Fig. 77.—Endometrium of premenstrual stage. (Twenty-five to twenty-seven days after the first day.) Marked tufting of the dilated glands which are also increased in number. Notice the superficial compact layer and the deeper spongy layer similar to a decidua. This is due to the large amount of progestin from the mature corpus luteum present in the ovary at this time. Gyn. Lab.
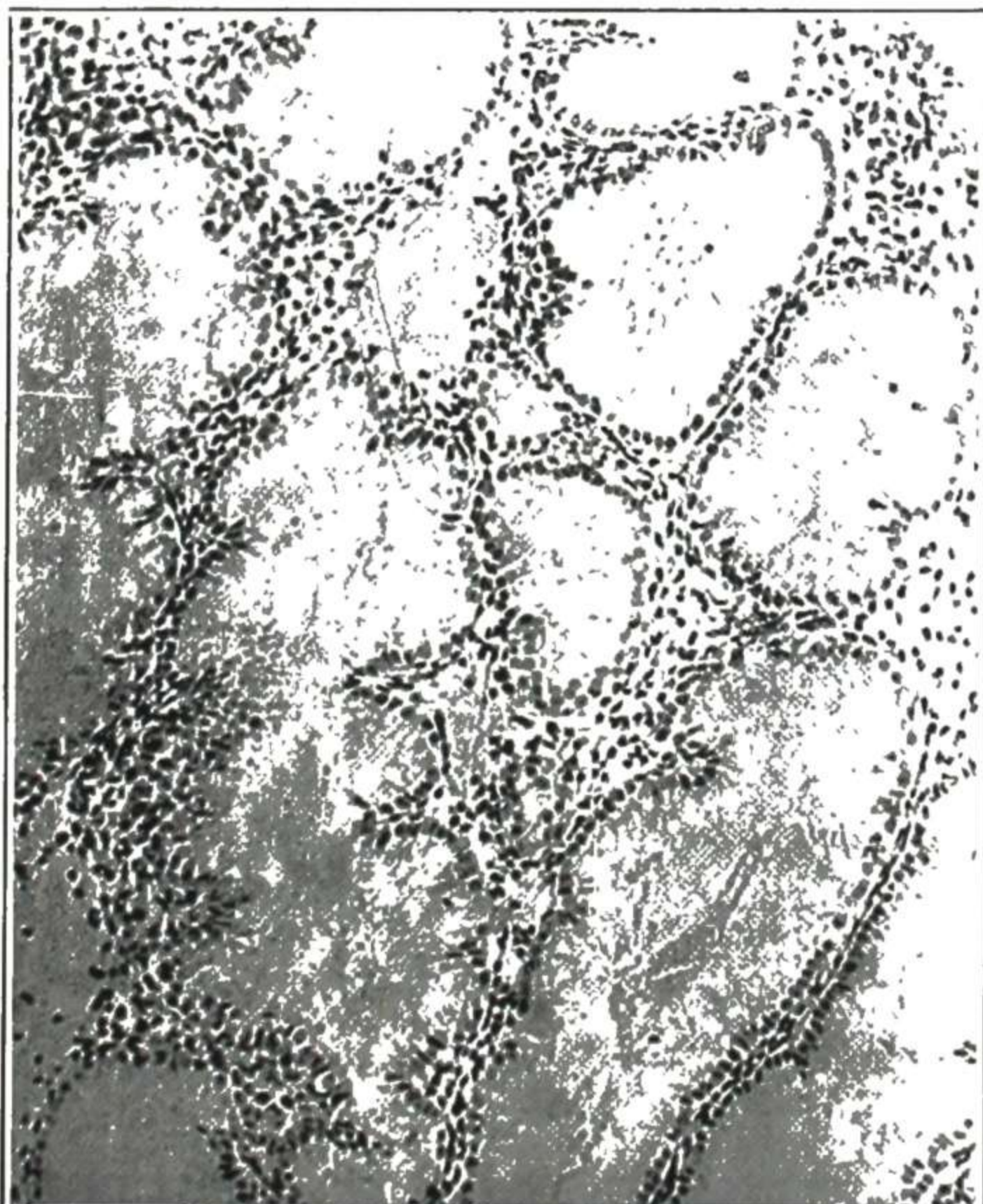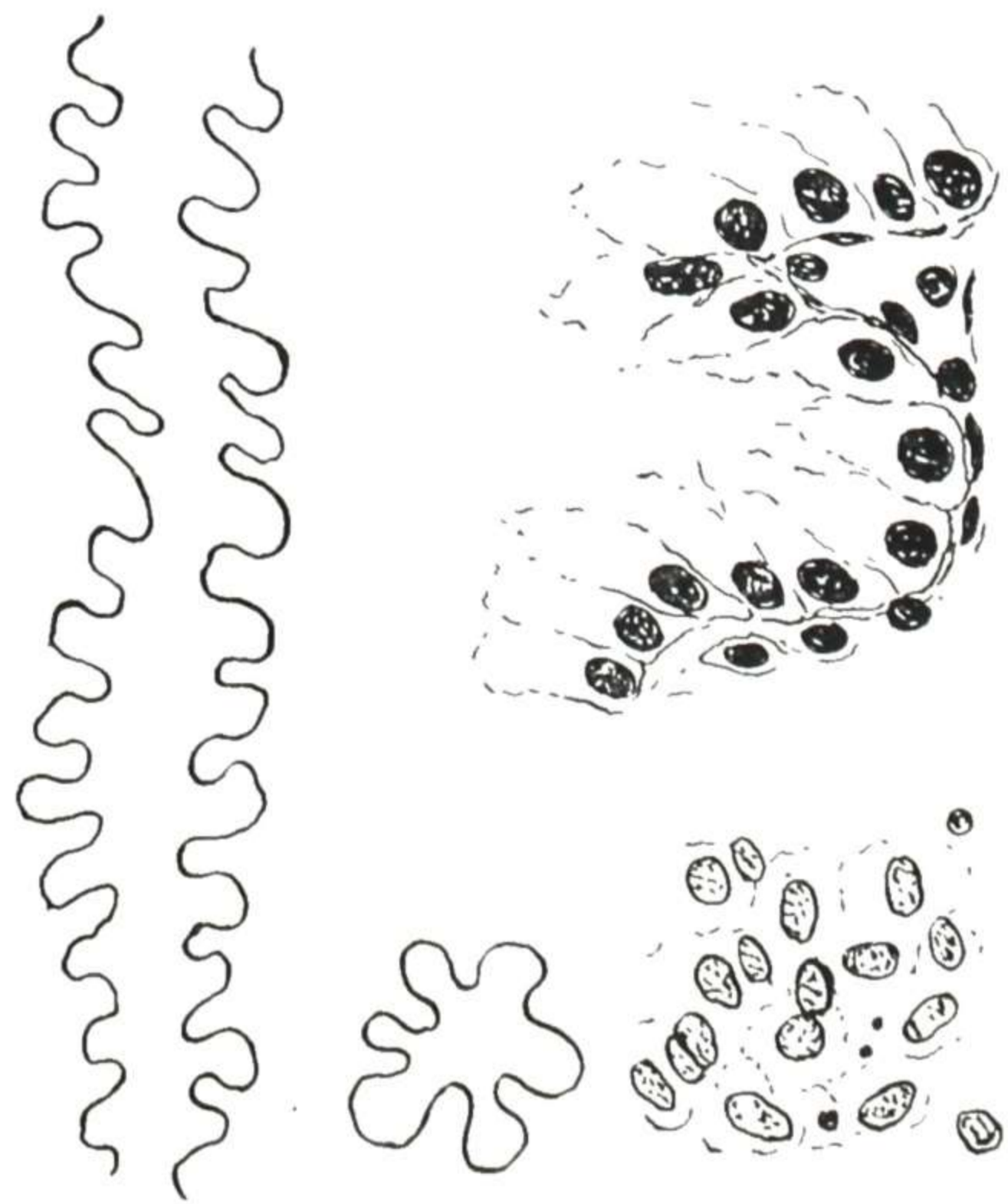
A.   B.

Fig. 78. *A,* Premenstrual endometrium. High power of Fig. 74, showing the markedly distended tortuous glands and the large stromal cells. A capillary distended with blood elements just below the center of the section. "Tufting" effect well shown. Gyn. Lab.

B, Diagram showing the characteristics of the premenstrual stage mentioned in *A.* Longitudinal section showing the saw-toothed edges of the gland, shown also in cross-section. The large epithelial cells covering the tufts are illustrated as are also the large clear stroma cells.

graph in Fig. 77. The stromal cells in the superficial compact zone become edematous and large and resemble decidual cells, but differ from them in that they contain no glycogen.

The great thickening attained by the endometrium in the premenstrual stage is shown in Fig. 81, which is a uterus removed just before the menstrual breakdown. Notice the distinct rolled margin at the lower portion of the full-functioning endometrium where it joins the mucosa of the "isthmus," which is the transitional area of the uterus where the corpus shades into the cervix.

Growth ceases four to five days before the onset of the menses, and a period described by Markee as a period of regression begins, terminating in menstruation. In the early part of the period there is a dehydration of the edematous portion of the endometrium due primarily to the death of the corpus luteum and consequent withdrawal of estrone and progesterone. Several explanations have been offered for this. Markee feels that there is a shift from the estrogen-induced vasodilatation with increased permeability of the vessels to decreased permeability of the vessels with a withdrawal of estrogen, resulting in a loss of fluid from the stroma. Schlegel and others feel that the arteriovenous anastomoses open and aid in the dehydration process.

As explained later, under Cyclic Arteriole and Venous Changes, this shrinkage of the endometrium is one of the important factors in this slowing of circulation and onset of menstruation. Just before the onset of menstruation the reticular framework of the stroma disappears and the stroma becomes infiltrated with leukocytes and lymphocytes, and marked vascular congestion is present.

MENSTRUAL STAGE (BREAKDOWN).—Just before the onset of menstruation subepithelial hematomas appear under the surface of the endometrium due to rhexis of the capillaries and spiral arterioles and also probably to diapedesis (Fig. 79). Eventually, desquamation of compact layers and most of the spongy layer occurs. The basal layer does not participate in these changes and remains as the regenerative bed for the new endometrium.

In the ocular transplant in the monkey, Markee found that there was a reduction in the area of the transplant of 60 per cent during bleeding and that about three-fourths of this reduction was due to resorption of fluid and one-fourth to desquamation.

In the human being Schröder found that the endometrium was cast off to the basal layer, but in a more recent study Watson and McHenry concluded that only the glands which had been fully activated by progesterone, together with their supporting stroma, were cast off after progesterone withdrawal. Various stages of regression and desquamation are present throughout the endometrium so that it is normally desquamated over a period of four to five days. During this period of piecemeal desquamation, regeneration is progressing in other areas; Fig. 80 shows the endometrium in this stage. Fig. 81 shows a uterus in premenstrual stage. Novak calls attention to the strikingly different characteristics which the original coelomic epithelium develops in the different segments of the genital canal. Even in this single segment (endometrium), a stimulation brings different functional response in different parts, as manifested in the so-called "stratum reaction."

