Uterine Hemorrhage Due to Extra-Uterine Influences

by

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Instructor in charge

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Head of Department

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UTERINE HEMORRHAGE DUE TO EXTRA-UTERINE INFLUENCES

Introduction

This paper deals with a study of uterine hemorrhage in which the etiological factors are not within the uterus itself as is the case in myomata, carcinomata and the like, but are outside the uterus. Here we find no change in the anatomic structure of the uterus except for possible enlargement. Changes may occur in the endometrium and these are usually proliferative in nature.

The etiology of hyperplasia of the endometrium has been sought in every portion of the endometrium and myometrium and each alleged cause has regularly failed to withstand critical inquiry. The pendulum has now swung to a theory of constitutional disturbance, especially among
the glands of internal secretion.

**Approach**

My approach to this problem has been through surgical and clinical material at the Halstead Hospital, Halstead, Kansas, and postmortem and surgical material in the Pathology Department of Kansas University at Rosedale, Kansas.

At the Halstead Hospital a hundred fifty-eight women entered the gynecological surgical service in the past year because of irregular uterine bleeding and in one-fourth of these no gross uterine pathologic condition was found. Forty-one of the latter group were personally attended.

It has been my impression that when stress and strain enter the life of a woman with a constitutional endocrine diathesis, irregular and profuse uterine hemorrhage may occur. That this reaction takes place through the glands of internal secretion is probably true, but it is suggestive that a psychic factor may also be involved when improvement or cure is brought about through an adjustment.

Among the Kansas University files were twenty-
nine cases of organic endocrine disease which led to the death of the patient. This material, tabulated, is as follows:

<table>
<thead>
<tr>
<th>Death due to</th>
<th>Number</th>
<th>Clinic</th>
<th>Menstrual</th>
<th>Pelvic</th>
<th>Necropsy Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td>None</td>
<td>Mentioned in 4 cases. No blocks or sections on ovaries. 1. Hydrops follicularis of ovary. 2. Anthracocosis over surface of bladder and uterus and broad ligaments. Endocervicitis. 3. Uterus normal. Ovarian veins show numerous varicosities. 4. L. ovary shows cystic degeneration. R. ovary fairly large hemorrhagic corpus luteal body.</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenals</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>Pelvic contents mentioned in 2 cases. No block or section. 1. Myomata 1-6 cm. One pedunculated. 1 ovary small and contracted. The other embedded in a mass of adhesions. 2. Multiple myomata. Endometrium thickened and congested.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No pelvic tissue available. Not mentioned in autopsy protocols.</td>
</tr>
<tr>
<td>Pituitary</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>No blocks cut. 1 had a bilateral oophorectomy 25 yrs. D. at 33. In other uterus, tubes, ovaries o.k.</td>
</tr>
<tr>
<td>Thymus</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>Necropsy material consisted of brain only.</td>
</tr>
<tr>
<td>Pineal Gland</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>29</td>
<td></td>
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Fifty-three surgical slides had been diagnosed hyperplasia of the endometrium.

Eight of these cases were not associated with other pelvic pathology.

Forty-five were combined with other pathologic conditions as follows:

1. Fibroids 31 cases 2 associated with displacements
   2 associated with inflammations
   1 associated with polyps

2. Displacements 5 cases 2 associated with fibroids
   2 associated with inflammations

3. Inflammation 11 cases 2 associated with fibroids
   2 associated with displacements

4. Polyps 4 cases 2 associated with fibroids
   1 associated with fibroids and inflammations

5. Ovarian cystomata 3 cases
Terminology

Hypertrophy of the mucous membrane and hyperplasia of the mucous membrane are terms which have been applied to this condition of the endometrium. In general there is a normal numerical enlargement of the mucous membrane; namely, the surface epithelium, glands, connective tissue, and blood vessels, which is the premenstrual stage. This picture is now considered one of hypertrophy in contrast to hyperplasia of the endometrium in which there is also a numerical enlargement of the surface epithelium, glands, connective tissue and blood vessels, but it is associated with afunction or dysfunction. It is not always easy to designate where one condition ends and the other begins. The functioning hypertrophy may be of various individual thicknesses to the extent that it may be similar, but not identical to the gravid mucosa and this is contrasted to hyperplasia in which great thickness may exist and function fail utterly.

Hyperplasia is a term generally applied to the endometrium only. We shall also mention a smaller group of cases of hyperplasia of the cervical mucosa.
Plan

The first part of this presentation will describe the histology and physiology of the endometrium and glands of internal secretion in relation to menstruation as a foundation for the discussion on hyperplasia of the endometrium.

Part I. A. Normal changes in the Endometrium in Menstruation

B. Hormones in Relation to the Endometrium in Menstruation

Part II. Hyperplastic Conditions of the Uterus.

Microscopic studies of endometrial and ovarian tissue have suggested the method of repair of the endometrium and corpus luteum. This will be explained briefly and illustrated.

History

A brief history of hyperplasia of the endometrium has been compiled by Robert Meyer(40) and begins in 1850 when Recamier gave an accurate microscopic description of hyperplasia.

Pozzi, Paris, Also Olshausen (1875) were the first in Germany and France to hint as to the meaning of "endometritis fungosa".
Ruge (1880) presented the first systematic study, arranging his "glandular endometritis" among the hyperplastic forms. He classified his cases as 1. Glandular hypertrophy; 2. Glandular hyperplastic endometritis.

Von Brennecke (1882) conducted the first investigations to give hyperplasia a special place. He called it a "pure hyperplasia", and declared the origin of premenstrual congestion without menstrual disintegration due to interrupted ovulation.

DeSinty (1884) gave the following classification:

1. Glandular proliferation with hypertrophic glands
2. Embryonal tissue with sparsely dilated blood vessels
3. Vascular proliferation (true polyps).

Schmal, (1890) (after Driessen), believed it was not a question of inflammation, but a true hypertrophy of the mucous membrane. Doderlein (1896), Pfannenstiel, Bumm, and Menge were inclined to regard hyperplastic endometritis as a separate pro-
liferative disease because of negative bacteriological findings (Schauta, 1896, Doderlein, 1897, Amann 1897, Cullen 1900). Hitschmann and Adler (1907) in discussing endometritis, described hyperplasia again as a disease, wholly independent of inflammation. Later Hartje, Buttner, Thielhaber, R. Schroeder, Schottlander, Rode and Gade, Schickele and Aeller, Smith, Forssner, and O. Frankl appraised the occasional finding of inflammation as an incidental accompaniment. R. Meyer, Albrecht, Lofquist represented the opinion that, although of lesser importance, inflammation can lead to hyperplastic gland proliferation. This same belief was held by Thorn, Henkel, Himmelheber, Essen-Moller, Buttner, Voigt, Bridoux, Gardner, Ellenbock, Mittelmann and Hegar. Keller and Shickele had written reviews.

Good descriptions of the battle to determine the demarcation of hyperplasia from endometritis have been given by L. Adler (1927) and R. Schröder (1928) Review and Monograph.
Part I

A. Normal Changes in Endometrium in Menstruation

Intermenstrual Period

The normal endometrial microscopic picture (18,37,63) is variable and depends upon the time in the menstrual cycle. During the intermenstrual period (Fig. 1) which includes the post menstrual and interval periods as classified by some authors, the mucosa is thin; the glands far apart. An interval between the glands on transverse section is 4 or 5 times the diameter of the gland. Their course is straight. The cells of the glands form a single layer of columnar epithelium with centrally located, deeply staining nuclei. The lumen is empty. Lymphoid cells with prominent nuclei and scant cell body are found closely packed in the intraglandular connective tissue. O'Leary and Culbertson (1922) (42) found that basal buds appear as a constant finding in the early intermenstrual period.

Premenstrual Period

This stage remains more or less stationary during the time the graafian follicle is developing.
As it nears the time for rupture and maturation of the ovum, the premenstrual period (Fig. 2) or period of secretory activity begins and continues until the ovum is or is not fertilized.

The individual glands increase in size and tortuosity and when this picture becomes generalized, the glands are in close approximation and give varied and bewildering pictures. At first, they are corkscrew and later become convoluted with contracted and dilated segments. Epithelial cells increase in size, boundaries toward the gland lumen are irregular and less distinct, nuclei stain poorly and cell bodies are distended with secretion. Toward the end of this period epithelial activity is so great that groups of cells are forced outward toward the lumen forming projecting clusters called pseudopapillae. The lumina are filled with secretion consisting of mucus, partially disintegrated cells and detritus. Mitoses are present in surface and gland epithelium.

In the stroma, the bodies of the lymphoid cells increase in size, the nuclei are less closely packed and cell boundaries are visible. Individual
cells can be recognized. These changes first occur and remain most marked beneath the surface and around the circumference of capillary vessels. The changed cells are decidua cells. Toward the end of this period, capillaries clogged by innumerable red blood cells become plainly visible. As this stasis, and probably the permeability of vessel walls increases, edema of the stroma develops.

Thus the premenstrual or pregravid stage consists of secretory activity, engorgement and edema. Barthelmez (1931) (7) obtained specimens from Culbertson and found a shrinkage of fifty per cent in the thickness of the human uterine mucous membrane, preceding extravasation and desquamation. The gland cells showed a reduction in size and a variability in degree of involution and the entire spongy zone was not always lost.

