specific hormones. At this time there was an unfortunate tendency to extend
to the human problem the results of studies upon the lower animals.

Many investigators at this time on the bases of histological studies suggested that the human cycle exhibited important differences and that the follicle hormone could scarcely produce the entire endometrial cycle, and that in all probability another hormone produced by the corpus luteum was essential. In other words, the histological evidence pointed to a follicle phase and a luteal phase in the human cycle. The scientific corroboration of this view appeared in 1928 when Cornier and Allen (12) were able to extract from the corpus luteum a substance with exactly the effects which had been presupposed for it. They summarized their work as follows: Experiments show that extract of corpus luteum contains a substance which induces alteration of the endometrium identical with the progestational proliferation. Extracts of follicular fluid do not produce progestational proliferation. It appears, therefore, that the corpus luteum has a special hormone one of whose functions is to prepare the uterus for implantation. Willard M. Allen (6) in 1929 devised a new procedure for the preparation of a hormone of the corpus
luteum which produced progestational proliferation and presented evidence to show that it is destroyed by alkalies, thus differentiating it from folliculin. He also suggested that this specific hormone be named progestin.

Allen, Pratt, Newell and Bland (2) in 1930 extensively studied the hormone content of human ovarian tissue and made the following observations:

1. High yields of hormone giving positive tests, was obtained from recent corpora lutea removed from the 13th to the 17th day of the menstrual cycle. There is considerable decrease in amount by the 20-22 day. Corpora of the first third of gestation contain considerable amounts. Two full term corpora gave negative results. This last result indicates definitely that toward the end of gestation the corpus luteum of women does not share the responsibility for the large amounts of hormone present in the blood and urine.

2. Liquor folliculi and follicle walls contained large amounts of hormone. In two cases of long continued bleeding large yields of hormone were obtained from cystic follicles. In one case of amenorrhea large amounts of fluid from cystic follicles returned negative
results.

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

4. These results indicate that as far as the secretion of this hormone is concerned, the human corpus luteum merely continues an activity which is primarily follicular. This hormone content of the human corpus 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.

5. Removal of parts of ovaries most active in this function—that of secreting hormone—when done during the inter-menstrual phase, usually results in the appearance of menstruation within the next forty-eight hours. These observations suggest that menstruation is a degenerative process and primarily due to decreased action of this ovarian hormone after it has induced a certain amount of growth in the uterus.

From the evidence collected it is reasonably safe to say that the ovary produces two separate and specific
hormones, at least. It is also probable that they differ chemically as shown by Allen. In addition Kylin has shown that extracts of folliculin caused in every case a rise in blood sugar while extracts of progestin caused a decrease in blood sugar. Many other investigators have also observed that the two hormones are separate and distinct and even go so far as to say that they are somewhat antagonistic in their effects. The work of Frank and Loeb would support this theory. Assuming that folliculin initiates the cycle by stimulating growth changes, the progestin then takes over the situation and initiates the progestational proliferation so that the endometrium is prepared for the reception and implantation of the ovum. At the same time it has an inhibitory effect upon the follicles so that they cannot produce more folliculin. Then when the corpus luteum degenerates the follicles again hold the balance of power and so starts another cycle.

However different the two hormones may be it has also been established without reasonable doubt that the two are essential, in the human at least, in order to complete the cycle. That is, one is complimentary to the other. Leonard, Hisaw and Fevold point out
that the production of progestional proliferation required the combined action of folliculin and progestin and that the folliculin acted first. They also show that if folliculin and progestin are injected simultaneously, the result to be expected depends upon the higher dosage of either hormone. Thus, the duality of ovarian secretion and the "one-two" reaction of the hormones seems to be established beyond doubt.

It has been known for many years that some relationship existed between the anterior pituitary and the gonads, but the experimental basis for this belief was not great. It consisted chiefly of a study of the ablation effects and of the effects of pituitary lesions on the genital system. The remarkable results obtained by Evans and Long by the injection of properly prepared extracts of the anterior lobe may perhaps be taken as the starting point of the newer knowledge on this subject. They assumed that the anterior pituitary produced two ovary stimulating hormones. Fluhmann(22) concludes a definite relationship between the anterior hypophysis and the pelvic organs. Hypophysectomy results in atrophy of genitalia. Transplants stimulate immature ovaries to activity. During pregnancy and
following castration there is marked hypertrophy of the anterior lobe, and, irradiation of the hypophyseal area for certain pelvic disorders has yielded satisfactory results. Smith, Engle, Zondek and Aschheim have also obtained striking results. Fevold, Hisaw, and Leonard (23) have succeeded in extracting two gonad stimulating hormones from the anterior pituitary tissue. One of these stimulates follicular growth and the other one stimulates luteinization. However, the second will not act until an immature ovary has been stimulated by the first. This fact further suggests the relation to the ovary and also strengthens the belief in the duality of ovarian secretion and its "one-two" reaction. Since the presence of the two hormones has been established, Fluhmann (19) suggests that the term Prolan A be applied to the anterior pituitary hormone which stimulates Graffian follicles and Prolan B to the hormone which stimulates the corpus luteum. Another vital point in these studies is the fact that, if the test animal has been previously castrated, no direct effect on the uterus or vagina is produced (13). This indicates that the pituitary produces its effect only thru the agency of the ovary. In the words of Zondek and Aschheim, the anterior lobe
is the "motor of the ovary". It follows, therefore, that the anterior lobe hormone is ovary stimulating in its effect but not a true maturity hormone.

