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Menstruation

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MENSTRUATION

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by

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"A knowledge of the physiology of Menstruation and its clinical application has widened the gynecologists' vision far beyond the pelvic brim."....Collins (79)

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INTRODUCTION

Menstruation, like sex and syphilis, has always been a subject spoken of very quietly, and then in the confines of secretive quarters. It has been considered a curious blending of speculation and superstition, with very little foundation of real fact. The element of mystery in the phenomenon seems to have inhibited intelligent efforts to study it fully. It was the "curse" which befell women, and not much more was said about it.

However the fertile field of Endocrinology has sprung the trap door and brought the subject out into the realm of reality. As soon as this was done, thought turned in that direction, and only now are we beginning to have a thorough understanding of the phenomenon.

It occured to me that the average physician, has a great number of women patients. Woman is beseiged with many diseases, a great number of which manifest themselves with menstrual disorders. How can we interpert these so called irregularities, if we do not know the length, duration, amount of flow etc., of the normal menstrual cycle? Another factor is found

in irregularities of the mechanism itself. How can we treat these rationally, if we do not know the normal endocrine relations in controlling this process?

I have, in this paper therefore, attempted to give the prevailing concept, of the process as it occurs, with its wide range of normal variations.

I

HISTORICAL

Menstruation, from the very earliest times, has been a subject of great mystery. The older ideas always had a curious blending of superstition and speculation, with very little foundation.

Women with their periods were always abhorred. We see even in the Bible (1) this epitomized: "And if a man shall lie with a woman having her sickness, and shall uncover her nakedness, he hath discovered her fountain, and she hath uncovered the fountain of her blood and both of them shall be cut off from among their people."

Crawfurd (2) has made a very intensive study of the superstitions of menstruation and has given many interesting facts. He finds that Aristotle explained menstruation as a process necessary to get rid of the excess blood that had accumulated in the interior of the body of the woman, and his theory was ardently supported 1500 years later by his great commentator Averhoes. In transalating Pliny, Crawfurd found that he thought that women who did not menstruate were incapable of bearing children, because it is of this substance that the infant is formed. The seed of the male, acted as sort of a leaven, causing it to unite and assume a form,

and in due time it acquired life and assumed a bodily shape.

Pliny also held the idea, "If a woman strips herself naked while she is menstruating and walks round a field of wheat, the caterpillars, worms, beetles, and other vermin will fall off from the ears of corn. In other places again it is the usage for women to go barefoot, with hair disheveled and the girdle loose; due precautions must be taken, however, that this is not done at sunrise, for, if so, the crops would wither and dry up."

We find a modern echo of the procedure in Hiawatha's injunction to Minehaha (3),

"You shall bless to-night the cornfields,
Draw a magic circle round them
To protect them from destruction
Blast of mildew, blight of insect.
In the night, when all in darkness
Rise up from your bed in silence,
Lay aside your garments wholly,
Walk around the fields you planted,
Round the borders of the cornfields,
Covered with your tresses only,
Robed with darkness as a garment."

Menstrual fluid was even thought to have curative powers. The first napkin used by a healthy virgin was preserved for use in plague, malignant carbuncles, and many other diseases. It was merely dampened with water and topically applied. In Bavaria it was held even to have prophylactic powers against wounds, was given internally for erysipelas and calculi, and esteemed a good cosmetic to drive away pimples. (2)

Another superstition might be mentioned -- that coitus with a menstruating woman would bring forth monsters. This belief was very widespread. Ambroise Paré affirmed his belief and rested it on a dictum of the non-canonical Book of Esdras, stating that "Menstrous women shall bring forth monsters." (4)

Ancient mythology attributed the deformity of Vulcan to the union of Jupiter with Juno during her menstrual period.

According to Novak (4) the really scientific study of this process dates from the work of Negrier, in 1832, but the most valuable contributions for a thorough understanding of this mysterious process, have all come in the twentieth century. The endocrinologists at present are still finding this the most fertile field of endeavour, as it is far from being fully explained.

II

GENERAL CONSIDERATION

Age of Puberty.

The age of puberty represents a very critical time in the life history of every young woman. It is the period which eventuates into maturity, and it is accompanied by a number of important changes in the organs of internal secretion; by the development of the secondary sex characteristics; by the cessation of increase in stature; and by a psychic transformation.

On the basis of present available information, the average age of puberty is 13 to 14 years. (5) It is a generally recognized fact that in warmer regions the first menstruation of females begins earlier than in the colder countries. Yokai Boku (6) compared the school girls of Chosen and in 3364 cases studied, he compiled the following figures,

Region	Average age at first menstruation
North Part	15 yrs. 1.96 months
Middle "	14 " 9.67 "
Southern "	14 " 7.44 "
All Chosen	14 " 1.35 "

In comparing them with Japanese girls in Japan proper, he found that the girls of Chosen had a later commencement of their first menses. He also noted in his study that the most frequent month of the first menses was in August, and secondly in April, both corresponding

to school vacation periods.

Engelmann (7) studying a world wide series noted that the average age in his large series was approximately at 14 years. He observed that it was much earlier in the tropics, the age being 12 years; about 15.5 years in the temperate zone and delayed up until about the 16.5 years in the cold climates.

All manifestations of the pubescent and the adolescent periods are considered due to the activity of the glands of internal secretion, which we shall see as due to changes in the ovaries, and secretions of the hypophysis.

Length and Duration.

What is the normal duration of the flow and what is the normal length of the cycle? This has been a question asked by patients millions of times. One flows for seven days and thinks she has an excessive period, another for two days and thinks her periods too scant.