Another indication of the variability of cellular response to stimulation is seen in the development of tubal types of epithelium in the endometrium. This is rare in the normal endometrium, but with a slight shift in endocrine balance, as in hyperplasia, there may be reversion to the tubal type in spots. Fig. 82, *A* shows in the endometrium the ciliated type of tubal epithelium, and Fig. 82, *B* shows the secretory type. This reversion to the tubal type of epithelium is seen even in the cervix occasionally.

Fig. 79.—Late premenstrual. Two days before menses. The glands are distended and the papillary infoldings of the lining epithelium have been flattened out. Note engorgement of thin-walled venules and massive extravasation into stroma. Near central gland, *A*, a venule has ruptured (see arrow) with local hemorrhage. (×210.) (From Sturgis and Meigs: Am. J. Surg., September, 1936.)

The ovarian-pituitary (endocrine) factors causing menstruation have been discussed, but there may be also a local factor increasing the permeability of the vessel walls to the blood cells. The origin and nature of this factor have not yet been determined. Probably it is also concerned in preventing coagulation of menstrual blood. Frankl thinks that a tryptic enzyme secreted by the endometrial glands is responsible. Smith and Smith have described a fibrinolytic enzyme.

Cyclic Arteriole and Venous Changes.—These changes occur simultaneously with the above-described cyclic epithelial and glandular changes and

are an integral part of the mechanism of menstruation. They are discussed separately to avoid confusing the two phenomena. Although William Hunter in 1774 illustrated spiral arteries in a gravid uterus, and Saito in 1926 described cyclic variations in the endometrial arteries, it was not until the work

Fig. 80.—The endometrium on the first day of menstrual flow. This section shows three stages of the process of menstruation: vascular congestion on the right; beginning rhexis of vessels and extravasation of blood in the center; actual desquamation and tissue loss on the left. Observe the basalis, which remains intact and little altered through the whole process. (Bartelmez: Contrib. Embryol., Carnegie Inst. of Washington, 24.)

of Daron on the arterial pattern of the endometrium in the monkey and of Markee on the changes occurring in endometrial tissue transplanted into the eye of rabbits and monkeys, that our knowledge of the mechanism of menstruation was clarified. Some of the observations made by them in animals

have been made also in human beings by means of hysteroscopic studies. Mikulicz-Radecki described transient blanching of the endometrium just before the onset of bleeding. Schröder confirmed this and described a pale, swollen, glassy mucosa on the twenty-sixth day of the cycle. It is now known that the recurring vascular cycles of the spiral arterioles are the same in cyclic uterine bleeding whether the endometrium is proliferative or secretory or hyperplastic, hence menstruation in the human being is fundamentally a vascular phenomenon. That the coiled arterioles are not necessary for menstruation in certain monkeys was shown by Hamlett in 1939 and Kaiser in 1947. Kaiser found that in the Rhesus monkey there was a striking difference in the distribution and the thickness of the wall of the spiral arterioles between the ovulatory and anovulatory cycles.
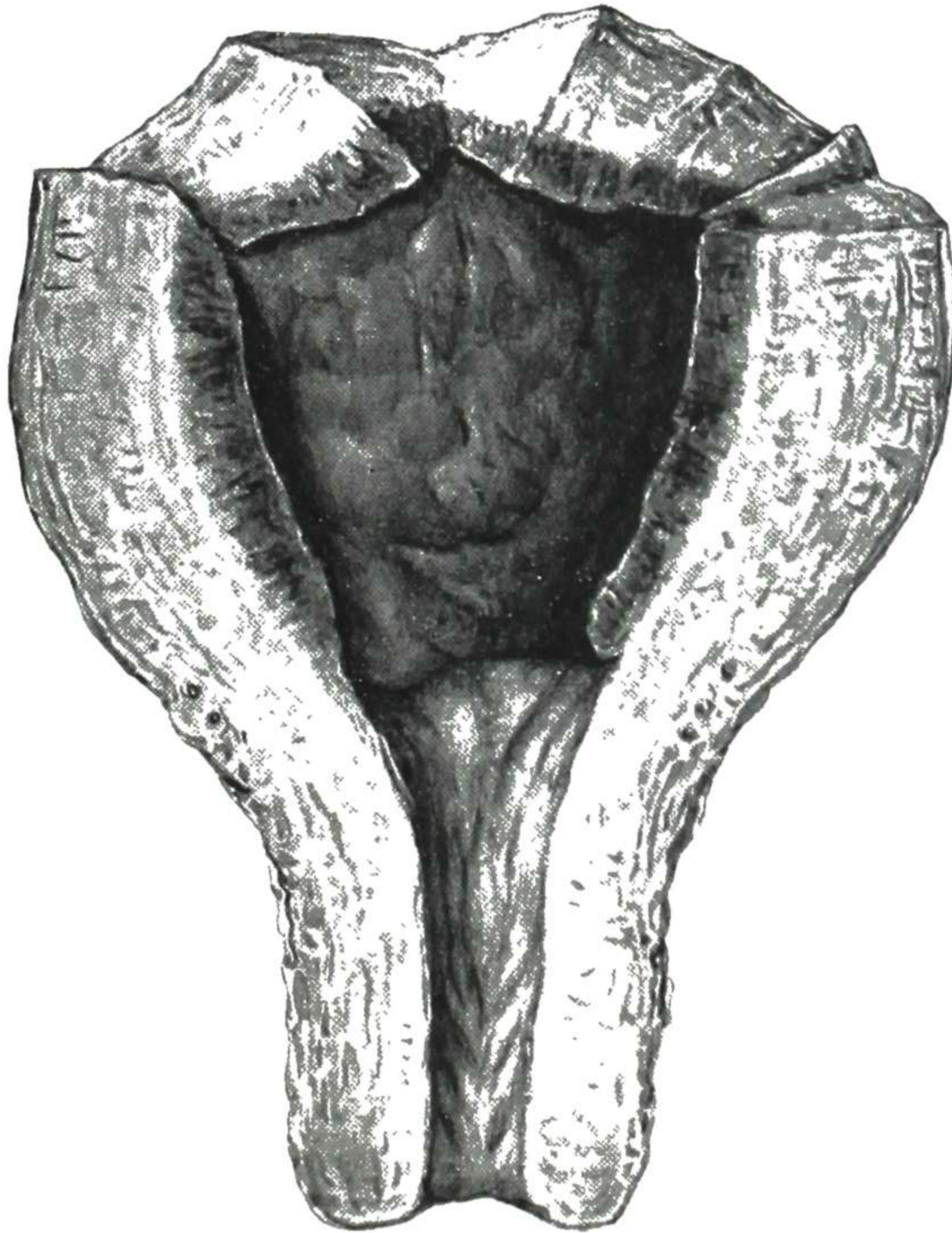

Fig. 81.—A uterus removed in the premenstrual stage, showing the marked thickening of the endometrium. In this specimen the "isthmus" of the uterus stands out clearly. The "isthmus" is the intermediate zone lying between the fully functioning endometrium and the cervix, and represents a transition from endometrial to the cervical type of mucosa. Notice the thick roll at the lower border of the functioning endometrium. Gyn. Lab.

The **spiral arterioles** arise from the arcuate branches of the uterine artery in the middle third of the myometrium and extend inward. In the inner fourth of the myometrium they are perpendicular to the uterine cavity; as they extend through the endometrium they give off minute branches to the glandular walls, finally ending in a fine network of capillaries under the surface epithelium of the endometrium. As they pass through the inner fourth of the myometrium they are surrounded by specialized muscle tissue made up of fibers from the surrounding myometrium. These periarteriole collections of

special muscle fibers were called *contraction cones* by Markee, who described them in the monkey. In human beings, groups of longitudinal muscle fibers immediately beneath the tunica intima of the arterioles in the female genital tract were described by Bucura. These fiber groups, named "polsters" by Bucura, are especially abundant around the arterioles of the inner fourth of the myometrium, and Keiffer has shown that the fibers of the tunica are continuous with the intrinsic muscle fibers of the myometrium.

A.   B.
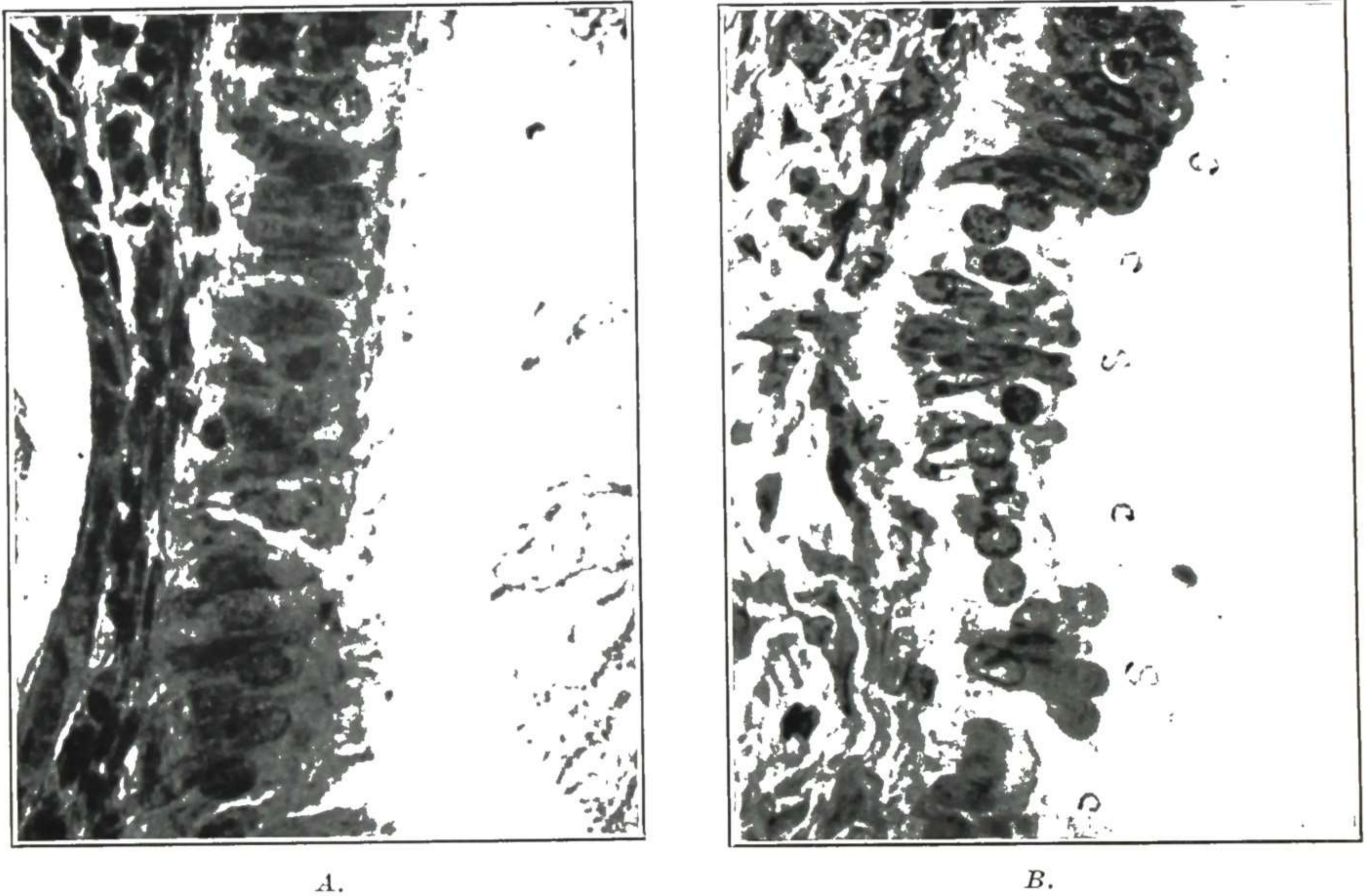
Fig. 82.—*A*, Endometrium in a case of hyperplasia showing ciliated cells lining an endometrial gland. Cilia are rare in normal endometrium, but in hyperplasia one often finds scattered endometrial areas exactly resembling tubal epithelium, with all three of the characteristic tubal cell types. *B*, Another example of tubelike epithelium in the endometrium of a case of hyperplasia. Ciliated cells (*C*), and secretory cells (*S*). (From Novak: Am. J. Obst. & Gynec.)