**Menstrual Period**

The menstrual period (Fig. 3.) is ushered in by the appearance of red blood cells, singly and in groups sufficiently large to obscure most other details. These cells are most numerous beneath
the surface epithelium. They then appear within the lumen of the uterus.

The theories of mechanism of menstruation are:
1. Schroeder(54). The compacta and spongiosa necrose piecemeal and are cast off in small fragments recognizable in the menstrual blood. The uterus is then lined with the basal layer.
2. Gebhard(21). Subepithelial hematomata are formed and red blood cells are found in gland lumina.
3. Corner(2,53), in Macacus rhesus, found a resting endometrium during menstruation and described the process as due to diapedesis through the unchanged mucosa.

As a rule, after the second day of menstruation, the mucosa is thin and its surface is devoid of epithelium except where gland fragments adhere to the stroma. Regeneration takes place during the time the last portions of destroyed tissue are cast off.

Repair of the Endometrium

There have been no accounts of the actual steps occurring in repair of the endometrium. Maximow(37) states the process is complete by the seventh day.
after menstruation has begun. This seems an unusually long period in those women who menstruate 3-4 days, and from the study of surgical slides it is my opinion that regeneration has been completed simultaneously with the end of the menstrual period. Microscopically, the evidence at hand shows that repair of the endometrium follows the laws of formation of fibrous tissue and tissue repair (31, 32). The cyclical growth and degenerative processes of this tissue are initiated and controlled by factors we do not fully understand and which we attribute to hormonal influences of the ovary and pituitary in particular.

In the healing of wounds by primary union fibrillar fibrin appears within a few minutes in the exudate between fresh surfaces as a bridge and this remains to form adult fibrous tissue. The conditions for the formation of fibrillar fibrin are met most completely in coagulation of blood. Anything which prevents the coagulation of blood, prevents the formation of fibrillar fibrin and granular fibrin is laid down. Granular fibrin may react in one of two ways: either it
may be resorbed and replaced by fiber bundles de-
posited by fibrin bundles from fibroblasts, or
the formation of adult fibers does not follow, and
previously agglutinated surfaces separate.

The discharge of menstrual blood, initiated
by degeneration of the corpus luteum, must be com-
plete within the endometrium before regeneration
can occur, for menstrual blood is non-coagulable.
Blood, capable of coagulation, fills the cracks
and crevices of uneven tissue about the basal
glands and stroma and is also found on the sur-
face of the endometrium (Fig. 4). A layer of
delicate fibrin bridges the blood-filled spaces
and other fibrin bundles form either parallel
to the surface or in a network beneath. Figure 5
shows a line of demarcation; fibrin formation
bridges the crèvices in the endometrium and this
will become the surface of the endometrium. Excess
fibrin formation is seen above this line.

Mononuclear leucocytes or polymorphonuclears
can be found along the bundles of fibrin (Fig. 6)
or in the network. Those cells beneath the sur-
face become spindle or stellate-shaped and their
processes extend along the fibrin threads. These cells on the surface become flattened and serve as a support over which epithelial cells from gland fragments may glide (Fig. 6). The excess fibrin formation on the surface is released (Fig. 7) as the epithelium of the glands covers the surface. The fibrin above the surface in which is enmeshed mononuclears and polynuclears is freed in a manner analogous to the release of a scab (Fig. 7). In this fashion the surface epithelium becomes intact with the termination of menstruation.

The picture of the premenstrual or pregravid mucous membrane of the uterus is the one most likely to be confused with the irregular forms found in hyperplasia of the mucous membrane. There are cases of normal premenstrual swelling, however, with a microscopic picture of hyperplasia of the endometrium (Fig. 17), and the only way to differentiate them is by the clinical history.
B. The Endocrine System and Its Relationship to Menstruation

Normal Ovary

A study of menstruation and menstrual variations requires as a prerequisite a study of the ovary. For, regardless of the innumerable factors which may or may not influence menstruation and the growth of the sex organs, they are directly controlled by the internal secretion of the ovaries.

The functions of the ovary comprise the activity carried on within the ovary itself; also that which is influenced by hormonal control of internal secretion.

I. Within the ovary, there is the growth and development of the egg until it is ready for fertilization.

II. Changes without the ovary dependent upon the ovary are:

1. Prepubertal development of primary and secondary sex characters and to some extent normal bodily growth.

2. Onset of puberty
4. Cyclical changes in endometrium
5. Maintenance of maternal soil for nourishment of growing embryo.
6. Preparation of genitalia (in animals) for mating and ovulation.
7. Changes in the breast necessary for lactation.

A study of the hormones or the physiology of the ovary presupposes a knowledge of the constituents of the ovary. A rather detailed description will therefore follow.

**Embryology**

Sexual differentiation in female embryos can be distinguished when they are from 18 to 20 mm. long. The plica urogenitalis appears first as a longitudinal fold on both sides of the midline on either side of the root of the mesentery. This fold contains a mesonephros. A thickening of the mesodermal epithelium on the median surface is the anlage of the primordia of the gonads. This epithelium is separated from the mesonephros
by a layer of mesenchyme and is made up of two kinds of cells (Fig. 8). One kind is small, irregularly cuboidal or columnar, arranged in several layers, the other is large and spherical and is scattered between them. These are the primitive sex cells and are much less numerous. Proliferation of the germinal epithelium is directed toward the mesenchyme so that sex cords composed of the two kinds of cells are formed.

The mesenchyme at the same time grows into the sex cords and loosens them into thin, irregularly arranged, medullary cords. These contain primitive ova and may show a tendency to form primitive follicles, if the ova become surrounded by a single layer of small, follicular cells. There is usually little trace of these in the adult ovary. Not until the fourth or fifth month is the tunica albuginea formed (Fig. 9). At this time a new layer of epithelium is formed on the cortex, and mesenchymal strands proceed toward the cortex and subdivide into cell clusters. When the mesenchyme reaches the surface layer of the germinal epithelium it spreads along this surface
and forms the albuginea of the ovary and this separates the epithelium of the surface from the definite cortex.

**Histology**

In the later embryonic or adult ovary(37), then, we have the surface epithelium, and it is the accepted opinion that it is developed secondarily and separated from the cortex by the tunica albuginea, which thus prevents the formation of new ova from the germinal epithelium (Fig. 9). There is evidence of new formation of ova in some animals, the mouse particularly, but this fact has not been demonstrated in the human and it is still believed that the total number of ova are determined in the formation of the ovary.

The cortex or zona parenchymatosa is the broad peripheral layer of firm consistency in which follicles are found in the connective tissue stroma.

Medulla or zona vasculosa is the inner softer area of connective tissue containing many blood vessels and devoid of follicles. The rete ovarii is found here in later embryonic stage composed of epithelial tubes lined with small dark cells.
which divide and anastomose to form a network with a distinct, sometimes large, lumen. It is believed these tubules either occur through an ingrowth of mesonephric tubules (the epoophoron) into the hilus of the ovary, or that they are derived from the germinal epithelium and grow into the underlying connective tissue with the medullary cords, before the second development of germinal epithelium and formation of tunica albuginea.

Growth of the ovum involves the formation of:

Primary follicles or primordial follicles

I. Through progression these develop into:

1. Growing follicles

2. Mature or graafian follicles during which time ovogenesis and maturation of the ovum occur.

3. Rupture of graafian follicle and ovulation

Depending upon the fate of the ovum we have:

4. Formation of corpus luteum spurium

5. Formation of corpus luteum vera

II. Regression of primary follicles leads to:

1. Involution of follicles--atresia

2. Formation of interstitial cells.

Primordial follicles are most numerous, the younger the individual--Waldeyer's figures are
100,000 in the newborn--35,000 at puberty according to Henle and seldom seen at climacterium. However, Häggström(27) counted 400,000 in ovaries of a 22-year old woman.

These follicles (Fig. 9) are found most often in the outer periphery of the cortex as an uninterrupted layer under the tunica albuginea and may be the only ones present at the end of the embryonic period.

They consist of a slightly oval cell 42-45 u. in diameter, in the center of which is the round ovum and around which are 7-10 small squamous follicular cells.

Progressive development of the primary follicle consists in growth and structural changes in the ovum. The egg cell develops in a layer of connective tissue 60-80 u. in diameter with concomitant enlargement of the nucleus, disintegration of mitochondria which becomes evenly distributed in the protoplasm, and appearance of yolk granules in the deeper parts of the cell body. A distinct cell membrane on the surface becomes the zona pellucida (Fig. 11).
Growing Follicles

Increase in size of the follicle takes place by multiplication of follicular cells (Fig. 10). The squamous cells which surround the primary follicle, first become cuboidal and then columnar and surround the ovum in one layer in a radial manner (Fig. 11). As new cells form they are forced to the periphery so that on the surface of the ovary the cells take a regular form and radiate as stratified epithelium. The follicle takes on a distinct oval form by accumulation of follicular epithelium on one side of the ovum. The larger mass of epithelium and the ovum is directed toward the deeper portion of the follicle. The follicle recedes from the superficial to the deep layers of the cortex.