Fluhmann (8) in a series of 823 cases studied, found the average to be 4.6 days. It varied however from three to seven days in the majority of instances, and no relation between the length of the menstrual cycle and the duration of the flow could be demonstrated by him.

One of the largest studies ever attempted was given by Sanes (9) who after reviewing 4500 menstrual histories, found that the greatest number had three day periods, with the second greatest number having 4 to 5 day periods. By far the greatest number had 28 day cycles.

Davis (10) finds that the normal should not exceed six days nor be less than two days. He also states that the 28 day cycle is the one most commonly found, and considered anything less than 21 days or more than 33 days as abnormal.

Allen (11) as the result of his work gives the following chart;

	Accurate	Questionable
Total No. of Cases	110	21
No. of Periods	1291	231
No. of individuals showing absolute regularity.	0	0
No. showing absolute irregularity.	30	14
Variations of intervals.	1.3-84 days	11-72 days
Duration of period.	12 - 3-5 days 21 - 4-5 " 20 - 4-6 " 8 - 4-8 " 11 - 5-6 " 9 - 5-7 " 6 - 5-8 "	2 - 3-5 days 4 - 4-6 " 1 - 4-8 " 2 - 5-6 " 3 - 5-7 " 3 - 6-7 "
No. of pads.	50 - 6-12 60 - 12-30	10 - 6-12 11 - 12-30

He noted the marked irregularity in the whole process. He also kept records of the duties performed by each, but could find no effect of these on amount, duration etc. After this extensive work he came to the conclusion that the idea, that the periods should come every 28 days, should be abandoned.

Menstrual Discharge.

The character of the flow differs in various women. At first it is mucoserous, then bloody, then almost pure blood, which does not coagulate. It consists mostly of blood mixed with secretions and epithelium cast off from the uterus and also some epithelium from the vagina. (12)

Menstrual blood has the peculiar quality of not coagulating. This feature has been studied by many workers. Sturmdorf (13) showed that the blood in general circulation shows normal coagulability. He also showed that the endometrium, during menstruation, recieves normally coagulable blood from the general circulation and it gives vent to this blood in a noncoagulable state. He attributes this property to the endometrium, which supposedly gives to the blood a substance generated in loco and it is not the result of a dialytic process. He proved his contention by placing a small drainage

tube into the interior of the uterus, made an incision into the uterus outside the endometrial zone, and saw blood from the wound coagulate, while menstrual blood did not. Novak (4) also holds this view.

Others do not agree with this view. Dogliotti (14) thinks that the lack of coagulability is due solely to the absence of both fibrinogen and thromgoben. Florian (15) emphasizes the difference between normal circulatory and menstrual blood, and ascribed lack of coagulability of the latter to the deficiency in fibrinogen and richness in tryptic ferments. Both claim however the circulatory blood before and during menstruation is also less coagulable, a view not proven by others. The question is not entirely settled, but most authorities seem to favor the former view.

The question of blood loss, change in the red blood picture, and hemaglobin determinations during menstruation is also a moot question. In one hundred apparently normal women, Barer (16) found the menstrual blood loss to range from 6.55 c.c. to 178.69 c.c. with an average of 50.55 c.c. Fifty per cent of the women lost between 23.21 c.c. and 68.43 c.c. The methods used in determining the blood loss have varied so greatly that we have an adequate explanation for the great variance in figures given. Some use vaginal cups, while others

use cellul-cotton pads etc. In the latter they were analyzed for iron, this value changed to hemoglobin, and then to the amount of blood. Others give the normal amount lost as 5 to 10 oz. (10) (12) For clinical purposes 12 to 14 napkins during the period, or three per day at the height of the flow is considered the usual normal by clinicians. (10) (12)

Many workers have taken daily hemoglobin and erythrocyte counts, with varying opinions and results. Leverton and Roberts (17) did hemoglobin and red blood counts on normal women during successive menstrual cycles and found no consistent measurable effect of the process on the daily values of either hemoglobin or red cells in the subjects studied. They did find occasional marked daily variations, but these were irrespective of the different phases of the cycle. Smith (18) comes to the same conclusions.

However Duckler and Elvehjem (19) find that there is usually a diminution in the hemoglobin during menstruation, the amount varies considerably with different individuals. During the post-menstrual phase of the cycle, there tends to be a rise in hemoglobin which continues to increase slightly during the intermenstrual phase.

Kato (20) in his studies on the blood during the cycle, finds that the number of blood platelets begin to increase in the premenstrum and decrease again with the onset of the flow, the lowest figures being found on the second day. If the flow lasts several days, the number of platelets again increase before the flow has stopped. In the intermenstrum, the platelets are at the normal level.

III

HISTOPHYSIOLOGIC CHANGES DURING MENSTRUATION

Endometrial Changes.

This has been a most fertile field for the histologist, with as many opinions as workers. Kaufmann (21) finds that there are normally two layers to be considered in the endometrium;

1. Basal layer - lowest - which does not take part in the monthly cyclic changes. It serves only as a source of regeneration after menstruation.
2. Functional layer - develops from basal layer and undergoes changes.

The first ten days after menstruation the mucous membrane grows considerably and this phase is known as the proliferative phase, which he thinks is due to the ripening graafian follicle.

In the second half of the cycle, the proliferated mucous membrane becomes secretory due to the corpus luteum and when the corpus luteum retrogresses, menstruation begins. Edgar Allen (22) has the same opinion of this change.

Herrell and Broders (23) have made an exhaustive study, with special reference to histological changes. The article is quite recent, and I will quote it almost in toto.