The muscle cones surrounding these spiral arterioles are under hormonal control, and the terminal portions of the arterioles in the endometrium degenerate when there is constriction by prolonged contraction of the muscle cones. This interference with the blood supply to the endometrium in the area of the terminal arterioles affected causes disintegration of the endometrium in those areas (Fig. 83). In 1940 Hertig and Rock described a connection between the spiral arterioles and the accompanying vein. Recently Okkels has shown clearly that such anastomoses do exist, and Schlegel feels that the stasis present in the superficial portion of the endometrium prior to necrosis and bleeding is due to an opening of these arteriovenous anastomoses proximal to the superficial portion of the endometrium (Fig. 84).

The basal layer of the endometrium is supplied by another group of arteries, which are not under hormonal control and hence do not undergo cyclic changes. Thus the fundal portions of the glands, which lie in the basal layer, are preserved for regeneration of the endometrium. The various hormonal relations and vascular and glandular changes during the cycle are shown in **Fig. 85.**
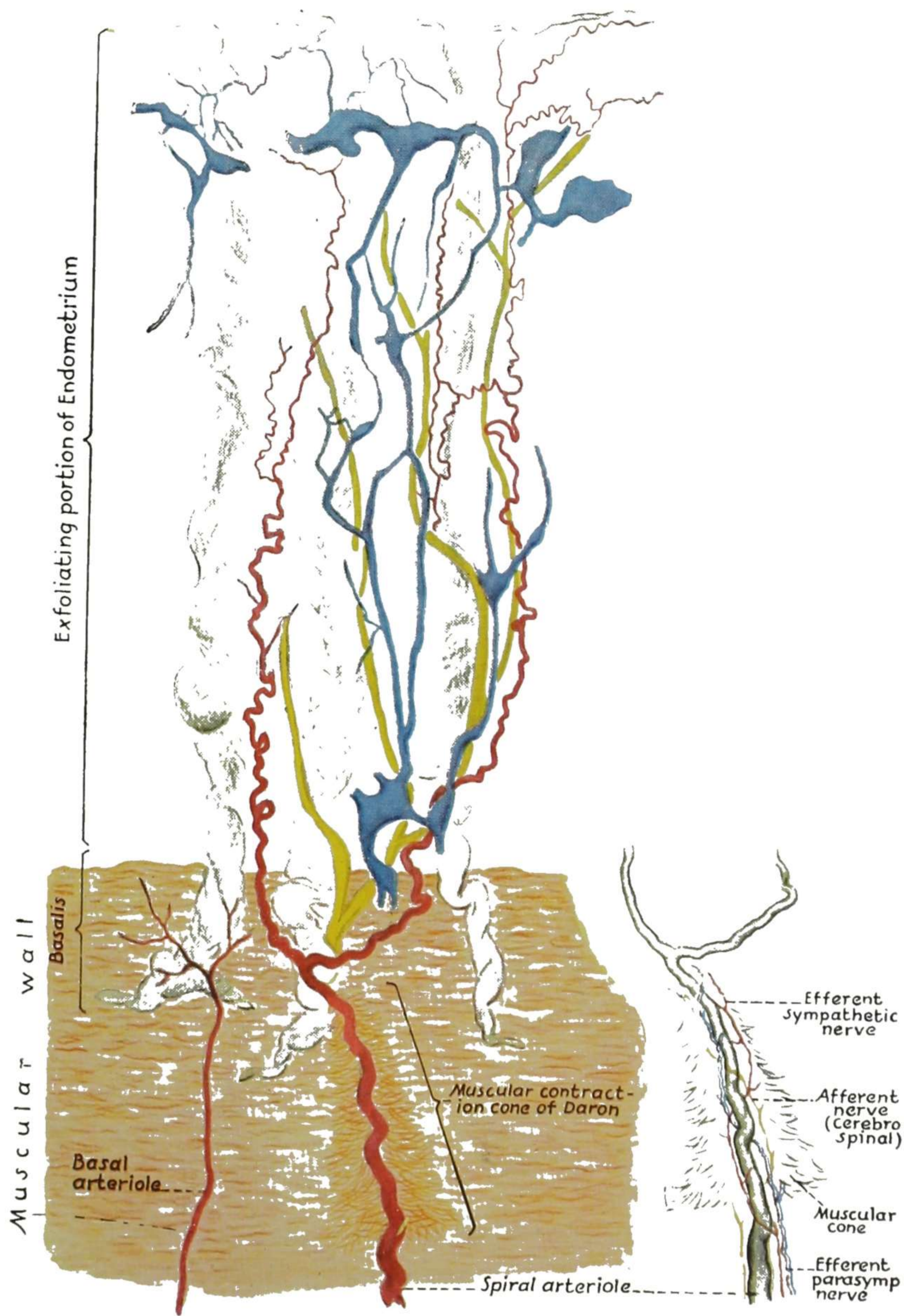
Fig. 83.—This colored diagrammatic illustration follows closely the original reconstruction of the elements by Bartelmez from serial microscopic sections of specially prepared and stained endometrial tissues.

The spiral arterioles of the endometrium are largely terminal and the blood supply through each is under the control of the muscle cone of Daron, shown in the illustration. Hence the nutritional integrity of the terminal area can be lowered by contraction of the arterial muscle cone, so that the area ceases to thicken by growth and later shrinks and disintegrates. The bleeding which follows is blood released by the cellular disintegration, apparently largely from the venous sinuses of the area.

The basalis zone of the endometrium is supplied by other arteries, not under hormonal control and not subject to the cyclic changes and exfoliation. Thus the deep ends of the glands are preserved for regeneration of the endometrium.

The nerves extend to, but do not enter, the middle third of the endometrium. They form a plexus, in the adventitial tissue of the vessels, of amyelinated fibers of the Remak variety. Evidence of the arteriole-venous anastomosis has been found by Okkel. The rapidity of change from degenerating arterioles to regenerating arterioles is probably facilitated by by-passing the blood flow through the anastomosis. This is probably the factor causing the anemia of the superficial layer of the endometrium preceding menstruation. (After Bartelmez: Am. J. Obst. & Gynec.)

During the first three weeks of the cycle the spiral arterioles alternately contract and dilate, causing periods of blanching and of blushing of the endometrial surface lasting from thirty to ninety seconds. During the premenstrual stage the endometrium becomes paler, and the blood flow through the superficial arterioles is markedly slowed. With the death of the corpus luteum and the consequent withdrawal of estrone and progesterone, the nourishment to the endometrium is withdrawn and there is a marked shrinkage due to water loss. These changes are believed by some to be due to the shunt caused by the arteriovenous connection. With the shrinkage of the endometrium the arterioles become tortuous and coiled, the blood supply is definitely impeded, and leukocytes invade the stroma.
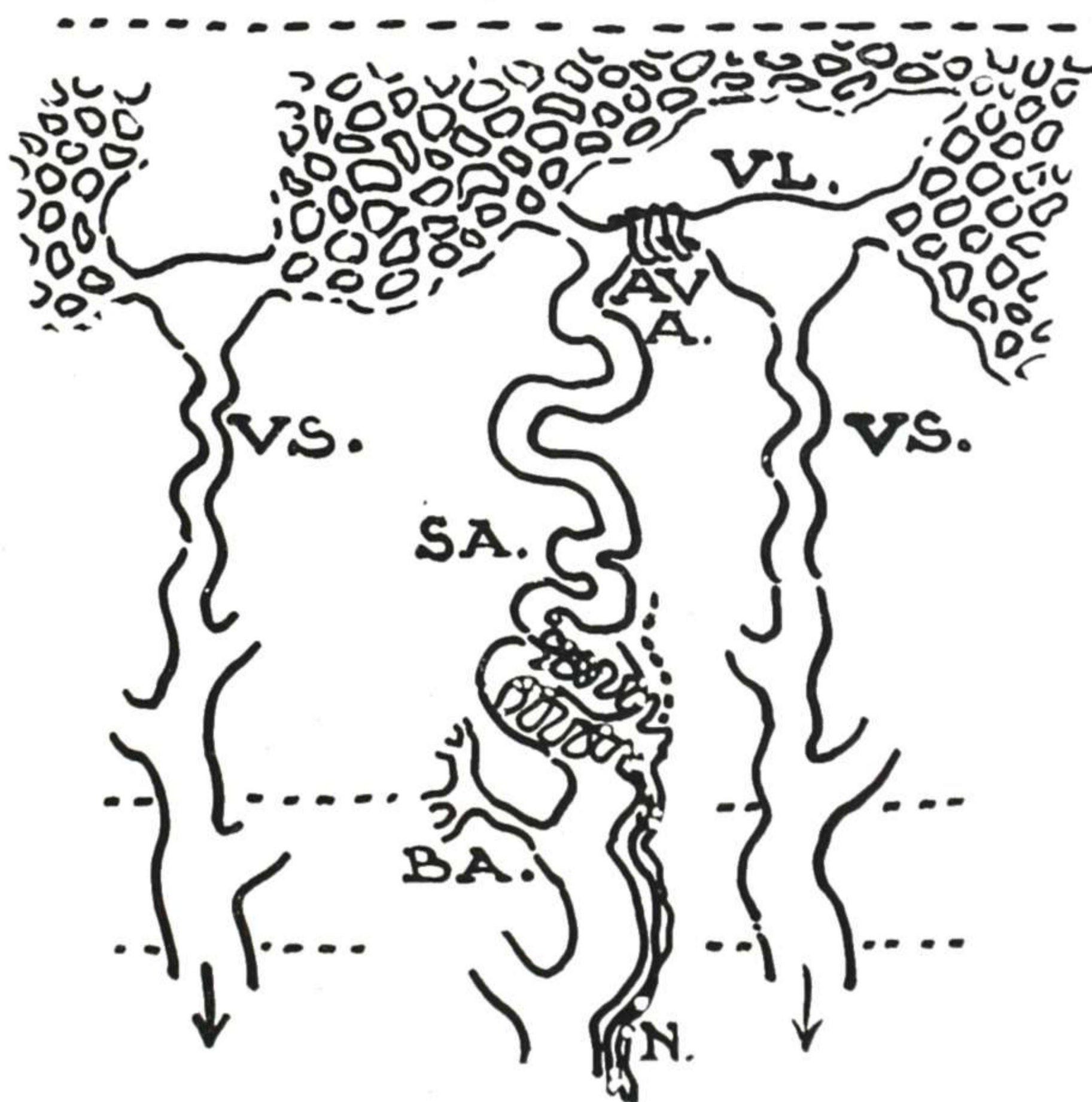

Fig. 84.—Diagrammatic representation of the vascular pattern of the human endometrium, together with the periarterial nervous plexus, according to Ikkels, Schlegel and Dalgard. *VL*, venous "lake"; *AVA*, arteriovenous anastomosis; *VS*, venous collecting stems; *N*, periarterial nerves. (From Wislocki and Bunting, in Menstruation and Its Disorders, Charles C Thomas.)