At about 2 mm. in size several irregular intercellular spaces appear between follicular cells usually in the peripheral eccentric portion. These spaces are filled with fluid secreted by the follicular cells and is called liquor folliculi. As the liquor increases, separate cavities unite forming one large cavity (Fig. 10). This pushes the
ovum, with follicular cells surrounding it, to one side of the follicle where the mass of follicular cells surrounding the egg remain in connection with the peripheral layer. The follicular fluid never comes in contact with the ovum. Also the periphery of the follicle always keeps an uninterrupted layer of these cells in contact with surrounding connective tissue.

At size of 4 mm. the follicle has a polar structure. On one side, usually that toward the medulla, the ovum is embedded in a mass of epithelial cells called the cumulus oophorus or discus proligerus (Figs. 10 and 11). On the other side the stratified epithelium forms a continuous even layer.

**Theca Folliculi**

Due to stretching of the spindle-shaped connective tissue, by the growing spherical body, the reticulated fibers of the stroma become arranged in concentric layers around the basement membrane of the granulosa layer. This is called theca folliculi and divides into two layers (Fig. 10).

**Theca interna folliculi** composes the layer
immediately surrounding the basement membrane. In it the loosely arranged connective tissue cells increase in size, become loosely arranged with very thin fibrils between and an increasing number of blood capillaries develop.

Theca externa folliculi composes the outer layer and retains its dense structure of concentrically arranged stroma cells. However, there is no sharp line of demarcation between the two layers of theca or between the surrounding stroma.

Because of the rapid proliferation of follicular epithelium and progressive secretion of follicular liquid, the position of the follicle again changes, so that the cumulus oophorus moves toward the surface of ovary and the follicle extends more and more toward the free surface of the ovary.

**Mature or Graafian Follicle**

It is difficult to tell when a follicle becomes mature. When mature, the follicular epithelium or membrana granulosa is separated from the theca by a so-called glassy membrane (Fig. 11) which adheres everywhere to the basement membrane. The cumulus oophorus has receded from the external pole of the follicle nearest the surface of the
ovary and is now located on the side wall. Inter-
cellular spaces filled with liquor appear between
the follicular cells of cumulus under the ovum,
so that the connection of the ovum with the wall
of the follicle is loosened. The ovum is then con-
ected to the granulosa by several epithelial
strands called retinacula. Also follicular cells
remain attached to the ovum. These are called
corona radiata, and show a distinct radial arrange-
ment on section.

The ovum is 100 u. or more in size containing
a nucleus of 25 u. in diameter (Fig. 11). It is
surrounded by a thick membrane, the volemma or zona
pellucida directly adjacent to protoplasm. The
perivitelline space between egg cell and zona
pellucida is not definitely demonstrated.

Theca externa is fully developed with concent-
trically arranged fibers and cells and large blood
vessels as well as the theca interna with several
layers of large, flattened or polyhedral epitheli-
cid cells with oval nuclei and fine lipoid drop-
lets in their protoplasm (Fig. 10).

It is during this time that maturation of the
ovum occurs.
Ovogenesis comprises periods of multiplication, growth and maturation of the ovum. Multiplication takes place in the primordial follicle stage, and it is during the time the follicle is growing that growth of the ovum occurs, and maturation may be completed in the last few hours before rupture of the graafian follicle. In this process the primary ovocyte undergoes two successive mitotic or maturation divisions. Four cells have haploid number of chromosomes. A large one remains for further development; the other three are small and are thrown off as rudimentary structures and degenerate.

Rupture of Graafian Follicle

As soon as the ovum is ready for fertilization the purpose of the follicle has been served and the graafian follicle ruptures. Theoretically this occurs through an increase in intrafollicular pressure, the superficial part of the follicular wall which bulges on the surface of the ovary becomes thinner and thinner, and the blood vessels are compressed. A small spot occupies the apex of bulging, the stigma, and yields to the pressure of the enlarging follicle and bursts. It has been
suggested that follicular fluid oozes into the peritoneal cavity through a small split in the wall of the follicle on the free surface of the ovary, and the ovum with its corona radiata is torn from the cumulus and is discharged together with the liquid. Ovulation, the process which frees the ovum and enables it to meet the male sex cell for the purpose of fertilization, is thus completed.

**Corpus Luteum**

The graafian follicle then becomes the corpus luteum (43) and its subsequent development depends upon the fate of the ovum. If it is not fertilized, pregnancy does not supervene and the corpus luteum spurium or corpus folliculare menstruationis develops. If pregnancy occurs, corpus luteum verum or corpus folliculare gravidatatis develops. Both of these are identical the first ten or twelve days.

When the wall of the follicle collapses, the epithelial membrana granulosa is thrown into folds and appears thickened (Fig. 12). The cavity is irregular, angular, or stellate shape, and the contour of the entire structure is festooned.
At the base of the folds of granulosa, the cells of the theca interna accumulate in triangular masses; between the folds they are scarce or absent. The theca externa keeps its regular circular outlines. The former conception of hemorrhage from blood vessels of the theca interna is now considered erroneous.

The principal changes take place in the epithelial follicular cells which become thickened and folded and piled up in numerous layers and through mechanical pressure are drawn out radially. Hyper trophy begins at once and the cells attain a large size in a couple of days. The cell bodies which are oval or polyhedral in shape are called lutein cells; however, lipoid pigment is present only in traces.

Spindle cells of theca interna, plus a multitude of capillary spouts, penetrate radially into the thick layer of follicular cells. The connective tissue elements reach the inner surface of the folded granulosa layer, form a loose gelatinous connective tissue which covers the inner surface of the wall and leaves a free space in the
center. This is filled with remains of liquor folliculi, transuded sera and a varying, though usually a small number, of extravasated erythrocytes (Fig. 12).

**Corpus Luteum Spurium**

Fourteen days after ovulation, the corpus luteum menstruationis reaches the climax of its development and its greatest size. When menstruation sets in, hemorrhage occurs throughout the corpus luteum and it is called corpus folliculare menstruationis hemorrhagicum. Blood from the sinusoidal capillaries pours into the cavity surrounded by loose connective tissue. It mixes with serous liquid which had previously filled the cavity and clots. Here as in the reparatation of the endometrium the healing processes take place according to the laws of repair of wounds by primary intention. We find fibrin fibrils forming in an amorphous exudate and these fibrin fibrils are transformed into connective tissue fibrils (Fig. 12). A few cells, mostly mononuclear leukocytes, but a few polynuclears also, are present in the plastic material which first escapes. These cells arrange themselves in the
columns along the bundles of fibrin or in the meshes of secondary fibrin network. This continues until the final stage when the hyaline of corpus albicans is entirely replaced by the new fibrous tissue (Fig. 13). This fibrous tissue is eventually incorporated in the ovarian stroma and no trace of a corpus albicans can be found.

This theory explains the lack of surface contractions on the ovary for each corpus luteum which has developed; also the absence of a corpus albicans for every corpus luteum that has formed. A scar likely occurs in the repair of a very large corpus luteum hemorrhagicum or if hemorrhage into the corpus luteum fails. In the latter case, collapse of the cavity takes place and the fibrin fibrils bridge the smaller space with a resulting depression in the surface.

**Corpus Albicans**

Hemosiderin accumulates in connective tissue cells. Later streaks of hyaline occur between lutein cells. The theca lutein cells become incorporated in the stroma again. The whole structure is transformed into the small, irregular hyaline scar, white microscopically, corpus albicans (candidans
or fibrosum). This may eventually be obliterated as shown above.

Corpus Luteum Verum

If pregnancy supervenes and menstruation is suppressed, no hemorrhage occurs in the corpus luteum and the progressive development of follicular lutein cells proceeds undisturbed. The distinct cavity is filled with serous liquid. Involution begins the fifth or sixth month of gestation. After delivery it proceeds the same way as corpus menstruationis. Because it is larger, it is reasonable to believe it makes a retraction on the surface of the ovary.

In a study of endometria and ovaries our attention has been arrested by the repair these organs undergo in their cycles. Our medical literature mentions the occurrence of these stages, but nothing has been stated in regard to the methods by which they take place. The subject needs a vast amount of study, but the evidence at hand indicates that repair takes place according to the laws of wound healing.
Atresia

At most, approximately 400 ova discharge in ovulation, which means that 100,000 or more original follicles gradually disappear through involution and degeneration which process is called atresia of the follicle. This process begins in the early stages of extrauterine life, is prominent in the prepubertal period, occurs on a smaller scale during sexual years and is almost completed after the menopause. It may affect a primordial, a growing, or a larger follicle. The factors which regulate it are unknown. The process has been defined as a reaction of surrounding tissue to the presence of dead material which has to be absorbed. The dead material refers to death of the ovum.

In those primary follicles doomed to destruction, the ovum first shrinks, then degenerates. The follicular cells first destroy, then engulf the debris. These degenerate. The small cavity in the connective tissue is closed leaving no trace.

In growing follicles the ovum and follicular cells show various signs of degeneration. Connective tissue cells penetrate into the epithelium and absorb it by means of theca and blood vessels.
The cavity is filled with young fusiform or stellate fibroblasts, wandering cells and blood capillaries, which develop along fibrin formed in the follicular fluid. Remnants of degenerate, follicular epithelium are rapidly absorbed. The folded and collapsed zona pellucida may remain alone amidst connective tissue elements, surrounded by a broad, festooned layer of epithelioid cells of theca interna. Microscopically it looks like a corpus luteum, called corpora lutea atretica. Its final stage is shrinkage. The epithelioid cells may be broken up into separate cell islands, scattered in the stroma, which cells are designated as the interstitial gland.