They find that the glands in the basal layer of the endometrium remain essentially the same throughout the cycle; and suggest that in dilitation and curettage the basal layer can give no cue as to the phase of the cycle. The surface and outer layers however afford a means of accurately determining the phase of the cycle if specimens are gotten by this procedure. They divide the cycle into the following phases, which will be discussed fully.

1. Menstruating phase: There were five specimens obtained during this stage of tissue loss, and according to the observations made there can be no doubt that the loss of tissue is complete in the first 24 hours of menstruation and that the remaining part of the period is one of secretion and hemorrhage. They find that the average loss of endometrium is ¾ of the thickness, and only the basal layer remaining which normally measures about .5 m.m.

2. Early reparative phase of migration and rearrangement of cells: The next 24 hours of the cycle are taken up with reorganization, rearrangement, and migration of cells. From their microscopic studies they were able to learn that the cells lining the remaining glands take part in the resurfacing of the endometrium. This was also noted by

Novak and Te Linde in their studies. (24)

3. Early proliferative phase - first to seventh days: This corresponds to the previous stage but is more advanced. It is characterized by active division of cells, resurfacing of the endometrium, and the formation of new straight tubular glands from the surface epithelium. They found mitosis active and cellular proliferation also occuring in the loose embryonal type of stoma. Novak (24) however remarked that mitosis was not a very frequent occurence, appearing to a greater extent when the epithelial layer was already complete. By the end of the first week in this phase the endometrium presented the following picture. The average number of glands per low power field is 3 to 4, and these glands are nearly straight tubules, the epithelium of which is of the moderately low columnar type, with their nuclei situated near the center of the cell. The measured thickness of the endometrium at this time is 1 to 10 m.m. in thickness. They suggest that one study the glands in the longitudinal view, however if seen in cross section, the phase is discernible by the characteristics just outlined. The tubular glands will appear in cross section merely as small circles.

4. Late proliferative phase - eighth to fourteenth day: This phase corresponds to the resting or interval endometrium of others. (22) They find that the phase is far from a resting stage. The very nature of the process of cyclic regernation prevents such an occurence, hence, from these studies, it became obvious that the earlier descriptions of the endometrium as a tissue of fixed, steriotyped, histological structure, were entirely erroneous. During this stage they found that proliferation continued rapidly, new glands were formed from the surface epithelium, and the stromal cells nearly doubled in number. The average number of glands per low power field is six to seven by the end of the second week of this stage. These glands are somewhat dilated but remain of the straight tubular type and show little if any evidence of a differntiative change. The endometrium in this stage is grossly 2 to 2.5 m.m. thick. They found that this stage corresponded to the life of the graafian follicle, and it would seem therefore that the graafian follicle has to do with the proliferative phase of this process. This is true as we shall see later in a discussion of the endocrinology of the menstrual process. At the end of this phase, proliferation is on the decline,

however, evidence of slight proliferation is seen in the next phase, another striking correspondence to the failing follicular activity.

5. Early differentiative phase - fifteenth to twenty-first day: One of the earliest indiciations of differentiation is the beginning convolution of the longitudinal glands. The epithelium shows a marked change, having been of the low columnar type up to this time, now becomes the tall columnar type and the nuclei migrate to the base of the cell. By the end of the third week of this early differentiative phase, the endometrium is grossly about 3 to 3.5 m.m. thick, but the number of glands has not increased in correspondence to the preceding phase. These glands are dilated and there is only an apparent increase in the stromal cells, which other workers call continued proliferation. They again noted that this phase corresponds with that of early activity of the corpus luteum and the failing graafian follicle, which histologically is expressed here as decreasing evidence of proliferation, and a rather sudden onset of all of the histological evidence of differentiation. This is the so-called interval phase of Novak(4) and premenstrual endometrium of Allen (22).

6. This may be termed the premenstrual phase, although such a term is not descriptive of the true state of the endometrium. In this phase differentiation is at its height. The glands show a marked change. They are now twisted on their longitudinal axes, producing the typical corck screw glands. In longitudinal section these glands look like a sectioned sea shell with the typical saw-toothed appearance of the epithelium. This twisting, they believe, is a characteristic of differentiation whereby the surface area is increased. The epithelium is now markedly columnar. They find a definite cytoplasmic increase, with a decreased nucleocytoplasmic ratio, a distinct differentiative phenomenon. Gloycogenic material is increased in these tall cells and the nuclei are found near the basement membrane. At this phase the lumina of the glands are increased in size, and hence, the stroma by mere mechanical pressure is apparently increased.

Just prior to menses there is a premenstrual engorgement of the stroma and infiltration with wandering cells, associated with some edema near the surface.

Tissue Loss.

Novak and Te Linde (24) based their study on twelve uteri removed during menstruation. They took exceptional

care in their removal and were put immediately into Zenker's fluid within 2 to 3 minutes to be fixed. They found that the entire superficial or compact layer is thrown off, as well as most of the deeper or spongy layer. On the first day, the surface of the mucosa may be quite intact, but usually shows beginning loss of tissue. By the second day, the tissue loss becomes very extensive, with all of the compacta and most of the spongiosa being gone. Regeneration is usually evident on the third day. This is not in accord with Herrell and Broders (23) who concluded as quoted before "that there is no doubt that loss of tissue is complete in the first 24 hours and that the remainder of the menstrual period is one of hemorrhage and secretion." Bartelmez (25) finds the amount of tissue lost as variable. He thinks that the stratum spongiosum of the progravid stage is never lost entirely. Watson and McHenry (26) state that the tissue loss from the endometrium during normal menstruation is limited to the epithelium of the glands which have been fully activated by progestin and to the stroma which supports those glands.