These events immediately precede menstruation, and in the course of the next twenty-four to thirty-six hours one after another of the coiled arterioles clamp down so that there is no movement of blood cells in the superficial zone, though the circulation is normal in the basal zone. The cause of this sudden clamping down of the arterioles is thought by Markee to be due to injured-tissue products which act as vasoconstrictors for the special muscle cones about the spiral arterioles, the tissue injury being due to the previous slowing of the circulation. Smith and Smith have described a menotoxin probably produced by the degeneration of the tissue in the superficial layers of the endometrium which caused a contraction of the cones at the basal portion of the coiled arterioles. They reported recently that this substance seems to be identical with necrosin, a toxic substance, previously described by Menkin.

Several hours after the arteriole cones have clamped down, some of the arterioles rupture and allow blood to pour into the surrounding tissue. In the course of a few minutes a subepithelial hematoma develops. It soon ruptures and dark blood streams out on the surface of the endometrium. Necrosis sets in at the surface and the ends of the spiral arterioles are sealed by dead cells. An arteriole that has bled usually does not bleed again during this flow. Small fissures appear at the edge of the blood-soaked area, and as they extend deeper into the tissue small areas of endometrium are loosened and cast off.

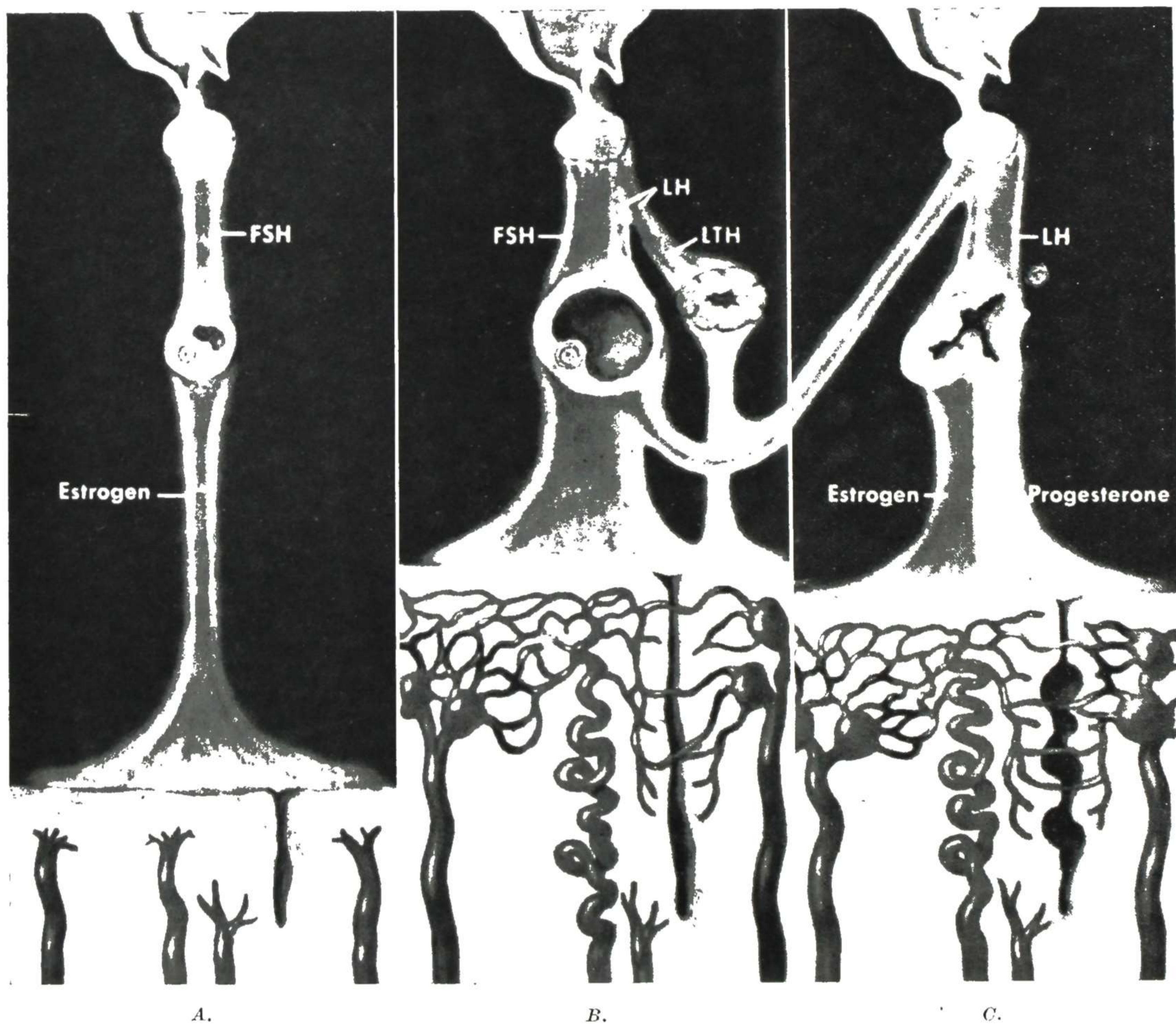A.   B.   C.

Fig. 85.—Stages in the menstrual cycle. Late in menstruation the high level of FSH has stimulated the formation of many follicles, which secrete enough estrogen to raise the blood estrogen level. This elevated level causes the straight arteries to carry more blood and decrease the amount of necrosis, thus shortening bleeding. After the necrotic tissue has been shed, new capillaries are formed and epithelial regeneration begins. (Courtesy Dr. Frank H. Netter and Seminar, Sharp & Dohme, Inc.)

A, The follicle that is to mature begins to enlarge and many others degenerate; therefore, the blood estrogen level falls slightly. Epithelial and capillary regeneration, which started at the end of the menstrual period, are now completed.

B, The high level of estrogen causes the hypophysis to liberate enough LTH to activate luteal tissue formed in previous cycles to produce a small amount of progesterone.

C, The combined action of the small amount of progesterone and the estrogen acts through the hypothalamus to cause the hypophysis to secrete enough LH to bring about ovulation. The disorganized, freshly ruptured follicle produces less estrogen but more progesterone. The stroma shrinks slightly but the glands begin to enlarge owing to increased flow through the capillaries to the glands.

This process is repeated in other areas during the next two or three days so that, by the third or fourth day of the flow, the endometrium is irregularly denuded. Regurgitated blood slowly oozes from the open veins and the surface becomes clean. This is soon followed by a migration of cells from the torn glands, and the surface epithelium is completely restored in the course of a few hours.

During the entire menstruation the basal circulation has continued, and it is now accelerated. From the stumps of the coiled arterioles capillary sprouts develop and the superficial capillary bed is rapidly re-formed. The new arterioles grow with the endometrium, and as their growth is more rapid than that of the stroma they become spiral.
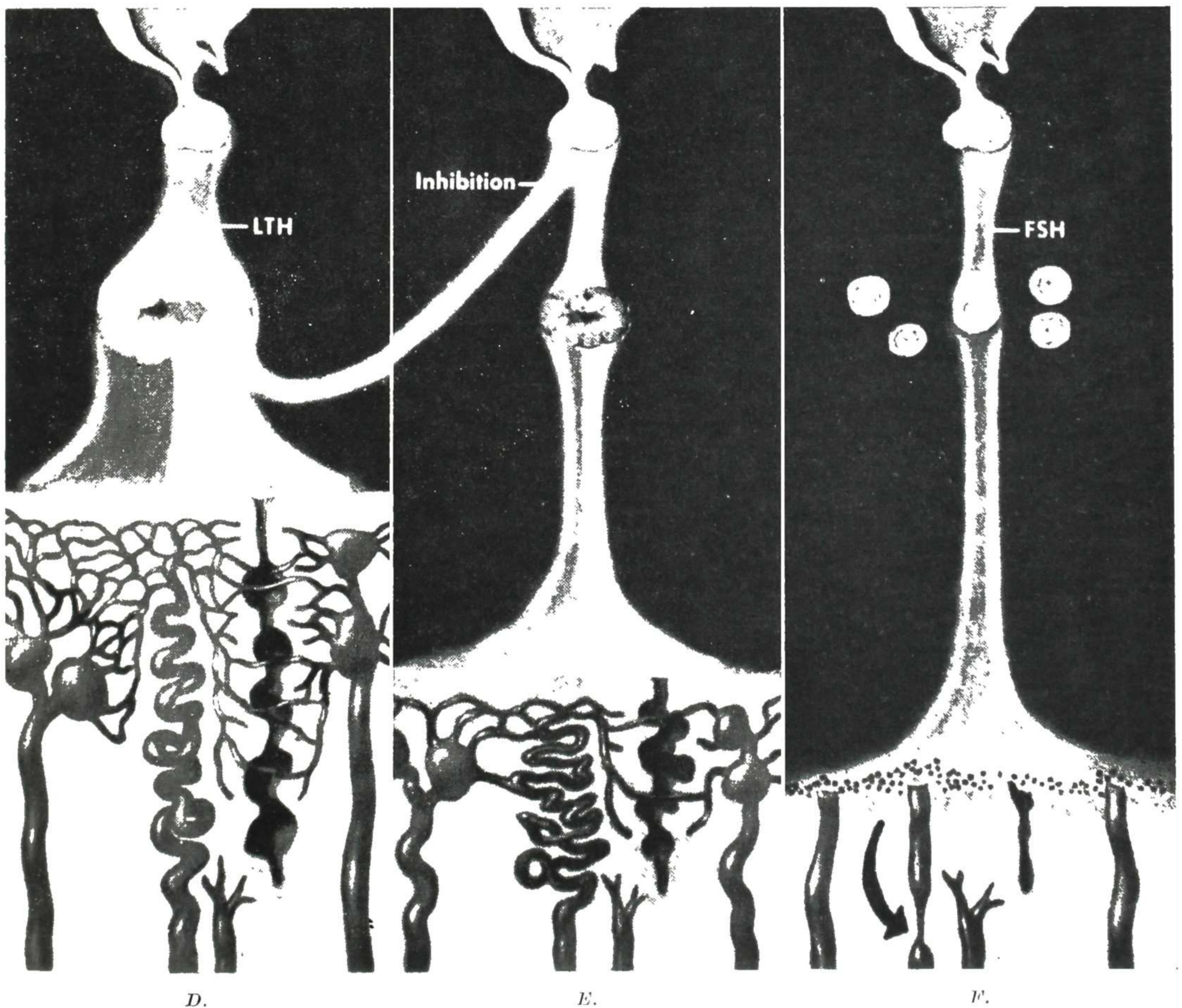

D.   E.   F.

Fig. 85 (*continued*).