**Interstitial Gland**

These interstitial cells are considered by some as a gland of internal secretion which has been made responsible for the sexual cycle as well as development of secondary sexual characteristics. These cells are best developed in the adult rabbit and are poorly developed in the adult human ovary. In the first years of life, atretic follicles are most numerous. At puberty many undergo involution. At the end of pregnancy they
may increase slightly for a short time. As stated above, the origin of these cells in post embryonic life is from the theca interna of atretic follicles and the interstitial gland reaches the height of its development when the ovary contains a maximal quantity of atretic follicles.

Hormones in Relation to Endometrium in Menstruation

Ovary

Physiology of the Ovary

A more or less detailed description of the histology of the ovary has been given so that we shall better be able to follow the physiology of this organ and its relationship to menstruation. Schroeder(25) (Fig. 14) has made diagrams which show the parallelism between the phases of the follicle and the endometrium during a normal menstrual cycle, between the ovary and endometrium in pregnancy and the follicle and endometrium in a typical case of hyperplasia of the endometrium.

The middle row of diminishing figures indicates the involution of the preceding corpus luteum. The upper row of figures illustrates the development of the graafian follicle. As it develops, the hormone produces characteristic growth changes
as previously described. Near the middle of the cycle the follicle bursts, ejects the egg and becomes a corpus luteum. The corpus luteum functions up to the twenty-eighth day and under its influence secretory changes in the endometrium take place. If the egg is unfertilized it is assumed death occurs on the twenty-eighth day. Then the corpus luteum begins to degenerate and gradually involutes. The cyclical changes have been described in the first part of this paper and are here illustrated.

In the second figure, the first part of the cycle resembles that of normal menstruation. If the egg is fertilized, the collapse of the corpus luteum and endometrium does not take place. The corpus luteum grows larger and continues its hormonal influence on the endometrium.

The endometrium persists as a secretory organ, becoming the decidua and retaining, as such, the characteristics of its premenstrual stage in a more pronounced form.

The third figure shows the follicle and endometrium in a typical case of hyperplasia of the endometrium. The top row shows the follicle developing, which at the proper time fails to burst,
discharge the egg and become a corpus luteum (ovulation). The follicle persists and continues to exert, by means of its hormone, a growth influence on the endometrium. The glands undergo an irregular hypertrophy. In the absence of a corpus luteum there is no secretory phase. In a typical case menstruation does not take place. The hyperplasia of the endometrium results in localized thrombosis and necrosis with subsequent crumbling and hemorrhage. The persistent follicle or follicles become cystic, and either by their own secretion or by that of the pituitary body the hyperplastic condition of the endometrium is maintained for an indefinite period.

Hormonal studies have been possible in the past fifteen years because it was in 1917 that Stockard and Papanicolaou (57) discovered that cyclical changes occurred in the vaginal epithelium in laboratory animals and that changes in time relation to oestrus could be determined by studying vaginal smears. They discovered a secretory activity of the vaginal epithelium at the time of oestrus which resulted in final cornification of
the epithelium. Hence it has been possible to carry on more and more detailed experiments in this subject. Dogs, pigs and cattle display periodic exhibitions of sexual excitement; humans and primates menstruate. The term "oestrus" has a different meaning for different classes of animals. It was first applied to sexual desire and was associated with animals which go into heat; then to the secretory changes of the vagina accompanying ovulation. It was an early idea that menstruation of the human species corresponded to oestrus of the lower animals, but it is now known it is contemporary with the time of ovulation.

The discoveries in relation to menstrual hormones began ten years ago with the work of Allen and Doisy in 1922 who used the discovery of Stockard and Papanicolaou relating to oestrus changes in uterine and vaginal epithelium of rodents and were able to identify an ovarian hormone. The greatest bulk of this work has been published in the last five years. We shall endeavor to describe what is actually known in these works, and even such a discussion will bring up many disputed points.
More Than One Ovarian Secretion Discovered

Antagonistic Action.- Fraenkel’s (15) and Loeb’s (35) experiments on the production of placentomas illustrated a sensitizing power of the uterine mucosa which was believed due to an inhibiting influence of the corpus luteum on the follicle. All of the changes in the endometrium could not be explained on the basis of a single hormone.

Corner, in 1928 (10), carried on experiments which demonstrated the dependence of the uterine mucosa on the corpus luteum for the production of a progestational or progravid state:

1. Ovaries or corpora lutea were removed from rabbits fourteen to twenty hours after mating—fertilized ova were in the tubes from four to ten hours.

   Typical progestational endometrial changes did not take place. Embryos died in four days.

2. A doe rabbit was mated and 18 hours later ovaries and a small portion of the uterus was removed. Corpus luteum extract administered for five days. Uterus developed characteristic progestational changes.

3. Same experiments as 2, using folliculín instead of corpus luteum. No changes.
Allen and Corner removed the ovaries from pregnant rats and administered corpus luteum extract and carried the pregnancies to term. The controls invariably aborted.

The hormone of the follicle was then called "oestrin". It is considered essentially a growth hormone on account of its wide distribution in growing animals and plants, its presence in the male and its specific influence during the proliferative stage of the menstrual cycle.

Corner called the extract of corpus luteum "progestin", because its action was antagonistic to oestrin and its specific function to sensitize and prepare the uterine mucosa for nidation of the fertilized egg. Menstruation is now thought to be the result of retrogression of the corpus luteum.

If the corpus luteum is removed during the progestational period of pregnant animals, oestrus and ovulation occur prematurely. During pregnancy, oestrus and ovulation do not usually take place due to inhibition by the persisting corpus luteum.

Loeb(35) removed the corpora lutea in pregnant animals and was able to produce ovulation without
disturbing the course of pregnancy.

Frequently the corpus luteum persists during lactation and there is an inhibitory effect on ovulation during that period.

Surgical removal of the corpus luteum during premenstrual periods leads to premature menstruation.

**Synergistic Action.** - In addition to an antagonistic action between oestrin and proestrin, there is a synergistic action. Corner(2) and Hartman(29), working independently on monkeys found that primates sometimes menstruate in regular course without any preceding ovulation or corpus luteum formation in the ovaries and no typical endometrial, premenstrual changes are present(53). If oestrin was injected into castrated monkeys, menstruation took place without premenstrual proliferation of the mucosa. Corner, also Hisaw, injected oestrin into monkeys, followed this with injections of progestin and obtained true menstruation with characteristic premenstrual proliferation. Hisaw and Leonard obtained the same results with spayed rabbits.
Hisaw has isolated a crystalline fraction A and a noncrystalline fraction B from sows's corpora lutea:

A causes relaxation of pelvic ligaments;
B promotes changes peculiar to progestin.

Pituitary

Physiology of the Pituitary

It has been known for thirty years(19) that an interrelationship existed between the internal secretion of the ovaries and that of the pituitary(23, 34). We are here concerned with the anterior lobe of the pituitary which, histologically, contains three types of cells that are distinguished by their staining reactions. Two kinds have an affinity for stains and are called chromaphile cells, an eosinophilic and a basophilic variety. One kind has no affinity for stains and is called chromaphobe cells.

The acidophile cells are polyhedral, with a nearly homogeneous cytoplasm, which is almost filled with coarse acidophilic granules. The nuclei are small, spherical and stain deeply with hematoxylin.
The acidophile cells are polyhedral, with a nearly homogeneous cytoplasm, which is almost filled with coarse acidophilic granules. The nuclei are small, spherical and stain deeply with hematoxylin.

The basophile cells are somewhat larger, the cytoplasm being filled with coarse basophilic granules and the nucleus slightly eccentric.

The chromaphobe cells are much smaller than the other two types, and not so well outlined. The cytoplasm is scant and the nucleus round, small and rich in chromatin.

Bailey and Davidoff found eosinophilic adenomata in acromegaly and no basophilic granules, so they believe the eosinophilic granules represent the secretory product having to do with growth.

Histological examination of the hypophysis in castrated animals shows a marked increase in the number and size of basophiles. It is believed these cells elaborate the hypophyseal sex hormone.

Increase in size of the hypophysis is the rule in pregnancy, especially in the later stages. Infrequently this is large enough to cause pressure
on the optic chiasma. Enlargement and coarsening of the features in late pregnancy is likely of pituitary origin. The chromophobe cells practically cease to exist as such, being transformed into large cells, with clear and somewhat irregular nuclei (Schwangerschaftzellen). It is the increase in these "pregnancy cells" which is responsible for the enlargement of the anterior lobe. Ordinarily they have returned to their normal state seven weeks after parturition.

The first definite results of interrelationship between ovaries and pituitary were obtained by Evans and Long (12) in 1922 who injected alkaline extracts of beef pituitary into young rats. Their conclusions were that the extract:

1. Promotes growth to the extent of gigantism
2. Luteinizes the follicles
3. Inhibits ovulation and oestrus.

Smith and Engle (55) in 1927 precipitated oestrus instead of delaying it. They introduced hetero-transplants from the rat, guinea pig and rabbit into the mouse, and by as early as the nineteenth day of life and forty-eight hours after the first
transplant, the mice mated. They called this abnormal fertility superovulation and superpregnancy. Smith (56) 1928, induced precocious sexual maturity by pituitary homeotransplants. Aschheim and Zondek (3) in 1928 transplanted fresh anterior lobe tissue into infantile mice and reached the following conclusions:

1. The hormone of the anterior lobe of the hypophysis, and only this, sets the ovarian function in motion and brings the mouse to sexual maturity.