Infiltration.

The large number of leucocytes in the stroma and within the glands has been noted by many observers since Kundrat and Englemann (27). Novak and Te Linde (24) noted that the desquamation of mucosa is preceded by extensive infiltration with polymorphonuclear leucocytes. This infiltration is marked for a short time before the actual clinical onset of the period. Bartellemez (25) thinks that the leucocytes play a part in loosening the tissue. There is a correspondingly large number in the discharge. (28)

Vagina During Menstruation.

Does the vagina have cyclic changes corresponding to the endometrium? That has been shown by some and not found by others. Papanicolaou (28) has given the subject considerable study and is one of the authorities concerning it. In his very lengthy work he divides the female sex cycle into four phases and one stage.

(a) the menstrual phase (1st to 7th days)

(b) the copulative phase (8th to 12th days)

(c) the ovulative stage (12th to 13th days)

(d) the proliferative phase (13th to 17th days)

(e) the premenstrual phase (17th day to the next menstrual period)

During the menstrual phase the vaginal smears are characterized by numerous erythrocytes. They increase in number up to the third day and then decrease. Polymorphonuclears are present in abundance, and mononuclears are more conspicuous than at any other time. The epithelial cells decrease while the bleeding increases, and one notices that they are chiefly squamous cells of the superficial type. Characterisitic aggregations of small cells, supposedly of uterine origin, are found when bleeding is intense. A sharp increase in the number of leucocytes toward the end of bleeding, and at times a real exodus, has been noted.

The copulative phase is characterized by a more or less complete leucopenia, and the epithelium is of the intermediate or superficial type with a tendency to cornification. Eosinophilic anucleated cells are much less frequent. Mucus secretion is generally increased.

The ovulative smear is characterized by a sudden increase in the number of leucocytes, noticeable particularily after a typical stage of leucopenia. The epithelial cells are still of the intermediate or superficial type. They differ from the preceding phase in that their contours are not as sharp. They form characteristic aggregations with leucocytes. Cornification is

very pronounced with most of the cornified cells nucleated. The number of erythrocytes tends to increase, with even small hemorrhages noticed occasionally. Mucus is on the decrease.

The vaginal smears during the proliferative phase show great variations, depending upon the extent of the cornification process and upon the preservation of the cornified zone. The leucocytes are scarce during this phase, and even a complete leucopenia may occur. When the cornification is less pronounced the number of leucocytes is usually greater, while the per cent of cornified cells shows a decrease.

The smears during the premenstrual phase are characterized by the presence of numerous cells and leucocytes. They show many differentiated forms and are mostly of the superficial type. The nuclei are larger, and the nucleated cornified cells are on the decrease. Erythrocytes are occasionally found, their number often being large especially near the beginning of the next menstruation. The smears are rich in mucus.

Zondek and Friedmann (29) could not find cyclic changes in the vaginal mucousa analogous to uterine mucosal changes by microscopic section studies. They did find that the mucosa shows a different microscopic

picture in different regions. They showed also that in primary amenorrhea, with a deficient ovarian function, the picture of the mucosa was similar to one with good ovarian function. By use of ovarian hormones, they could produce uterine changes, but no vaginal mucosal changes. Their studies were purely microscopic of tissue sections. They stated "that since the vagina is developed embryologically different, in different species, the different reaction of the vaginal mucosa is explainable."

Davis and Hartman (30) found changes in the thickness of the vaginal epithelium, with the greatest thickness in the midinterval, consisting at this time of an active basal layer, an inactive functional layer, and an intra-epithelial zone of cornification interposed between these two, which they called Dierks' layer. Following ovulation, they noted a desquamation, with a crumbling away of the functionalis, which is usually completely destroyed. They also observed that mitosis begins in the basalis on the first day of menstruation becoming most marked near the time of ovulation, and then gradually subsides. They also noticed that ovarian deficiency, menopausal or experimental, definately alters these physiologic changes. Papanicolaou and Shorr (31) also noted that the vaginal epithelium

changed, especially during the menopause. Papanicolaou (32) later showed by his vaginal smear method that the menopause does not mark the end of the sexual rhythm. In all cases examined up to ten years after the menopause, the sexual periodicity was still present, and the sequence of phases followed the same order as in young normal women.

The Fallopian Tubes.

Do they participate in this cyclic change? In 1928 Novak and Everett (33), from a study based on 236 cases in which all tubes used were normal, convinced themselves that cyclic changes in the tubes do occur. They found however that the change is not nearly so striking or sharply definable as that seen in the endometrium. They could not demonstrate that the tubes participated in the bleeding during actual menstruation.

Tietze (34) describes in detail the cyclic changes observed in 44 tubes removed from regularily menstruating women. He particularily noted alterations in the ciliated cells, which showed their greatest development at the 14th to 15th day of the cycle. This corresponds to the time of ovulation, when the ovum is transported to the uterine cavity.

At a more recent date Jaegerroos (35) insists that in his own investigations he definitely established in the human female participation of the tubes in the cyclic menstrual changes, but again no proof of their bleeding.

The Cervix.

Wollner (36) studied nine patients, taking periodic tissue specimens from the cervical mucosa with a Hyams' electrode (cutting current of high frequency). In six cases there was a definite histological evidence of a cyclic change. In one case, which had both ovaries removed, there was an atrophic change and an inactivity of the endocervix noted. In two cases no change could be found, but one later came to operation and it was found that she had definite ovarian pathology.

Vascular Changes During The Cycle.