D, The organized corpus luteum is stimulated by LTH and continues to secrete estrogen and a large amount of progesterone. The glands enlarge even more and the total amount of endometrium increases. At the end of this phase the ovarian hormones inhibit the hypophysis, and in the absence of a chorion the corpus luteum is no longer stimulated.

E, The corpus luteum degenerates and the level of ovarian hormones falls. The stroma and the glands shrink; the arteries become more coiled and produce stasis, which leads to necrosis.

F, Necrosin is formed, which constricts the vessels in the deeper portion of the basal layer and prevents excessive hemorrhage. The hypophysis has been freed from its inhibition and produces more FSH to start a new burst of follicular activity.

Daron made reconstructions of the spiral arterioles from serial sections of the menstruating endometrium in the monkey. Bartelmez made reconstruction of the elements of the endometrium in the human, showing spiral arterioles with their muscular contraction cones, and also the glands and venous sinuses, and it was from this reconstruction that the colored illustration, Fig. 83, was made.

The demonstration of this terminal arteriole control of endometrial nutrition and disintegration has been carried a step further by Jones and Brewer, who used uteri removed in tubal pregnancy cases for their studies. Such uteri are specially suitable for this purpose in that they are removed for a lesion outside the uterus, and the conditions inside the uterus closely simulate menstrual disintegration and bleeding. They demonstrated by photomicrographs the terminal arteriole and the endometrial disintegration in the area it supplied.

What controls the muscle cone governing the blood supply through the arteriole? Is it controlled by nerve impulses or by endocrine influence? Tracing the uterine nerves to their minute terminations, it is found that sympathetic and parasympathetic fibers pass to the functioning elements of the uterine wall, as shown diagrammatically in Fig. 83. Hence the arterial muscle cone is under control of the sympathetic and parasympathetic nerves. These nerves are influenced by various pharmacological substances, and by endocrines. It is well known that the cyclic changes in the endometrium are under endocrine control, and it is reasonable to suppose that this endocrine control is exercised through the neuromuscular apparatus just mentioned, for it is there ready and is well suited to the purpose.

The endocrine influence may be exercised by remote effect, through the nerves, or by direct local effect on the nerve endings and muscle fibers. Possibly both pathways are used, but the local influence is evidently large, for menstrual disintegration and exfoliation of the endometrium takes place a little at a time in a spotty way. Also, the same sequence of events takes place when remote influence has been eliminated by division of the sacral nerves, and with transplantations of endometrial tissue into the eye.

Cyclic venous changes have been described by Okkels. In the early proliferative stage there are two types of veins, the thin-walled distended veins and the thick-walled stems; the former are most numerous at this stage. In the late proliferative stage the venous stems increase in number and their walls become thicker due to a layer of elastin under the endothelium. In the early secretory stage there are distended thick-walled stems plus thin-walled venous sinuses or lakes. During the late secretory stage there are superficial large lakes and deeper thick-walled wavy stems extending to the basal layer. During menstruation necrobiotic changes occur in the veins and their capillary connections.

Cyclic Histochemical Changes.—In the past ten years the chemical changes occurring within the component cells of various tissues have been intensely studied. During this time our knowledge of the function of the various hormones has been greatly increased but we still know little about the exact mechanism of their action, though it is known that they participate in

the regulation of biochemical reactions in certain tissues. Since it is now generally recognized that biochemical reactions occurring in all living tissue are dependent upon enzyme-catalyzed reactions, it is thought that the hormones are important regulators of the enzymatic reactions.

Though the enzyme-hormonal relationships in the gynecologic field are still not completely clear, it is evident that many of the mysteries of normal and abnormal physiology will be solved by study of the biochemical processes occurring in the individual cells. Because of the importance of these studies to the future knowledge of pelvic function, mention of a few of the recent findings will be given. For more detailed reports the reader should consult the various studies of Wislocki and Dempsey, the excellent review by Meyer and McShan on hormone-enzyme relationships, and the symposium, *Menstruation and Its Disorders*, edited by Earl T. Engle. An account of methods of histochemistry has been presented by David Glick.
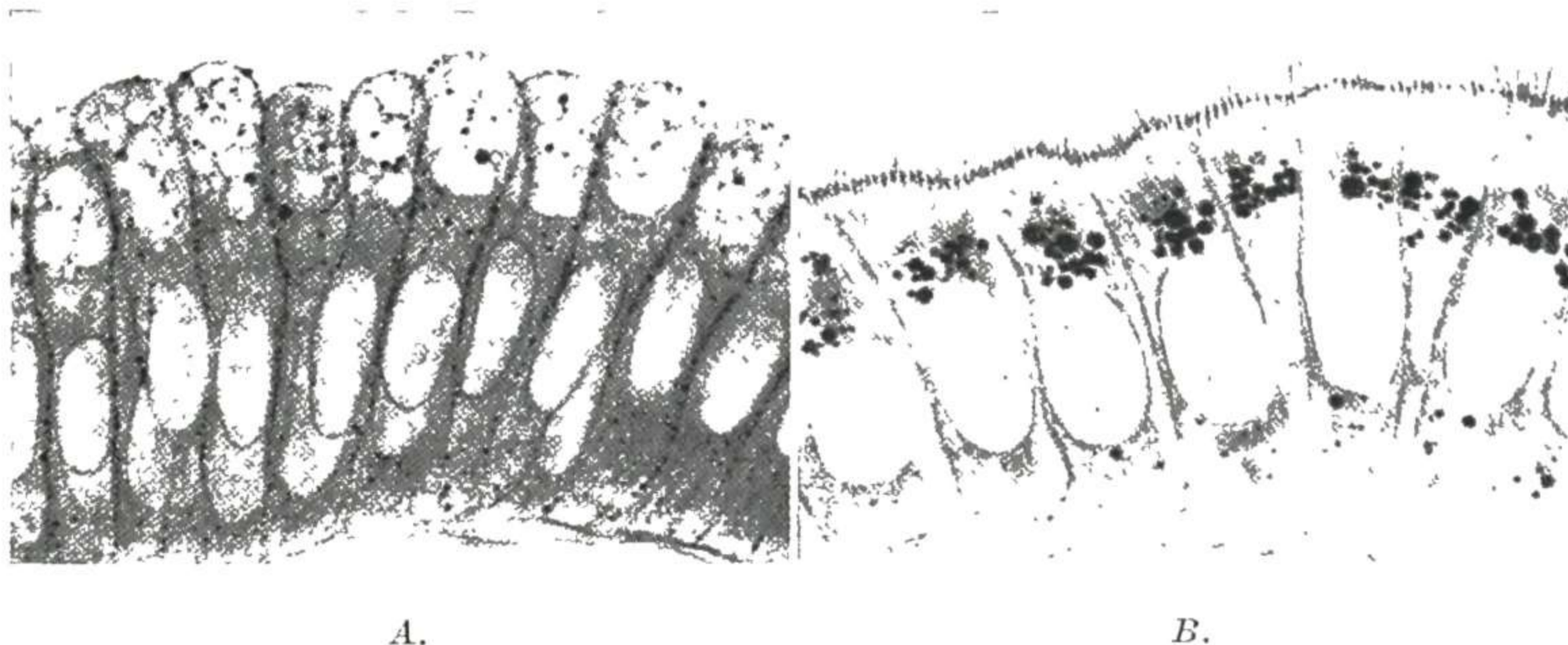

A.   B.

Fig. 86.—*A*, Epithelial cells from human uterine cervical gland stained for fat with sudan black, twentieth day of cycle. Fixation in 10 per cent formalin, frozen section, stained for one minute in a 70 per cent alcoholic solution of sudan black. ($\times 7$ ocular, $\times 90$ objective.)

B, Epithelial cells from neck region of a human uterine cervical gland stained for fat with sudan black, twentieth day of cycle. Fixation in 10 per cent formalin, frozen section, stained for 7 minutes in a 70 per cent alcoholic solution of sudan black. ($\times 7$ ocular, $\times 90$ objective.) (From Wislocki and Bunting, in Menstruation and Its Disorders, Charles C Thomas.)

Using histochemical methods of study, numerous chemical substances have been found in the ovary and endometrium. The localization of these substances in the organ and in the individual cells has been made possible by the use of various staining methods and also by the metachromatic reaction of certain substances to the same stain. By these methods it has been shown that there are present in the tissues of the reproductive organs not only carbohydrates such as glycogen but also fats (Fig. 86, *A* and *B*), proteins, vitamins, enzymes, and numerous other substances. The amounts of these substances present and their locations vary throughout the menstrual cycle. In this way the areas of activity in functioning tissues such as the ovary and endometrium can be localized so that the physiology and metabolism of individual cell groups can be definitely determined.

Although we are chiefly concerned with endometrium in this section, some observations on ovarian histochemical changes will be included.

ENDOMETRIUM.—There are some facts known concerning proteins, fats, and lipase in the endometrium, but the substances which have been studied most intensively are glycogen and the enzyme, alkaline phosphatase. As men-