2. The hormone of the anterior lobe of the hypophysis which produces oestrus in the female infantile mouse is present both in the male and female gland.

3. This hormone is still present in the female hypophysis after her own ovarian function has ceased, i.e., after the climacteric.

4. The hormone of the anterior lobe that produces oestrus in virgin mice is identical in animals and humans.

They found that the anterior lobe hormone has no effect on the vagina or uterus of an ovariectomized animal. In the normal animal it causes oestrus
changes in the vagina and uterus and also ovulation and luteinization in ovaries. Their conclusions were: "The hormone of the anterior lobe is the motor of the sexual function. This hormone is primary, the ovarian hormone is secondary. The anterior lobe hormone brings the follicular apparatus into action, discharges the follicle-ripening and mobilizes secondarily the ovarian hormone in the follicle cells."

The egg does not play the chief role in this process since hormone production can take place in the follicle without the egg.

They found that the anterior lobe hormone is present in high concentration in the blood and urine of pregnant women. By injecting small quantities of urine of pregnant women into the circulation of immature mice, constant reactions were observed in the ovaries 96 hours after the first injections which were:

1. Maturation of the follicles and appearance of oestrus
2. Marked hyperemia and hemorrhage into the enlarged follicles (Blutpunkte)
3. The formation of corpora lutea and the luteinization of many corpora a-tretica, i.e., corpora lutea with imprisoned ova.

The hormone which produced the above was isolated in chemical form and called "prolan". Prolan was compared with the alkaline extract Evans and Long had used and the two substances did not produce the same results. The extract of Evans and Long exerted a growth influence and its effect stopped at puberty when prolan first exerts its influence.

Kuestner and Plant--Liebeschitz isolated a substance from the anterior lobe called "praephyson" which regulated body metabolism. Prolan caused the same metabolic chemical reactions.

Prolan does not always behave the same:

Reaction 1 consists in normal ripening of the follicle with rupture and deposit of the ova in the tubes and the formation of a normal corpus luteum.

Reaction 2. The follicles would not rupture, the eggs would be retained and the entire cell apparatus of the follicle became luteinized.
If the potency of the extract was then increased, the entire ovary would be converted into a single lutein body and follicle ripening no longer possible.

There are steps in the hormones of the anterior lobe which are not clear. To date Zondek summarized the knowledge as follows:

1. Growth hormone
2. Prolan \( A \)-follicle ripening hormone superordinated
3. Prolan \( B \)-luteinizing hormone \{ sex hormone
4. Metabolism hormone.

Prolan \( A \) and folliculin (oestrin) have properties in common. Prolan \( A \) sets off follicle ripening and incites theca cells of follicle to production of folliculin which induces the proliferative phase of the endometrium.

Prolan \( B \) and corpus luteum secretion (progestin, lutin) have properties by which they effect the change of granulosa and theca cells to lutein cells and incite in them the production of progestin (lutin) which changes the proliferative phase of the endometrium to one of secretion. Chart(3) in Klin.Wochenschr.,1930,9,1,247 (Fig. 15) shows cor-
relation of anterior lobe of pituitary, ovarian hormones and endometrium and vaginal changes.

Wiesner (60, 61, 62), 1929-1930, reached much the same conclusions under a different terminology which is listed as follows:

Ovarian Cycle:

Alpha phase—oestrus cycle governed by oestrin, folliculine.

Beta phase—progravid or promenstrual governed by progestin.

During alpha phase—hypertrophy and cornification of vaginal epithelium.

Beta phase—secretory or decidual change in uterine mucosa also—mucification of vaginal epithelium.

Grafts and acid extracts result in only the first or alpha phase—oestrogenic. With Evans alkaline extract of posterior lobe, the beta phase could be obtained without oestrus or mating having occurred first, so the corpus luteum must depend for its action upon some agency higher up which can, itself unaided, perform the function of corpus luteum—called "kyogenic". He called
the secretion from the anterior lobe of the pituitary "gonadotrope" and divided it into two phases, the first oestrogenic—Rho 1 corresponding to Zondek's Prolan A. The second kyogenic—Rho 2 corresponding to Zondek's Prolan B. Heat and alkali are inimical to Rho 1. Heat and alkali are favorable to Rho 2.

This leads to a discussion of the theories of menstruation of which two types are now recognized—one preceded by ovulation, and the other is not. Of significance for this paper is the fact that E. Allen, and later, Hartman(29), were able to produce long flowing spells in castrated monkeys by administering oestrin (as amniotin) over a period of six to eight days and then suddenly withdrawing it. In Hartman's cases, the resultant bleeding lasted from eight to twenty days. He secured the same results in normal adult monkeys, amenorrheic adults and babies a year old, by the injection of amniotin (oestrin) into a hypophysectomized baby monkey without macroscopical or microscopical evidence of uterine bleeding. So he had
concluded that the stimulus for bleeding comes directly from the hypophysis and is independent of the "hyperplasia, swelling or even congestion of the uterine mucosa". Novak(47) believes menstruation is characteristically and usually preceded by ovulation but bleeding can take place without ovulation for typical dysfunctional bleeding is invariably accompanied by cystic follicles and absent corpus luteum. This bleeding may have a certain periodicity that simulates true menstruation excepting for its abnormal duration and amount.

During the last five years an enormous amount of work has been done on the glands of internal secretion. Hormones have been isolated and some confusing problems have been cleared. There is still a tremendous amount of unravelling to be done. Clinicians are eager to apply the results of animal experimentation to humans, but we cannot reason that what occurs in certain animals will always apply in man. Even different species of animals differ in their responses to certain experiments, and scientific investigators differ
among themselves as to their results.

**Thyroid Gland**

Changes in the thyroid gland (36) which take place during the various periods of female sexual function and especially during the time of puberty and pregnancy show a true connection between the thyroid gland and female generative gland. The ovary is not only influenced by the thyroid, but also a disturbance of thyroid gland function leads to changes in female genitalia (11). The reciprocal reaction between the two is not known. Some cases support the viewpoint that a diminished function of one gland liberates an increased function of the other; however, all facts do not fit into this scheme, for in exophthalmia as well as myxedema, a hypoplasia of the female generative organs usually occurs and menstrual irregularities accompany the adolescent goiter.

Engelhorn would make the corpus luteum responsible for thyroid changes. During pregnancy, for instance, development of the corpus luteum hinders ovulation which leads to a temporary hypofunction of the ovary, and later a hyperplasia of the thyroid
is developed. In his later lines on corpus luteum, he refers in a similar way to thyroid gland swelling at the time of puberty and menstruation. The theories of etiology on this subject are almost as many and varied as there are authors. We do know that changes occur in the thyroid and generative glands at menstrual periods; changes in the generative glands are found following removal of the thyroid, and are found in the thyroid after castration. The thyroid exerts an influence on growth and differentiation of the generative gland and in development of secondary sex characteristics. Because of lack of proper function of the thyroid, the generative glands remain infantile, and imperfect development leads either to no function or imperfect function. The ovary shows hypoplasia and small cystic degeneration.

**Adrenals**

The influence of the adrenal bodies on the genital system has been observed most often in conjunction with adrenal tumors. These occur mostly in children; and the clinical picture is one of precocious growth of the body generally,
and of the sexual organs particularly, an overgrowth of hair and fat, pigmentation of the skin and a lowered mentality. This condition is more common in females than males; however, there is a tendency to increase the male primary and secondary characters to a greater degree than the female. When the condition does occur in the male, the result is the infant Hercules, and these children may show true sex precocity. There is an enlargement of the adrenals during breeding and pregnancy.

Endometrium

The evidence of an endometrial influence on the ovary is clinical\(^*(4,6,48)*\). Following hysterectomy in a woman in the childbearing years, the ovaries will function from three months to two years, after which time the patient is thrown into an artificial menopause. If a small amount of endometrium is retained, these reactions are avoided.

Hormones Which do not Influence the Endometrium Directly

Parathyroids

No direct relationship has been established between the parathyroids\(^*(51,59)*\) and the female genital organs. No morphological changes in the parathyroids have been noted during pregnancy.
or menstruation. Tetany, however, a clinical manifestation of insufficient parathyroid function, is prone to occur in menstruation in pregnant and puerperal women as well as in gynecological diseases or in those operated on for gynecological conditions. Tetany in new born infants, the children of tetanic mothers, is usually fatal within a short time after birth.

**Thymus**

The fundamental problems of the thymus remain unsolved. It is possible there is a true hyperplasia of the thymus in a great proportion of all the cases of exophthalmic goiter. In its relation to the gonads practically all the work has been done on the testes. Pappenheimer, however, quotes one reference to the ovaries: Valtroti in 1909—who states that removal of the thymus in rabbits is followed by degenerative changes in the ovary—namely, a scarcity of primitive follicles in the outer zone and regressive changes in the follicles of the inner zone. These alterations were regarded as merely accompanying the general malnutrition of his animals.
It has been suggested that the thymus might have an inhibitory effect on other endocrine systems because it is largest in infancy and gradually diminishes in size until puberty, when other glands show a proliferation or enlargement.