Most histological studies of menstruation have incidental references to the blood vessels but until recently there has been no systematic study of cyclic changes in the vascular system of the uterus. Much of the work has been done by German workers which limits me in my explanation of this phase.

As early as 1899, Clark (37) in a study of uterine

hemorrhage in myoma uteri, observed the blood supply of the uterus and its mucosa. To briefly epitomize the results of his observations on the normal vascularization of the uterus: "It consists of the lateral utero-ovarian anastomosis which gives off excessively tortuous secondary branches, some of which penetrate the outer layers of the uterin muscle and finally terminate as delicate twigs in the uterine mucosa, while others extend across the uterus and fusing with similar branches from the opposite side form direct arterial communications. From the latter, branches are given off which also penetrate the deeper-lying musculature and terminate in the mucosa. Beyond establishing the fact that there are direct arterial communications besides the usual capillary anastomisis, I have established the main points as depicted by others."

Daron (38) in his studies on the arterial pattern of the tunica mucosa of the macacus rhesus found interesting arterial changes. He studied these arteries in a series of uteri injected intravitam. By this technique differences in their forms under different physiological condition could be observed. By reconstructions from serial sections done on these uteri, he demonstrated that the prominent arterial fields

represent sections through the coils of single tortuous arteries. He noted that they have few or no branches in the basal half, but the branching is almost exclusively terminal and abrupt. The locus of this branching presents a landmark for the study of the growth of the tunica mucosa as a whole. He recorded characteristic changes associated with the different phases of the menstrual cycle. In the early proliferative stage the arteries do not extend but a little more than halfway through the tunica mucosa. In the late pregravid stage they are found to reach almost to the surface epithelium. He also noted regions of contraction in certain of the myometrial arteries from which the spiral arteries of the mucous membrane arise. They were only seen however in late pregravid and menstrual stages. Bartelemez (25) also noted this vasoconstriction in different areas of the same mucous membrane, and thought that the duration of the flow depended upon it.

Daron (39) in a later study on the macacus rheus describes two distinct types of arteries, I, which he calls the large, tortuous, coiled arteries, and II, the small arteries which extend into the mucosa. He finds differences between ovulatory and anovulatory cycles. In the ovulatory cycle the coiled arteries exhibit a

progressive increase in extent toward the uterine lumen and they increase in tortuosity so that in the late pregraivd phase they are present immediately under the surface of the epithelium. During ovulatory menstruation the terminal branches, and parts of the coiled arteries are lost.

In the anovulatory cycle, the marked growth and differentiation noted in the preceding type does not occur, so he compares this at the time of menstruation with the proliferative phase of the ovulatory cycle. During menstruation in the anovulatory cycle there is no involvement of the arteries noted, as in the ovulatory.

Another great contributor to this study of vascular changes is Markee (40) who did his work on intraocular endometrial transplants in macaca mulatta. He studied this process in endometrial transplants in over 300 cycles. He noted the sequence of events occuring in both ovulatory and anovulatory cycles, following castration, after injection of oestrin, and after spinal resection. At first there was an anemia of the superficial two-thirds, which is supplied by the coiled arteries. Four to 24 hours later, circulation would temporarily resume, only in a

single field however, the rest of the transplant remaining anemic. Then blood would escape either from a capillary or arteriole almost immediately. Occasionally it would ooze for a short distance along one of these vessels, in which case a hematoma would form more slowly. Hematomata resulting from a ruptured vessel would begin to discharge in from one to 25 minutes. These hemorrhages were arrested by contraction of the appropriate coiled arteries or their branches. In some cycles, congestion and nearly complete stasis preceded the anemic stage by 2 to 4 days.

IV

ENDOCRINOLOGY

The entire phenomenon of menstruation is explainable by a study of the ovaries and their secretion, and their sentinel - the anterior lobe of the pituitary. The matter has been much complicated in the literature of today by the promiscuous use of the various names given to the hormones by different authors and drug manufactures. To somewhat clarify this I present the following from Meigs (41),

Prolan - from anterior lobe pituitary (Aschheim & Zondek)

" A - follicle stimulating hormone.

" B - corpus luteum stimulating hormone.

Theelin - ovarian follicular hormone. (Doisy)
Called follicular hormone and estrin.
Is that substance when injected into
castrated adult mice, estrus results.

Progestin - corpus luteum hormone.

	Prolan	Theelin	Progestin
Schering Co.	Prolan	Progynon	Luteo-hromone Proluton-B
Park-Davis	Antuitrin S.	Theelin Theelol	
Squibb	Follutein	Amniotin	
Winthrop	Antophysin		
Ciba		Sistomensin	
Segewap		Menformon	

With this brief introduction we shall now consider each organ and their hormones separately. I shall use the term theelin, when refering to follicular hormone, regardless of manufacturers names, and progestin, when refering to corpus luteum hormone.

Ovarian Function.

The ovaries are the sexual glands in which the ova are formed. They are also the site of formation of the two hormones which are so essential in the menstrual cycle of the female. Marshall (42) states that the internal secretions are elaborated by the follicular epithelial cells or by the interstitial cells of the stroma. Allen (43) feels that the ovarian follicular hormone ("theelin", "folliculin","oestrin") is the principle hormone. He finds in his experimental work that its principle effect is in causing rapid growth of the accessory genital organs. It also stimulates the vaginal epithelium, uterine epithelium, and the mammary glands. Then at the time of ovulation, there is a continued elaboration of the follicular hormone by this tissue. Therefore theelin from the corpus luteum must enter the blood stream along with the corpus luteum hormone, progestin.