tioned under Cyclic Glandular Changes, glycogen deposits in the cells follow a definite cyclic pattern, and it is known that the alkaline phosphatase is at least one of the enzymes influencing the glycogen metabolism (Fig. 87).   (See also article by Stuermer and Stein.)
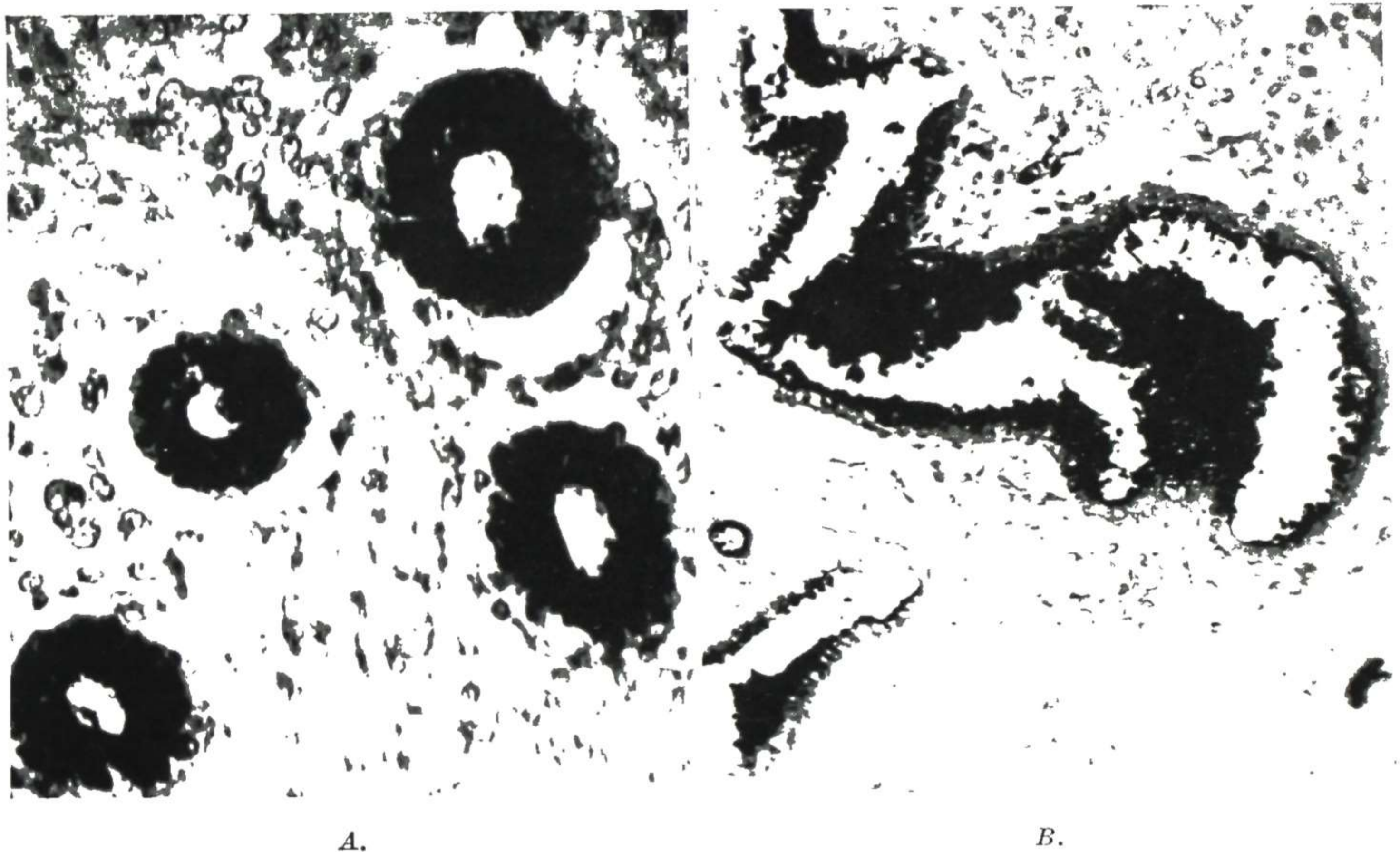

A.   B.

Fig. 87.—*A*, Endometrial gland epithelial cells containing alkaline phosphatase during the estrogenic phase. *B*, In the progestational phase only the secretions, capillaries, and sometimes the nucleoli show a positive reaction for the alkaline phosphatase. (From Arzac and Blanchet: J. Clin. Endocrinol., April, 1948.)

Fig. 88.—Glycogen in the endometrial gland epithelium during the estrogenic phase is present in coarse granules in the basal portion of the cells. (From Arzac and Blanchet: J. Clin. Endocrinol., April, 1948.)

Since the quantitative estimation of glycogen in the endometrium by Van Slyke in 1936, numerous articles have been written on the glycogen cycle in the endometrium. Spyker and Fidler found that in the early growth phase the endometrium contains only small amounts of glycogen and after ovulation the amount increases rapidly, reaching a peak around the fifteenth to the twentieth day of the cycle. Atkinson and Engle and, later, Arzac and Blanchet found that the alkaline phosphatase present in the endometrium shows a reverse relationship with the glycogen present (Fig. 88). The amount of this enzyme present was high during the early part of the cycle and it decreased during the last half of the cycle so that there was none present a few days before and during menstruation. Recently Atkinson found that the amount and distribution of alkaline phosphatase in the endometrium is correlated with ovarian activity. In castrated mice and monkeys estrogen treatment increased the phosphatase in the endometrial gland epithelium while subsequent progesterone treatment resulted in a diminution of the enzyme in the surface and glandular epithelium of the endometrium. Atkinson suggests that the phosphatase plays an active role in such hormone-regulated processes as endometrial growth and fat and glycogen metabolism.

Zondek and Hestrin found that the endometrium contains phosphorylase, an enzyme which catalyzes equilibrium between the cori ester and glycogen. The amount of the enzyme present in the endometrium varies with the deposition of glycogen. They feel that the phosphorylase synthesizes the glycogen for storage, and that amylase, which is also present in the endometrium, mobilizes the stored glycogen, converting it into sugars which are diffusible through cell membranes. It can be seen that the diffusible sugars are of tremendous importance to the implanting ovum and early ovular survival.

Hughes states that the amount of sugar stored in the endometrium is dependent, not only on normal hormone function but, indirectly, on the type of arteriolar development. Glycogen is not present in anovulatory cycles nor is it present in hyperplasia of the endometrium. Alkaline phosphatase is formed during the preovulatory stage in the endothelial cells of the arterioles in small amounts and in large amounts on the twenty-sixth day of the cycle, when there is very little or none in the glandular epithelium. It is possible that the amount of glycogen or glucose present is determined to a large extent by the type and development of the spiral arterioles.

The clinical importance of glycogen, alkaline phosphatase, and vitamin C in sterility and habitual abortion has recently been shown by Hughes. In a series of cases of sterility and habitual abortion, the chief factor seemed to be the failure of the endometrium to produce adequate amounts of carbohydrates.

Beta glucuronidase is another enzyme found in the endometrium; Fishman and his associates found that the amount of this enzyme present in the endometrium increased through the first three weeks of the cycle. It is important in the metabolism of the estrogenic hormones. Its concentration in human cancer tissue is much higher than it is in normal tissue. In a recent article, Fishman and his co-workers found that the vaginal fluid in women past the menopause contains more than that of younger women, and they feel

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a definite cyclic pattern, and it i t
least one of the enzymes influencin
also article by Stuermer and Stein.

A.

Fig. 87.—A, Endometrial gland epithelial
the estrogenic phase. B, In the progestation I p
times the nucleoli show a positive reaction
Blanchet: J. Clin. Endocrinol., April, 19

Fig. 88.— Glycogen in the endometrial   in   estrogenic phase
is present in coarse granules in the ba d portion   ate and Blanchet:
J. Clin. Endocrinol., April, 1948.)

SYSTEMIC CHANGES ASSOCIATED WITH MENSTRUATION

It is now known that menstruation, formerly considered a local phenomenon, is accompanied by systemic changes. The significance of these findings, a few of which are discussed below, is still not clear.

It has been shown by Brewer and also by Salvatore that there are rhythmic changes in the capillary fragility during the menstrual cycle of normally ovulating women. He feels that this change is probably due to vascular spasm. Capillary hemorrhage was produced more easily during menstruation and for several days prior to it, than it was during the rest of the cycle. These facts indicate that menstruation is accompanied by general as well as local vascular changes.

Davis and Hulit noted that the eosinophile count in the circulating blood dropped at ovulation and remained low during the luteal phase.

Mickelsen, Dippel, and Todd checked the vitamin C level of fasting plasma and found that there was a sharp increase with ovulation. This fitted in with the previous finding that the amount of vitamin C in the corpus luteum paralleled the degree of luteal development. In cattle it was demonstrated by Phillips and associates that the vitamin C level reached a peak on the day the cow came into heat. Later, Sutton and his co-workers correlated the ability of cattle to breed with the peak of the blood level of vitamin C. In some cases he was able to correct sterility by intravenous injections of large amounts of vitamin C immediately prior to breeding the cow. The hormone blood levels have been discussed under endocrines. The changes in the chemical constituents of the blood during the menstrual cycle have not as yet been extensively studied, but the presence of a menotoxin has been known for centuries, though its presence was not conclusively proved until Macht found it in the blood, sweat, and milk of women.

Temperature changes during the menstrual cycle have been discussed and are further elucidated under the chapter on Sterility.

Psychic changes during the premenstrual and menstrual period are common knowledge and it is hoped that the new psychosomatic approach to the problem will bring some explanation of the mechanism involved.

Menopause

In most women menstruation ceases at the age of forty-four to forty-seven years. There is considerable variation in this respect, the menses sometimes ceasing three or four years before that age or continuing some time afterward. This period of cessation of menstruation, known popularly as "change of life," is designated technically the "menopause." The two terms "menopause" and "climacteric" were formerly used interchangeably as though synonymous, but they really refer to two distinct though related phenomena. As our fund of knowledge increases and lines of investigation and discussion multiply, there is increasing necessity for exactness in the terms employed in medical study and exposition.

The changes that take place in the uterus during and after the menopause are similar to those occurring in all the genital structures, namely, a gradual atrophy of the functioning parts (endometrium and muscular tissue) and a general fibrous change (Figs. 89 and 90), and a slow diminution in size.

The menses usually cease gradually—that is, the flow may be less free or may continue a shorter time than usual, or the flow may be missed entirely for one or two periods. This partial and irregular absence of the menstrual flow may continue for one or two or three years before it ceases entirely. This gradual diminution of the menstrual flow is natural and there are frequently slight nervous disturbances ("hot flashes," etc.) that can hardly be classed as pathologic. But many of the symptoms that are ordinarily considered as part of the "change of life" are really not so; for example, increased menstrual flow, bloody discharge between the menstrual periods, leukorrhea, pelvic pain. These are due to pathologic conditions. They mean that something is wrong, and they require investigation, that the trouble may be remedied.