Pineal

There have been nearly seventy-five cases of tumors of pineal body (38) with necropsy findings. The clinical picture associated with disturbances in function appears in prepubertal years because involution of the pineal occurs at puberty. The clinical picture consists of pressure and neighborhood manifestations in the brain; early sexual development evidenced by enlarged genitalia, pubic hair, general body hair, early change in the voice. There may be precocious mental development as shown in maturity of thought and speech and general bodily overgrowth, to the extent that a child of 6 or 7 years may have the appearance of a child near puberty. Under ordinary conditions the function of the pineal is of minor significance in the general activity of the endocrine system.
Pancreas

A diabetic woman will have a disappearance of sugar in the urine during the latter half of her pregnancy with a return to its former severity after delivery, due possibly to the supplementary action of the fetal pancreas (2).

Menstrual disturbances depend upon the severity of the disease. It may cause amenorrhea, sterility, premature menopause and atrophy of the uterus.

Part II. Hyperplastic Conditions of the Uterus

I. Hyperplasia of the Endometrium

Hyperplasia of the mucous membrane of the uterus (13,14) is considered a pathologic entity when it is present as the only variation in the gross appearance of a uterus and not when associated with myomata, inflammations and the like. The condition may appear at any time during the years of sexual activity and also after the menopause.

The age distribution of the forty-one cases who entered the surgical service of Halstead Hospital during the past year is shown below:
Below 20 years.....1 case
20-29 " .....4 cases
30-39 " .....13 "
40-49 " .....16 "
50-59 " .....7 "

First in frequency are the cases that appear at the menopause. More adolescents are affected than these figures would indicate, because medical treatment of the thyroid-ovarian and nervous disturbances is effective in most instances.

Diagnosis is made on a history of more or less regular menstrual bleeding up to the time of the menopause, when the flow may be repeatedly delayed or an entire period missed, with a subsequent large hemorrhage.

These forty-one cases were submitted to the following operative procedures:
- Dilatation and curettage.............15 cases
- Defundation..........................16 "
- Dilatation and curettage--later de-
  fundation............................3 "
- Supracervical hysterectomy...........5 "
- Vaginal hysterectomy..................2 "
In this way 34 out of the 41 women have had a chance for normal functioning menstrual lives which is highly desirable in these women with a delicate endocrine-nervous balance. The supra-vaginal hysterectomies were done to conserve time in operations in poor operative risks, and the vaginal hysterectomies in two women six and eight years after the menopause who were suspected of having carcinoma of the fundus.

**Macroscopic Picture**

Macroscopically, the endometrium may be irregular and shaggy (Fig. 16) in places, or it may be the site of soft knot-shaped polyps, often spongy and bright or dark red. It may be thickened from 15-25 mm. as in Figure 16 where the endometrium was 25 mm. thick. Sometimes it is bloody throughout. The boundary between endometrium and uterine muscle is macroscopic unless adenomyosis is present. These changes begin in the basal layer and lead to a general hyperplasia in which the glands take on irregular forms with outbranchings and cyst formations. Connective tissue stroma also shows irregular proliferation.
Differential Diagnosis

Differential diagnosis must be made from (1) a high grade premenstrual state (Figure 17 gives microscopic picture), which on cross-section shows a glassy, transparent, regular swelling. In hyperplasia, thickening of the mucous membrane occurs at any time, not just at the premenstrual stage.

(2) Decidual formation, (Figs. 18 and 19) which is bulky and shows angulations and smooth swellings which simulate a quilted appearance. Hyperplasia forms more knob-shaped, round polyps which often have small pedicles.

(3) Polyps of great size which owe their existence to a local anomaly (22).

(4) Diffuse carcinoma of the body in which the growth may be shaggy but is friable, and yields curettings of much greater volume.

Hyperplasia can involve the entire corpus mucous membrane, most often the fundal portion, or a single area. Sometimes smooth prominences are more or less sharply circumscribed. When there is a tendency to necrosis, congestion in vessels, and hemorrhage, especially in the lower portion,
it may be difficult to distinguish from menstrual necrosis.

**Microscopic Picture**

Microscopically, hyperplasia occurs in surface epithelium, glands, connective tissue and blood vessels. The following pictures have been described as diagnostic:

1. Absence of three endometrial layers (Albrecht(1) and Hartje(28)), Figure 20;
2. Grouped vessels with thick walls (Henkel(30)), Figure 21;
3. Epithelium sharply defined against the lumen (Fraenkl(15)), Figure 22;
4. True intraglandular papillae;
5. Glandular hypertrophy with pseudopapillae.

Two of the cases reviewed for this paper were in women 25 and 40 years of age, each with an irregular menstrual history from the time of the menarche. The endometrium from both of these was of a different form from any of those described. Here glands are scarce (Fig. 23), even in the basal layer, and in the stroma, extending from the basal layer, are multitudes of thin-walled blood vessels in sparse connective tissue stroma. Attention is arrested by the resemblance to gran-
ulation tissue.

Glandular Changes

Consensus of opinion, places most importance on the absence of the three divisions, compacta, spongiosa and basalis, in the endometrium (Fig. 20). Here the abundance of glands and stroma is divided freakishly. Twisted tubes course perpendicular to the surface, the irregular, branching ones predominating. These lead to the stage of ramifications and cyst formation. Cyst formation has been attributed to constriction by the stroma. Inversion of glands is only apparent and is caused by branching, papillary and crested proliferation on connective tissue that appears little more than a groundwork for epithelial spaces. These gland ramifications may resemble malignancy.

The epithelium, which often becomes high and cylindrical, may be in two rows (Fig. 22) and the surface may assume the character of indented papillae with active epithelial new formation. The inner edges may be smooth. In other places there may be an absence of epithelium, and in very occasional cases, cuboidal cells may form a basal layer under-
neath the cylindrical cells. Then in the dilated portions of glands or cysts, it is low; however, there may be an increase in cells in proliferation cysts. In later stages these characteristics may be obscured by involution, necrosis, edema or maceration. A stratified ball in the lumen of the glands reminds one of prostatic concretions (Fig. 20).

Connective tissue is rich in cells and there is an astonishing rapidity of multiplication of spindle cells (Fig. 22). A moderate infiltration of leukocytes occurs in connection with hemorrhages--also lymphocytosis. In later stages the spindle cells are very long and collagen fibrils may sometimes be found in all layers. The older the process, the more collagen formation of fibers.

Hyperplasia can replace wide and thick layers of musculature completely or almost completely, and it gradually borders over into adenomyosis (Fig. 24).

Blood Vessels.- The above pictures occur in the presence of marked edema, little edema, congestion, stasis or thrombosis or in the presence of hemorrhage into the tissue. This has been
termed the "histological unrest of the capillaries".

The fundamental difference between hyperplasia of the mucous membrane (Fig. 20) and all other forms of hypertrophy (Fig. 17) is that it does not, or only imperfectly, participates in function and it lacks the morphological signs of a pregravid mucous membrane.

**Pathogenesis**

Many theories have been advanced to explain hyperplasia of the endometrium and it is not difficult to find cases to illustrate each theory(24, 32, 41, 44, 45, 46, 52). They fall into two classes relatively--those having to do with hormonal, and those with local conditions. The theories of physiology of the ovary and pituitary glands earlier described have indicated the mechanism of this pathologic physiological disturbance: however, the instigating factor concerned may be as elusive as life itself. We shall discuss first:

**A. Changes in the Endometrium Due to Hormonal Control**

**1. Nervous Stimulation**

The history and course of clinical cases has led to the opinion that the stress and strain of life on women with a general nervous instability
may cause a reaction characterized by profuse and irregular menstrual flow. The nervous instability may be endocrine in origin, bacterial, and in the last analysis chemical; but when the irritability of the nerves is reduced, cure may result and especially so in early cases.

This group does not offer an opportunity for direct study of tissue. A typical example is that of a widow of 47 years who was often in the presence of a man whose wife had been committed to an institution for the insane some fifteen years previously. During January, February and March 1931 this woman had almost constant bleeding, and at intervals, moderate hemorrhage to the extent that her hemoglobin was 60 per cent (Sahli) and red blood cells 3,700,000. Bleeding started during the time a bill was before the legislature of the state making divorce from the insane legal. At the time the patient came for treatment she had a very profuse flowing spell or moderate hemorrhage every time she attended a social function with this gentleman. The flowing stopped after ten days of absolute bed rest on heavy doses of
sedatives, and during these ten days the bill before the legislature was passed. The couple were married within the year. Her menstruation has been more or less regular but scant since then with an occasional period missed.

It is easy to reason that bleeding might have continued had an adjustment been impossible. The treatment would then have been control of the secondary hemorrhage even though the patient's illness would not have been cured.

Worry, excitement, or exertion under tension accompanies the onset of bleeding in these cases. So, even though hormonal secretions control menstruation, some other factor must be sought in the psychic make-up of an individual, that stimulates or inhibits endocrine secretions. We are acquainted with the case of a nurse who has menstruated every time she has attended an obstetrical patient, regardless of the time relationship to her own menstrual cycle, since her training school days began five years ago.