These two produce the premenstrual transformation of the endometrium and the continued growth of the mammary gland. He observed that if the amount of theelin was decreased, due to atresia of large follicles in normal animals, or to cessation of injection in ovariectomized rats, menstruation would occur within a few days. He came to the conclusion that theelin alone was sufficient to supply the essential mechanism of menstruation. Dickens and Brown (44) noted the same changes as those observed by Allen (43), but they also observed a change in the vascularity of the endometrium during this part of the cycle. In a further study on the follicular hormone and its relation to menstruation, they found that it increased progressively in the blood during the post- and premenstrual periods, and when present in sufficient concentration, it produced the changes in the accessory genital organs which have been enumerated before. They further noted that the concentration, when plotted, gave two curves. The first reached its height between the tenth and seventeenth day after the first day of menstruation, thus corresponding to the time of ovulation. The second curve reached its height between the 21st to the 24th day. This also was the finding of Fluhmann (45).

The proof that this follicular hormone produces

these changes in the accessory genital organs, has been mostly through animal experiments. However a few have been done on human castrated females. Corner (46) in his work on rabbits, brought the uteri to mature size by the injection of theelin and then to the progestational state by progestin. Allen and Doisey (47) from experiments on the monkey macacus rhesus, noted that the injection of theelin in immature monkeys produced the growth processes in the female genital tract and the mammary glands, and induced the external "sexual skin" manifestation characteristically found in mature monkeys during estrus. They observed partial growth in the endometrium with a beginning coiling of the glands and an increase in secretion. Hisaw et al. (48) in a series of five castrated monkeys produced premenstrual endometrial changes in only two out of five monkeys. They however combined both follicular hormone and corpus luteum hormone, and produced changes in the two recieving the larger doses.

There have been only a few experiments on the human. Werner and Collier (49) in their work found that theelin injections in the castrated woman restored the breasts and genital tract to apparently the normal sexual state after the previous castration atrophy. The hormone

produced changes in the atrophied endometrium corresponding to that, or equal to the interval changes found in the normal woman, at the time of ovulation. They could not produce however, the pre-gravid changes in the endometrium. They produced bleeding from the uterus in these women qualitatively indistinguishable from menstruation in normal women, although the bleeding was from an endometrium of the interval stage. Kaufmann (50) noted the same phenomenon.

The follicular hormone is the only one acting up to the time of ovulation, at which time we see the formation of the corpus luteum. In studying ovulation and its relation to menstruation, Corner (51), in his colony of macacus rheus, found that menstruation can occur without ovulation. Some of the monkeys died, and at postmortem no corpora lutea were found, although they had been menstruating regularly. They found that the endometrium was not the usual premenstrual type, but had the characteristics of the interval stage, produced by theelin alone.

The time of ovulation had always been computed by the appearance of the corpus luteum in the ovary, which was very inaccurate. Allen and Pratt et al. (52) however developed a technique of recovering the ova

from the fallopian tubes. They recovered six ova from the tubes on different occasions, and found that they appeared around the 15th and 16th days most generally. Only one was found on the 12th day. In another, a much larger series of 90 patients, Newell et al. (53) recovered ova from the fallopian tubes, five of which were successfully sectioned and definitely identified as tubal ova. In this series ovulation was on, or one or two days before, the fourteenth or morning of the fifteenth day following the onset of the previous menses. Wharton and Henriksen (54), in their study found that ovulation may occur any time between the seventh to the 22nd day. They had 61 cases who had a periodic intramenstrual pain at this time. The majority of them had it between the 10th to the 12th day. The patients described the pain as cramp like, intermittent, and localized in the pelvis. Most of them noticed a mucous discharge and some noted blood. The workers found that vaginal lavage showed blood in almost all of the patients. Thirty of their sixty patients came to operation, and in 15 they have records of the pelvic findings. They found large graafian follicles or corpora lutea, at times oozing fresh blood from the point of rupture. They kept the records of

these women for several years, and noted that the pains, "mittelschmerz", disappeared when the patients became pregnant or reached the menopause. Séguy and Simonnet (55) noted the appearance of a thick, translucent glairy secretion in the cervix, and they believed this to be the most evident and the commonest external sign of ovulation. They also observed that the titer of estrogenic substance in the urine reached its highest level at this time. They had a series of five cases which came to operation at this time, and in four they found ripe graafian follicles. Hartman and Squire (56) reported the record kept by an intelligent, scientifically inclined woman during her cycle, and she noted that in the mid-interval there was an evanescent overabundance of mucous secretion in the vagina. They interpreted this as being due to the high level of theelin at this time, basing their conclusion on what happens in the monkey if theelin is given.

When the graafian follicle has matured, the ovum is extruded, the walls collapse, and the central cavity is filled with blood from the ruptured vessels of the theca. The principle role in the formation of the corpus luteum is played by the epithelial follicular cells. They begin at once to hypertrophy and attain

a considerable size within a few days. These hypertrophied cells are the lutein cells, although the characteristic pigment, lutein, is present only in a small quantity. It is from these cells, that the corpus luteum hormone, progestin, is supposedly secreted. (57)(58) The physiology of the corpus luteum has been of special interest to Willard Allen (59). He produced progestational proliferation in the uterus of immature rabbits by the injection of progestin, only if the uterus was first brought under the influence of theelin. In an earlier work with Corner (60) he found that following ovulation, and the formation of the corpus luteum, the endometrium undergoes the histological changes, leading to the stage called progestational proliferation. This state occurs only in the presence of recent corpora lutea. They produced this experimentally in castrated adult rabbits by injecting an alcoholic extract of corpus luteum. They tried extracts of follicular fluid also, but could not produce the same results. They therefore concluded that it must be due to the hormone of the corpus luteum. Edgar Allen (61) in his studies on monkeys, found that removal of both ovaries on the first day of menstruation had no apparent effect on the period. He performed double ovariectomies, and injured

large follicles, toward the end of, or immediately after, the follicular phase of the cycle, and there followed an apparently typical cycle.