This is important especially in the case of vaginal discharge, whether bloody or leukorrheal. It seems to be the general impression among women that irregular bloody discharges are natural during the "change of life." But such discharges are not natural—they usually mean either inflammation or cancer. One of the saddest things in gynecologic work is that a large proportion of the cases of cancer of the uterus are beyond the possibility of a cure when first examined. In such a case it is supposed by the patient and her friends that the slight bloody discharge which at first appears is "natural to the change of life," and so no attention is paid to it. Later, too late, they find that it is due to serious disease, which, because of neglect, has progressed to such an extent that it is beyond cure. The physiology of the cervix has been discussed under Anatomy.
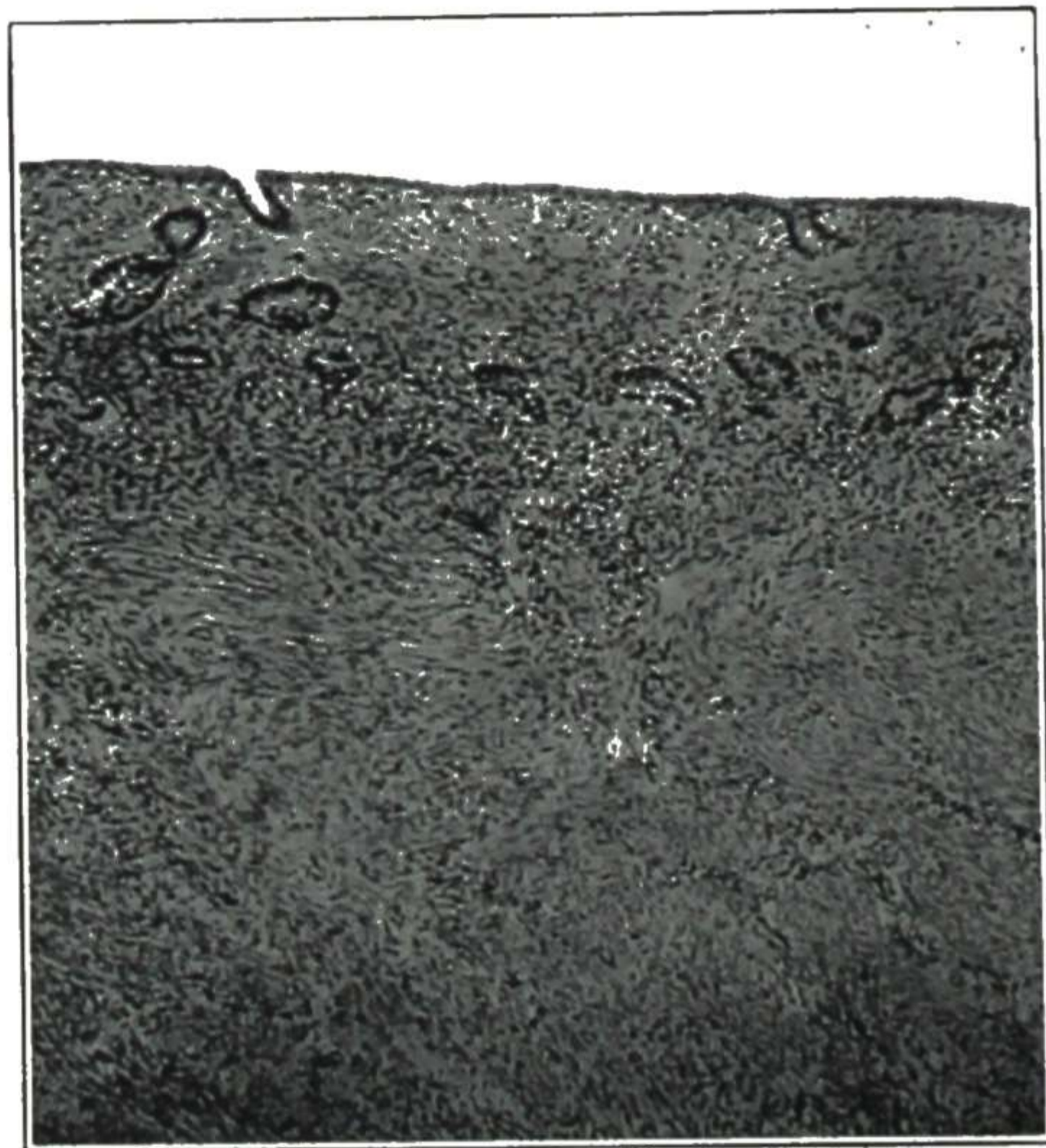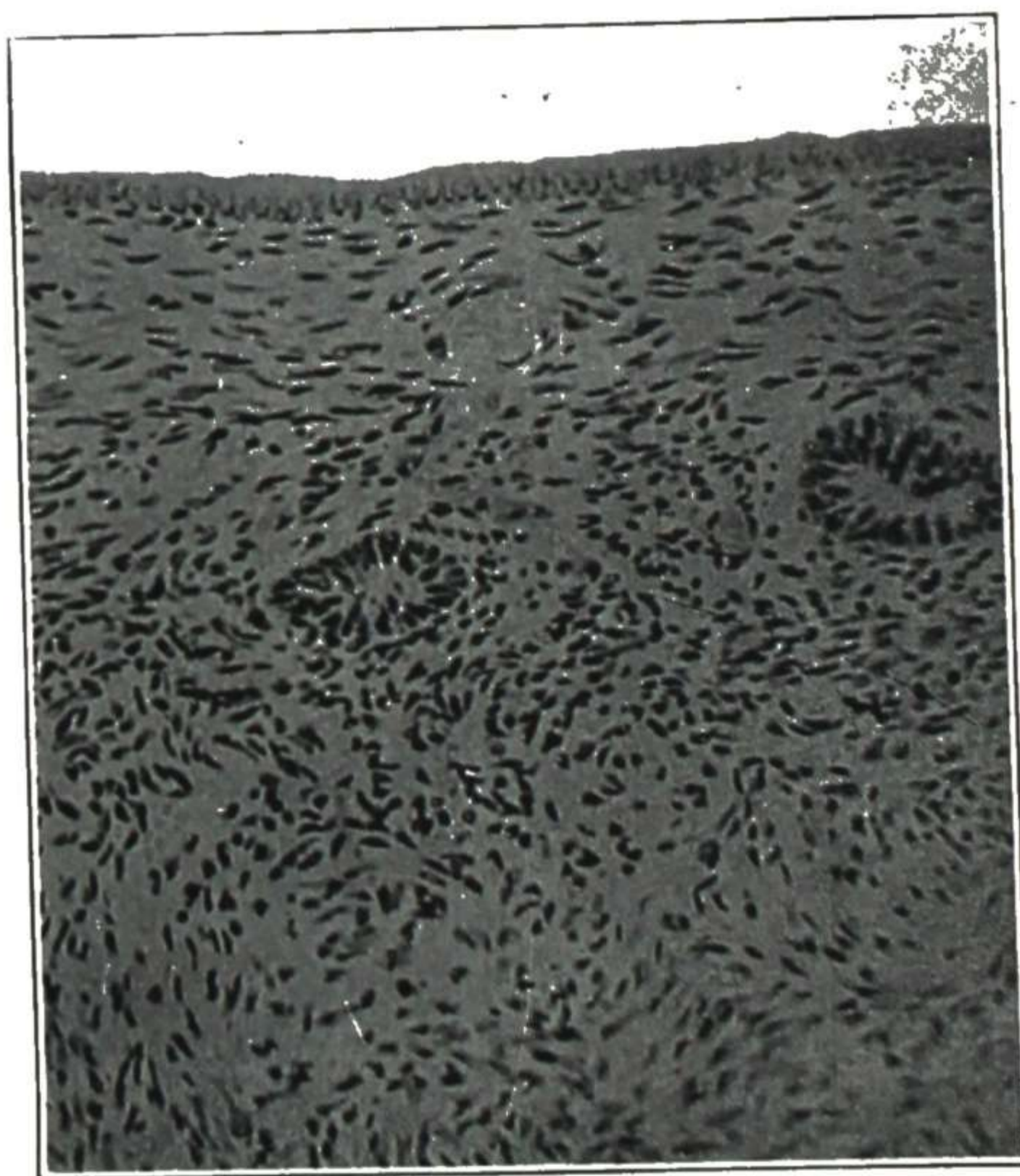

Fig. 89.   .   Fig. 90.

Fig. 89.—Senile endometrium, from patient aged sixty-two years, showing marked thinning of endometrium, stroma scant, and glands few. Entire thickness of endometrium only 0.5 mm.

Fig. 90.—High power of same specimen, showing the atrophic changes in the stroma and glands. Gyn. Lab.

FALLOPIAN TUBES

The fallopian tubes, or oviducts, are two small muscular tubes, one on each side, which extend from the fundus uteri outward in the upper part of the

broad ligament toward the pelvic wall (Figs. 45 and 58). Each tube has a small central cavity extending its whole length. The inner end of this cavity communicates with the uterine cavity and the outer end opens into the peritoneal cavity. Thus there is a direct opening from the outside of the body into the great peritoneal sac, through the vagina, uterus, and fallopian tubes. This is why infection of the genital tract in a woman leads to peritonitis so much more frequently than infection of the genital tract in a man—the infection in the vagina simply extending along this mucous tract directly into the peritoneal cavity.

The tubes vary considerably in size and somewhat in shape in different individuals. The length of each tube is from three to five inches and the direction is outward, backward, downward, and inward—somewhat resembling a shepherd's crook—and partly surrounding the ovary.