After a review of the literature it is apparent that much conclusive knowledge of the female sex hormones has been determined, although, as yet it has not been entirely linked up and as mentioned in the introduction, the final chapter is yet to be written. This information suggests great possibility in the field of management of gynecological problems, and while some gratifying results have been obtained with the use of ovarian products, they have not proven entirely satisfactory. It would seem that better results could be obtained by employing anterior pituitary products and perhaps future work will bear this out.

Before concluding such a discussion it would seem advisable to include the present idea in regard to the mechanism of menstruation, as set forth by Allen.(1)

In outlining the conception of the probable mechanism of the menstrual cycle from recent experimental evidence, it might be said that toward the end of menstruation rapid growth of the follicles under stimulation of Prolan A from the anterior lobe of the hyp-
ophysis (Smith and Engle, Zondek and Aschheim) induces secretion of folliculin to produce the growth phase in the accessory genital organs. This includes accelerated growth of the vaginal epithelium, growth of the glands of the cervix and body of the uterus to the interval condition, probably some repair of the ciliation of the tubes (29), and, toward the end of this interval, the initiation of growth in the mammary tree including the nipple. Ovulation in women, judging from the recovery of tubal ova (4) occurs on or around the 14th day after the onset of the previous menstruation in the regular cycle. Following ovulation, as the ruptured follicle becomes transformed into the corpus luteum, there is a continued elaboration of folliculin by this tissue. Therefore, folliculin from the corpus luteum must enter the blood stream along with such specific corpora lutea hormones such as progestin, resulting in premenstrual transformation of the endometrium and in continued growth of the mammary gland. Ovulation with corpus luteum formation, although essential for the premenstrual endometrial transformation, is not necessary for menstruation. As the progestin diminishes, the endometrium begins to break down, and menstruation starts.
At the same time the inhibitory action of progestin is lost and follicles are again stimulated and the cycle begins again.

In the case of pregnancy the human corpus luteum continues the secretion through the third or fourth month at least. During the later half of pregnancy this function wanes. The human corpus luteum probably loses the function of production of progestin before the end of the third month, or, at least, continuation of this secretion is not essential to normal gestation. Beginning with the second month the chorion and placenta probably participate in the secretion. This continued secretion of progestin during pregnancy probably is sufficient to explain the inhibition of menstruation during gestation. Most specific actions often attributed to corpus luteum hormone apparently require a preparation by the growth stimulus of folliculin first. The action of corpus luteum hormone is therefore directly complimentary to the action of folliculin.

A chart will be included on the next page which will clearly demonstrate the association of anterior pituitary hormones and those of the ovary.
Excess of Prolan A—Shortens space between periods.
Excess of Prolan B—Lengthens space between periods.
Summary

1. It was formerly believed that the gonads constituted the primary sex characteristic and the secondary characteristics are dependent on internal secretions arising from the gonad in question. At the present time evidence seems to indicate that the factor responsible for sex determination is present in the fertilized ovum and pervades all of the tissues of the foetus—including the other organs of internal secretion and they are all associated in the development of the secondary characteristics. Thus the gonad is not solely responsible.

2. Normality of ovarian function is essential for the proper metabolic balance. Under normal conditions the general metabolism is keyed to reproductive needs, which no longer exist after the usual ovarian secretion is removed.

3. Experimental evidence indicates rather conclusively that the ovary produces two separate and distinct hormones—folliculin and progestin. Folliculin from the Graffian follicle which stimulates growth in the reproductive organs, and, progestin from the corpus luteum which stimulates progestational proliferation in
the uterus. Folliculin and progestin are complimentary in that progestin is only effective after initial stimulation by folliculin. Progestin inhibits follicular activity and therefore is concerned in maintaining the regularity of the female cycle and also in preventing menstruation during gestation. Progestin is also liberated by the chorion and placenta during the later months of gestation.

4. Further study has revealed the fact that the anterior pituitary also produces two specific sex hormones--Prolan A and Prolan B. Prolan A stimulates the Graffian follicle and Prolan B the corpus luteum.

5. Most of the experimental work has been done with animals, and the results obtained with them have been very gratifying. However, the application to humans has not been so satisfactory and further investigation is necessary.
Bibliography


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