One should not harbor the impression that during this phase in which the corpus luteum is dominant, that the follicular cells are not still secretory. The follicle does become transformed into the corpus luteum, but there is also continued elaboration of follicular hormone by this tissue. (43) (62)

In summarizing the present day concept of these two hormones, Dickens and Brown (44) state that theelin causes increased growth of the uterus and tubes, changes in the epithelial lining of the uterus and vagina, and morphological and function changes in the glands of the endometrium, and an increase in the vascularity of these structures. The corpus luteum hormone, progestin, must have theelin to produce its effect. Progestin has no effect whatsoever unless the uterus has been first activated by theelin. Progestin therefore, when the uterus is first activated by theelin, produces proliferation of the endometrium and a quiescence of uterine muscle, coupled with the harmonious action of theelin, create a condition similar to that observed in early pregnancy.

Anterior Lobe of the Hypophysis.

The anterior lobe of the pituitary is considered the sentinel of the reproductive system. The dependency of the ovarian function upon that of the hypophysis, through the agency of the two pituitary gonadotropic hormones, is well established. (63)

Smith and Engle (64) produced precocious maturity of the female genital system by anterior pituitary transplants. They could not produce the changes however, if the ovaries were absent. They noted that the transplants produced a specific effect on the follicles, greatly accelerating their growth. In one mouse they found 42 ova in the tube. Performing hypophysectomy in adult mice, they noted a marked atrophy of the genital system. In the ovary the most characteristic effect was a cessation of follicular development and atresia of all follicles other than primordial. Smith (65) produced the same effects in his work on the pituitary problem. Zondek (66) a pioneer in this pituitary work, studied the hibernating bat, and showed that the corpora lutea could be produced by the means of prolan, even though the ova were pressed to one side or destroyed. He aspirated ova from the follicles in rabbits, and after the injection of prolan, such a follicle was converted

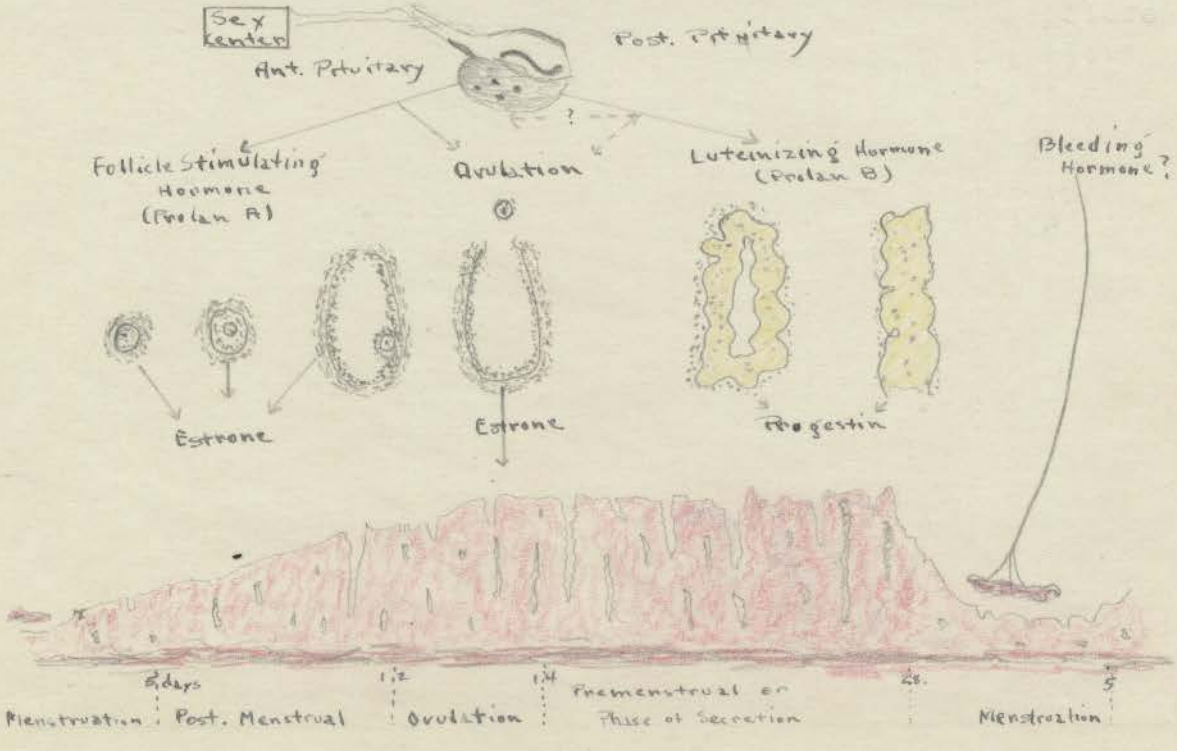
into a corpus luteum. He therefore concluded that the gonadotropic hormones of the anterior pituitary lobe effect the ripening of the follicle and the development of the corpus luteum.