2. Ovary

The ovary as a whole and various structures in
the ovary have been assigned as etiological factors of hyperplasia of the endometrium.

a. The Large Ovary.—The large ovary (Fig. 25) is one in which the surface is smooth and the albuginea thick due to an excessive amount of fibrous tissue. There is a tendency toward the formation of small follicles without development of the corpus luteum which in turn leads to failure of the corpus albicans. The presence of such an ovary is considered by some as a criterion of faulty constitution. It bears a relationship to other functional disturbances, especially thyroidea and occasionally myxedema (20). A majority of cases of thyrotoxicosis have scant, irregular periods, or amenorrhea. Seven of the forty-one cases of hyperplasia of the endometrium had definite goiters, either nodular or diffuse and firm, but none of these cases were toxic. One of the cases was a marked myxedema, thick dry skin and tongue, coarse hair, slow pulse, low blood pressure, B.M.R minus 26 per cent. She complained of irregular and profuse menstruation of two years' standing. Her uterus was uniformly
enlarged, being twice the normal size. Her hemoglobin was 35 per cent and the red blood cells numbered 3,000,000. Operative procedures on the uterus were advised but the patient refused. On thyroid extract she has had no uterine bleeding for four months.

b. Primary Disease at the Menstrual Cycle is the term applied to hyperplasia in adolescents when a fundamental disturbance of internal secretion, including ovarian, is present. The condition seems to be constitutional and incorrigible. The endometrium from a case of this type is shown in Figure 23. This girl of 25 years had her uterus removed because of irregular and prolonged periods which set in four months after the menarche at 13 years. She "used to flow most of the time" but kept up with a normal school and social life until 19 years of age. Because of several attacks of severe right abdominal pain, not associated with nausea or vomiting, the right tube, ovary and appendix were removed and a cyst on the left ovary incised. A year later periods were again irregular and continued so for five years. At this time
hemoglobin of 68 per cent and red blood cells numbering 3,400,000 and B.M.R plus 4 per cent were significant laboratory findings, in that the body had responded well to the disturbance. Because no uterine pathologic condition such as myoma or polyp was demonstrable, a hysterectomy was performed by the surgeon in charge. A diffusely enlarged, elastic thyroid gland was palpable on physical examination.

c. Transitory disturbances may result in a temporary disturbance in metabolism. The cases of young girls, who develop a hyperplasia of the mucous membrane of the uterus and then recover with regular periods after curettage, belong to this class. The cause, which also obtains in those cases which occur at the menopause, is assigned either to a persistence of the corpus luteum or persistence of the follicles. A student nurse of nineteen years has had profuse menstruation since the onset of her periods at 13 years. Three uterine hemorrhages have occurred each while playing basket ball during a menstruation period. This patient also suffers from migraine headaches for two or three weeks at a time every three or
four months. Her periods have been regular for four months following curettage.

**d. Diminution of function of the ovary** is a regular finding at the menopause and is a general outstanding cause. It is associated with:

(1') a **persistence of the corpus luteum** which is connected with a disturbance in maturation of the ovum. This is considered an essential finding by some writers. But a corpus luteum is not always present and an explanation of that fact follows.

During imperfect function of the ovary, there may develop a hyperplasia of the endometrium, so that the first returning corpus luteum formation may occur simultaneously with a hyperplastic mucous membrane—and it may require the development of one or more cysts until the mucous membrane gradually casts off the diseased, changed portion, and the normal functional behavior is re-established.

Thus a mixed picture of the endometrium may exist for a time. So at the menopause, a completely developed ovum may be checked one or more times and hyperplasia intervene until a recurrence of complete ovum development with corpus luteum for-
(2') In the majority of cases, however, corpus luteum formation is lacking, and one or more large follicle or theca cysts are found. Among the forty-one Halstead cases three were associated with follicle retention cyst, two of the ovaries were large and white, and all of the others were small and sclerotic with numerous small retention cysts. Brennecke advanced the idea in 1882 that ovulation was absent and that new follicular formation led to repeated premenstrual congestion, with menstrual casting off. R.Schroder(54) considered persistence and hypertrophy of the follicles as the stimulation to hyperplasia of the mucous membrane. R.Meyer(40) correlated imperfect development and occurrence of formation of the lutein body, with general bodily development. The lack of development of corpus luteum permits new maturation of the ovum and new stimulation to proliferation of the mucous membrane. It is recognized among veterinarians that sterility in cows is associated with follicle cysts of the ovary. These are ruptured by massage through the
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rectum and the cows are then able to conceive.

e. Muscle Hypertrophy.- There is also a hyperplasia of the mucous membrane occasionally associated with muscle hyperplasia in old age.

f. Cases After the Menopause.- Hyperplasia may occur in women several years past the menopause when ovarian stimulation is not considered a cause. However, the bleeding in these cases has been stopped by roentgen rays and ovarian stimulation cannot be excluded as a cause of the hypertrophy. One of the cases reviewed, on whom a vaginal hysterectomy was performed, was eight years past the menopause.

g. Ovarian Tumors.- According to R. Meyer folliculoma granulosa cell tumors, sarcomas and fibromas may be associated with hyperplasia of the endometrium in women from four to twenty years after the menopause. Ordinary uterine carcinoma, papilliferous cystomata, dermoid cysts and others have no part in uterine hypertrophy. The uterus is atrophic in uterine carcinoma of old women. In the case of sarcoma and fibromata of ovaries
at Halstead Hospital, there has been more often an amenorrhea or delayed menstruation than menorrhagia. Mrs. I., 45 years old, had a papillary carcinoma of the left ovary removed 6 months ago because of irregular uterine bleeding of three years's duration. Bleeding has persisted and the pelvis is now filled with metastases.

3. Pituitary

In direct association with ovarian variations is the role of the anterior lobe of the pituitary. We have earlier noted that the anterior lobe of the pituitary in young female animals causes sexual early development and an imitation of early puberty is shown in infant mice. Miss A. is 25 years old, weighs 190 pounds, is large-boned, with marked protrusion of lower jaw. Pains of ovarian distribution, profuse irregular periods and anorexia are her complaints.

B. Changes in the Endometrium Due to Local Stimulation

A local stimulation has been emphasized by Declos who stimulated the mucous membrane by mechanical or chemical means and caused a thickening of the mucosa with epithelial proliferation and enlargement of the ducts—also a thickening of muscle wall. Loeb(35) observed decidual formation in the time of heat, through mechanical interferences in
the mucous membranes.

Kohlbrugge believed that spermatozoa by local stimulation called forth a proliferation of uterine epithelium.

Mention must be made of change of position of the uterus, incomplete abortion, repeated inflammation and myomata as causes of hyperplasia. That their presence is associated with hyperplasia of the endometrium is noted in the chart of K.U. cases in the introduction in which 45 cases out of 53 were associated with some other pelvic pathology.

Hyperplasia of the endometrium has been described as occurring in pregnancy. Hyperplasia decidua tuberosa was first described as endometritis decidu-alis tuberosa by Virchow. The discussion of this condition resolves itself around the question whether the hyperplasia of the mucous membrane existed before the pregnancy, or whether the hyperplasia is due to the pregnancy as a strong reaction from hormonal influence.

If a diffuse hyperplasia of the mucous membrane originates from hypofunction of the ovary, as was mentioned earlier in the pathogenesis, it could hardly develop in relation to pregnancy.
Some authors are of the opinion that decidual polyps can develop from the decidua vera or decidua capsularis. Ahlfield describes these as having a central blood vessel in addition to the rich supply of vessels found in the decidua. He also believes that these polyps develop following the death of the embryo which results in abortion.

II. Hyperplasia of the Cervical Mucous Membrane

Hyperplasia of the cervical mucous membrane has been neglected until recently, likely because it did not fit into a hormonal etiology.

Macroscopically the entire cervix is hypertrophic, the mucous membrane is protuberant and decorated with numerous small knot-shaped and polypous growths and may bleed easily. It is soft to the touch. The cause of the bleeding is readily understood by reference to Figure 26 which shows the cervical surface covered with granulation tissue.

This condition develops independently from changes in the corpus mucous membrane, so that cervical mucosa is brought away by the curette.

Microscopically the tissue is like that of
glandular polyps due to active glandular hyperplasia covered by granulation tissue. The epithelium may lose its cervical character in that it is less high, secretes very little and the nucleus is not basal but more central. The glands give up their acinous form for an entirely irregular formation. Also there may be segmentation of mucous cysts, especially in the deeper portions of the cervix, and there may be an inclination toward heterotopic gland proliferation which may assume an adenomatous character.

III. Hyperplasia of the Myometrium

There are cases in which irregular menstrual bleeding occurs, following the menopause, in which no evidence of endometrial hyperplasia is present—rather the uterus and lining may appear atrophic. Sclerosis uteri, fibrosis uteri, or arteriosclerosis uteri have been names applied to this condition while searching for the cause of the disturbance within the uterus.

An increase in musculature was first considered the etiological factor by von Finn in 1868, also by Frankl in 1914. Virchow in 1862 believed
an increase in connective tissue was the cause as did Klob in 1864. DeSinety in 1874—also Theilhaber, believed the prevalence of connective tissue and insufficient musculature were responsible for the bleeding.

Schiickel and Koller, also Abreiner could demonstrate no specific variations or cause for the bleeding in the connective tissue or musculature so Aschoff and Pankow called it "metropathica chronica". Myopathia uteri means the same.