C.A. Elden (67) presents the report of a rare case. The patient was a fifteen year old colored girl who began menstruating at twelve. The periods were regular every 28 days, lasting 3 to 4 days with no dysmenorrhea. The patient came to operation, a craniotomy being done, and the pituitary gland was completely coagulated by electric endotherm electrode. A pelvic examination ten days later showed everything normal. She then began to lose weight, became lethargic, and ceased to menstruate. Five months after operation the patient was begun on hormonal therapy. She was given 50,000 international units (10,000 R.U.) of progestin ("Progynon-B") at each injection on the 1st, 4th, 8th, 11th, and 15th days. She experienced cramps on the 23rd day and bleeding started on the 24th day. Six pads were required and the flow was fairly moderate. He repeated the procedure and the bleeding was again produced. These results suggested to him that in women, neither the anterior nor the posterior lobe of the pituitary were necessary for the action of theelin so far as bleeding is concerned,

and that the hormone acts directly on the uterus and not through the pituitary glands.

Meigs (41) in summarizing the present day concept of the pituitary hormones (gonadotropic) states that there are two. Prolan A, which is the follicle ripening hormone, and its action is to start the primordial follicle of the cortex of the ovary along in its development into the graafian follicle, with the consequent production of the follicular hormone, and to conduct it to its rupture. Prolan B is the so-called "stimulator" of the corpus luteum. After the graafian follicle has ruptured, it causes a proper development of the lutein tissue from the theca or granulosa cells into the mature corpus with the consequent production of progestin.

The following chart is from Kurzrok (68) which summarizes the entire problem of endocrinology.



"Cause" of Menstruation.

Many experiments have been performed in recent years in an attempt to discover the factor or factors concerned in the production of menstrual bleeding. Throughout the literature we see the suggestion of the nervous system controlling the sexual function. Robinson (69) in 1891 brought forth the view that menstruation is governed by the ganglia situated in the uterine walls and along the tubes, and closely connected with the ovaries. He states that as all viscera are controlled by nerve centers, so the uterus must be also. Martin (70) was struck by the periodicity of menstruation. Quoting him "The menstrual clock is, so to speak, wound to go for 33 years, and strikes once every lunar month. I submit that this rhythm of function must be due to rhythmical changes in a controlling nerve centre." To prove his contention, he states that at each recurring period, many women suffer marked nervous symptoms. Lunatics and epileptics are worse at this time. There is even a "menstrual epilepsy" occuring only at the time of the period. He cites a case of a monster, which was separated at the third lumbar spine, had two uteri, and both menstruated together, suggesting to him a nervous control. Collins (71) also held that

there was a menstrual centre, and that the disappointed decidua, became a necrotic foreign body, and stimulated the nerves to cause menstruation. We still find this idea expressed, but not proven, in 1936. Theobald (72) accepts the fact that the cycle is dependent upon varying amounts of the hormones etc., but feels that the regularity of the menses suggests a central rather than a haphazard hormonal control.

Wilson and Kurzrok (73) offered the "hypothesis", that the bleeding mechanism is due to a special hormone elaborated by the anterior lobe of the hypophysis. They feel that it is separate and distinct from the follicle-stimulating and luteinizing hormones. It is supposed to act directly on the endometrium. The actual onset of bleeding occurs when a certain concentration of the bleeding hormone has been reached, provided it is not inhibited by corpus luteum. Bleeding then stops when the hormone is exhausted. Cannon (74) also believes that there is some type of toxin which causes decidual necrosis. He thinks that it must be in the hypophysis since theelin won't produce bleeding in castrated monkeys after partial hypophysectomy.

The two hormonal theories at present holding sway are the 1. Estrin-deprivation theory, and 2. Progestin

withdrawl theory. Allen (61) in his experiments given before, came to the conclusion that menstruation was probably due to an absence of follicular hormonal stimulus after it had been acting for a certain period of time. In this connection it should be noted that the presence of the follicular hormone has been demonstrated in the human corpora lutea. (58) It seems quite possible that the corpus of the monkey may also continue to secrete the follicular hormone, thus postponing the onset of menstruation. (61) Fluhmann (75) by studying the estrogenic hormone content of the blood during the cycle, found that uterine bleeding may take place at a time when there is a high amount of estrogenic substance in the blood and conversely a rise and fall of the hormone content may be associated with amenorrhea. He admitted that the results were open to several interpretations, but at any rate it seemed probable to him that estrin-deprivation alone was not sufficient to account for the occurence of menstruation.

Engle, Smith et al. (76) state that is is a generally accepted fact that in the mature monkey, uterine bleeding occurs after deprivation of the estrin supply of the animal by any method. This bleeding can be prevented by the administration of the hormone of the

corpus luteum, progestin. This prevention had been for the duration of the treatment, bleeding again occured 3 to 5 days after cessation of progestin treatment, and only then. Uterine bleeding which follows cessation of progestin therapy occurs within the expected time, even though estrin administration is instituted at once and continued until bleeding occurs. From their work they concluded that in the ovulatory menstrual cycle, menstruation results from a cessation of the secretion of the corpus luteum, and that it occurs in the presence of a high estrin content of the blood. This was also shown by Fluhmann.(75) Young (77) also considered the degeneration of the endometrium consequent upon the withdrawl of the luteal hormone.

In conclusion of the discussion of endocrines I quote Bartelemez (78) who I think sums this question up beautifully. "In reading the descriptions of experiments with endocrines, one is reminded of other physiologic studies in which the problem has been clearly formulated and the procedures meticulously carried out, but the interpretations were vitiated by the operation of factors unsuspected at the time the experiments were made. If an observer may venture an opinion I would suggest that if we are to progress in our

understanding of Menstruation we need detailed studies on the physiology of the uterine vascular system instead of more experiments on the effects of extirpations and implantations of endocrine glands and injections of extracts of hormones."

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