Because of the variable findings in the uterus, Aschoff, Pankow and Aschner all considered the ovary as the etiological factor. However, these findings are not present with hyperplasia of the mucous membrane. Other influences considered have been sexual stimulation, endometritis and venous stasis.

Macroscopically there is a uniform thickening of the entire uterine body, sometimes three times the normal thickness. It may be soft as pulp, progressively hardening to a firm, even fibrous uterus, approaching the firmness of a myoma. It is gray and reddish in color. In advanced cases, the gray substance is interwoven about whiter, more
fibrous fibers in irregular arrangement.

Microscopically there is a proportional increase in the musculature, connective tissue and blood vessels.

Pathogenesis in this condition has also been attributed to every portion of the myometrium. Sinety considered lymph vessel dilatation as the cause for hypertrophy of the wall. Assertos believed it was caused by changes in the media (Fig. 27). Smith—hypertrophy of vessel wall (Fig. 27). Von Pankow—sclerosis of blood vessels. Woltke—increase in elastic fibers. Ehrmann, Anterberger and L. Meier saw fat infiltration in the muscle cells. Any one or several of these conditions can be found in normal uteri of old women in whom no bleeding has occurred.

Muscle hyperplasia due to repeated hyperemic conditions is now considered the most constant finding, and the repeated hyperemia is due to ovarian function.

The abnormal ovarian function of older women may produce a nutritional increase in musculature as well as hyperplasia of the mucous membrane; however, in younger individuals there is more
liklihood of gland hypertrophy within a muscle of normal thickness.

There is also an increase in musculature in uteri in which myomata are present. Occasionally small foci of circumscribed hypertrophies are found in myometria as in the case of Mrs. McG. Among multiple myomata, one small one had to be incised for removal instead of shelling out as was expected.

In these cases endothelial proliferation of the capillaries may be marked as well as an increase of small vessels.

In the same category as the myohyperplasias of the uterus, is also found rare cases of angio-myohyperplasia (33) in which vessel wall hyperplasia develops at the same time with striking enlargement of the larger vessels.

The typical picture of wall hypertrophy does not show a hyperplastic thickening of the vessels. The thickening of the corpus wall is produced only through moderate general muscle hyperplasia and chiefly through small and smaller vessels with cell-rich walls. Numerous small dilatations of vessels just visible to the unaided eye make
the tissue cavernous. The musculature surrounding the vessels is everywhere hyperplastic.

Summary

A study of uterine hemorrhage due to extra-uterine influences was undertaken on the basis of:

1. Forty-one cases personally attended at the Halstead Hospital, Halstead, Kansas;
2. Twenty-nine cases of organic endocrine disease from postmortem material on file in the Pathology Department of the University of Kansas, Rosedale;
3. Fifty-three surgical slides diagnosed hyperplasia of the endometrium, on file at the University of Kansas.

Those cases attended personally offered the most valuable source of material in that accurate menstrual histories were available and social histories proved valuable.

In view of the endocrine, etiological theory of hyperplasia of the endometrium now prevailing the embryology and histology of the ovary, the pituitary and the endometrium were studied. Two
hundred and more ovaries and endometria were examined microscopically and it was noted that obliteration of the follicles and the corpora lutea in the ovary, and repair of the endometria, follow the laws of tissue repair now generally recognized as applying to the healing of all wounds.

Theories of the physiology of the endocrine glands in relationship to the female genital system are discussed. The hormonal influences of the ovarian and the pituitary secretions on the endometrium during menstruation and in hyperplasia of the endometrium are described and are no doubt of etiological influence.

The balance between the endocrine and nervous systems may be upset by the exigencies of life in a person with an endocrine diathesis and result in menstrual variations. These variations may correct themselves when adjustment has been made to the disturbing situation.

No pathognomonic microscopic picture is present in hyperplasia of the mucous membrane of the uterus. The endometria and myometria show variations in every constituent and these same variations may be found in uteri not the seat of irregular uterine bleeding; also in uteri associated with myomata,
pelvic inflammations and the like.

The fundamental difference between hyperplasia of the mucous membrane and all other forms of hypertrophy is that it does not, or only imperfectly, participates in function.

An abnormal endocrine function is more likely to cause hyperplasia of the endometrium in younger individuals and hyperplasia of the myometrium in older women.

The endometria from two uteri removed for irregular uterine bleeding showed microscopically a picture of granulation tissue.

Varied microscopic pictures of the ovary, not possible of differentiation from the normal were also associated with hyperplasia of the endometrium.

Irregular uterine bleeding may result from hyperplasia of the cervical mucous membrane when granulation tissue has developed on the surface. The bleeding is due to injury of the granulation tissue.
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Fig. 1. Postmortem specimen of intermenstrual endometrium from 16 year old girl who had a normal menstrual history. Glands are surrounded by a single layer of columnar epithelium. Lymphoid cells are closely packed in interglandular tissue.
Fig. 2. Premenstrual swelling from patient 26 years of age. Saw tooth appearance; contracted and dilated swellings are the cause of pseudo-papillae in the glands. The stroma is filled with red blood cells.
Fig. 3. Menstruating endometrium shows masses of red blood cells, A, and fragments of endometrium, B. Basal layer, C, is intact here.
Fig. 4. Onset of repair of endometrium.

Interstices in stroma and about gland remnants are filled with blood. Fibrillar fibrin can be made out at extreme right, A.
Fig. 5. Endometrium from patient 31 years old whose menstrual flow checked the day of admission to the hospital. Line of demarcation, A-A, indicates the boundary between excess fibrin formation and regenerating surface of endometrium.
Fig. 6. Higher power of Figure 5 included between A-A. Mononuclear or polynuclear leucocytes along bundles of fibrin. Epithelial cells, B, grow along fibrin and fibrous tissue foundation.
Fig. 7. High power of figures 5 and 6: shows dissolution of fibrin, A, above epithelial cells as they spread along fibrous tissue.
Fig. 8. Ovary from an embryo between 3 and 4 months' gestation. Primitive sex cells, A, are surrounded by small follicular cells (barely perceptible) and form medullary cords separated by mesenchyme, B.
Fig. 9. Ovary from a child of 7 months shows germinal epithelium, A; tunica albuginea, B; primordial follicles, C, in cortex; and growing follicles, D, toward the medulla.
Fig. 10. Growing follicle shows multiplication of follicular cells, A; cumulus oophorus, B, or discus proligerus; and theca interna, C; and theca externa folliculi, D.
Fig. 11. Ovum surrounded by well defined zona pellucida in cumulus oophorus. Formation of retinacula, A, is shown; also the glassy membrane, B.
Fig. 12. Corpus luteum hemorrhagicum. Festooning of granulosa cells (lutein cells), A, surround irregular stellate cavity, B. Triangular masses of theca interna, C, are at the base of granulosa folds.
Fig. 13. Obliteration of corpus albicans.

Hyaline degeneration entirely replaced by new fibrous tissue on left, A. Hyaline of corpus albicans still present on the right, B.
Fig. 14. Diagram from Schroeder published by Graves, Am. J. Obst. and Gynec., 1930, 20:500. It shows the parallelism between phases of the follicle and the endometrium during a normal menstrual cycle; between ovarian and menstrual cycle in pregnancy and the follicle and endometrium in a typical case of hyperplasia of endometrium.
Fig. 15. Diagram by Aschheim and Zondek, Klin. Wochenschr., 1928, 7, 2, 1404-1453. It shows the interrelationship between hormones of the anterior pituitary, ovary and the different phases of the endometrium.
Fig. 16. Polypoid hyperplastic endometrium. Endometrium is irregular and shaggy. Definite line of demarcation, A-A, between endometrium and myometrium.
Fig. 17. Premenstrual swelling in endometrium from a woman of 34 years removed the day before menstruation was due. It would be difficult to diagnose this from hyperplasia of endometrium without a history of the case.
Fig. 18. Early decidua formation among hyperplastic endometrial glands. This picture should institute a thorough search for chorionic villi.
Fig. 19. More advanced stage of decidua formation shows greater hyperplasia of glands and stroma.
Fig. 20. Hyperplasia of endometrium.
Absence of three endometrial layers; compact, spongiosum, and basal. Cyst formation, A. Concretions, B.
Fig. 21. Hyperplasia of endometrium.
The grouped vessels have thick walls, A. Interglandular papillae, B. Necrosis of peripheral layer of endometrium, C.
Fig. 22. Hyperplasia of endometrium. The epithelium of one or more rows is sharply defined against the lumen. Low epithelium lining a cyst is in upper right hand corner, A.
Fig. 23. Hyperplasia of endometrium. Endometrium resembling granulation tissue from a woman of 25 years. Few scattered basal glands, A. Menses always irregular: "bled almost all the time".
Fig. 24. Adenomyosis in a woman 64 years old. There is absence of three endometrial layers. Endometrial glands in myometrium, A-A.
Fig. 25. Large ovary with smooth surface contains numerous small follicles.
Fig. 26. Hyperplasia of cervical mucosa. Granulation tissue on surface of cervix, A, in which cervical gland, B, proliferation was also present.
Fig. 27. Hyperplasia of myometrium. Blood vessels in myometrium show hypertrophy of the muscle wall by increase in the media.