That portion of the tube lying in the uterine wall is known as the **interstitial portion** or uterine portion. It has a very narrow lumen (Fig. 91). That portion of the tube extending from the margin of the uterus to the beginning of the curve is called the **isthmus**. It is about an eighth of an inch in diameter and is firm. The lumen is small, but becomes gradually larger toward the outer end (Fig. 92). The outer, curved, dilated portion of the tube is known as the **ampulla**. It is about the size of a lead pencil and the lumen also is much larger than that of the isthmus (Fig. 93). The outer end of the tube is known as the **fimbriated extremity** or the infundibulum. This consists of a funnel-shaped expansion surrounded by a fringe of slender, fingerlike processes called "fimbriae." One of these, which extends to the ovary and is attached there, is called the "ovarian fimbria."
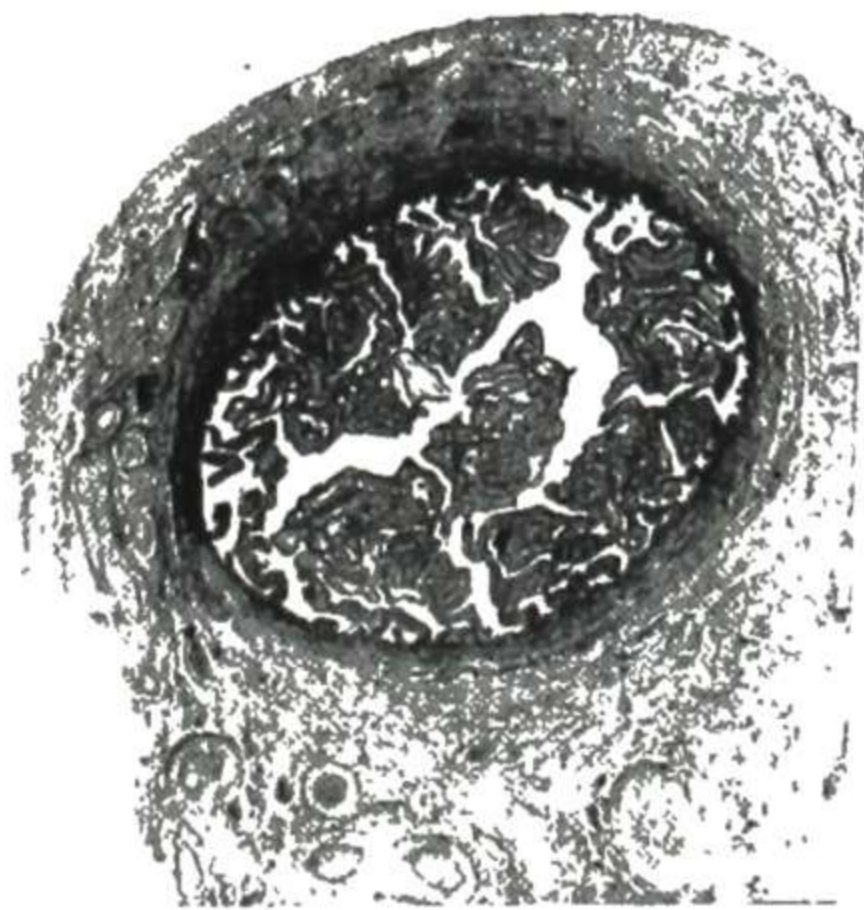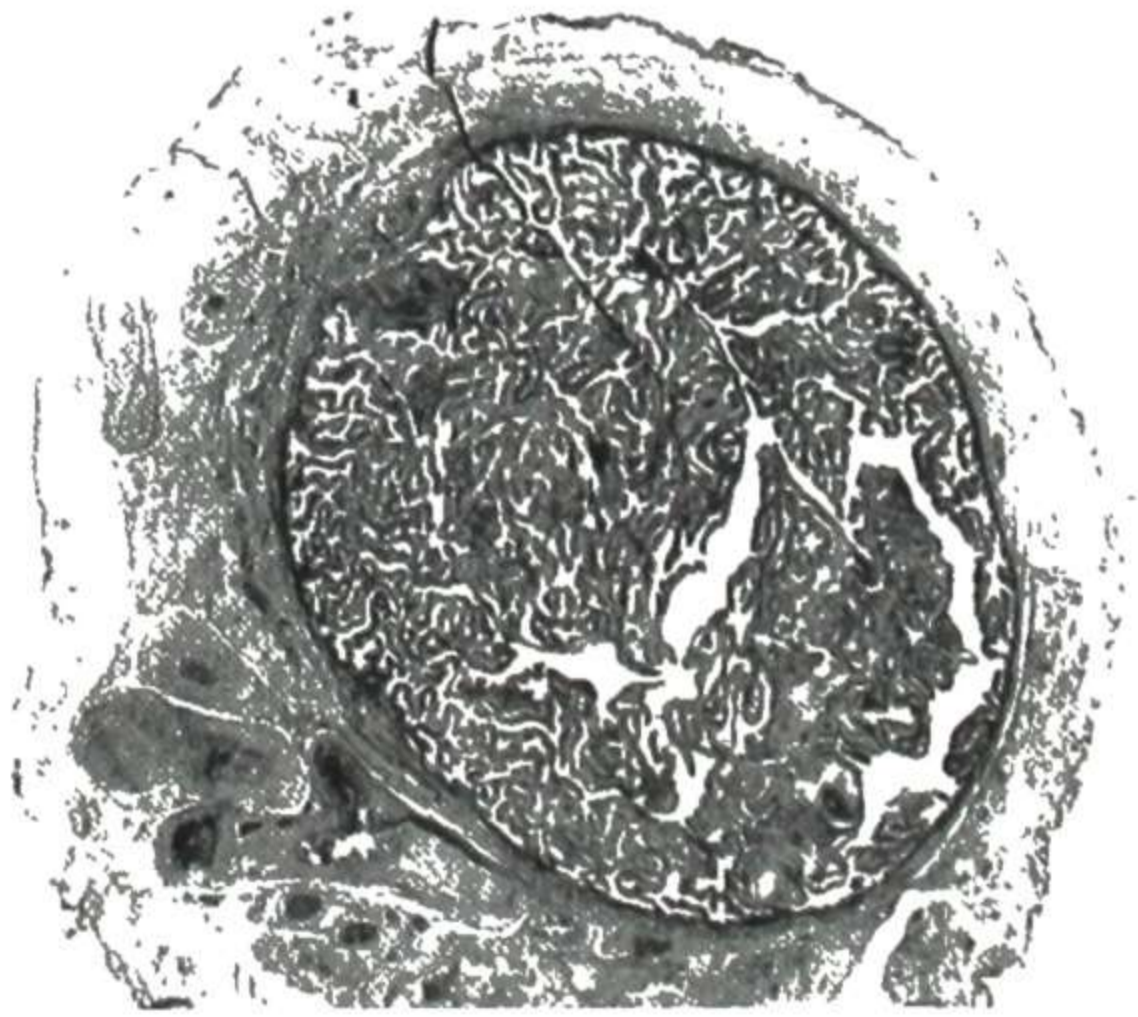

Fig. 91.   Fig. 92.   Fig. 93.

Figs. 91 to 93.—The lumen of the tube at different portions. Notice the progressive increase in size of the lumen from the uterine end outward. Fig. 91, the uterine end; Fig. 92, the middle; Fig. 93, near the outer end. Gyn. Lab.

In structure the wall of the tube is largely muscular, resembling the uterus. In fact, it is derived from the same fetal organ as the uterus. The tube lies beneath the peritoneum of the upper margin of the broad ligament, and its wall presents three layers: peritoneal, muscular, and mucous.

The **peritoneal layer** does not differ materially from peritoneum elsewhere. It is composed of flat endothelial cells lying on a basis of firm connective

tissue. Immediately beneath the peritoneum is a layer of connective tissue sometimes called the subperitoneal layer. In this run blood vessels and lymphatics. The interstitial portion of the tube has, of course, no peritoneal layer, as the muscular tissue of the tube is in immediate contact with the muscular tissue of the wall of the uterus.
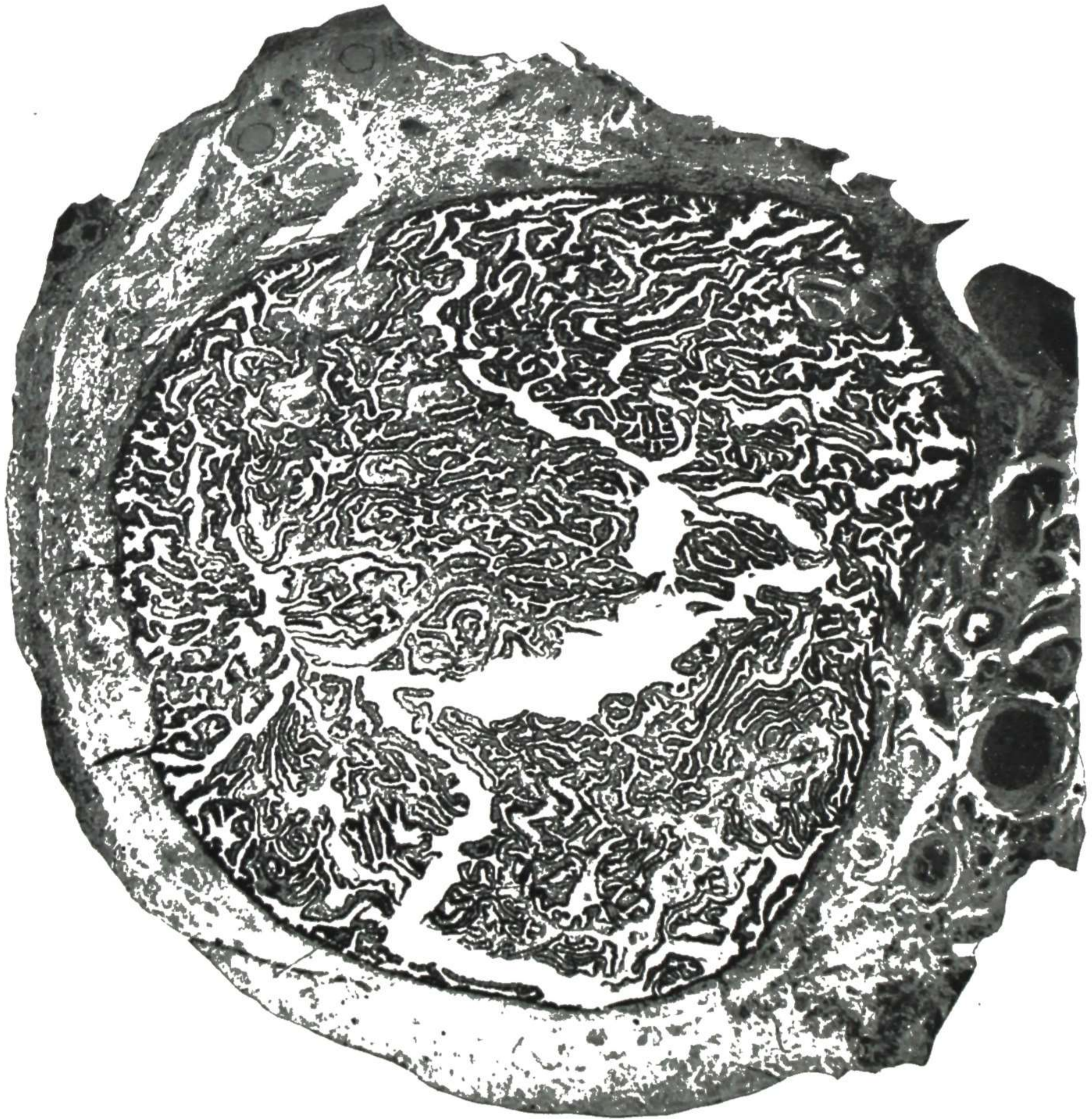
Fig. 94.—Section of the tube near the outer end. The extensive longitudinal folding of the mucosa produces the spaces that give the glandlike appearance in the section. In this mass of delicate folds inflammation would quickly cause disorganization. The intricacy of the folds in the normal tube is well shown in this photomicrograph. Gyn. Lab.

The **muscular layer** of the tube is composed of involuntary muscular tissue, disposed in two strata, an outer longitudinal and an inner circular. Both of these strata are continuous, with similar muscular strata in the uterus. The internal stratum sends prolongations of muscular tissue into the four principal folds of the mucosa. The muscular layer is thinner at the abdominal end than at the uterine portion of the tube. The increased thickness of the wall at the abdominal end of the tube is due to the many folds of mucosa.

The **mucous** layer of the tube, like the uterine mucosa, is placed directly upon the muscular layer—there is no intervening submucosa. The tubal epi-

thelium consists of two types of cells: the ciliated or nonsecretory and the nonciliated or secretory. Beneath the epithelial layer the mucosa is composed of "stroma cells," very much like those found in the uterus, except slightly smaller. Between the stroma cells is a delicate connective tissue framework. There are found also capillary blood vessels and small lymph channels.

There are no glands in the tubal mucous membrane. The depressions which look like glands are due simply to the folds of the mucous membrane. As there are no glands in the tube, there can be no mucous secretion, such as takes place in the uterus. The fluid by which the tube is distended in certain pathologic conditions is inflammatory exudate and not glandular secretion.

The mucous membrane is much folded longitudinally. There are four principal folds into which prolongations of the muscular tissue take place. There is no muscular tissue in the many smaller folds. In the interstitial portion and in the isthmus the folds are few and simply longitudinal, but in the outer portion of the tube (the ampulla) they become very complex and fill the tube with folds extending in every direction (Fig. 94)—so much so that it is sometimes difficult to decide which is the main canal of the tube. The cilia of the epithelium project into the lumen of the tube and by their movement toward the uterus aid the passage of the ovum in that direction. In the presence of this delicate and much-folded mucous membrane, inflammation in the tube quickly causes serious changes. The cilia are lost, the folds become adherent, pockets of serum or pus form, and the picture of the tubal interior may be so changed as to be hardly recognizable.

Vessels and Nerves.—The blood supply of the tube comes from the ovarian artery through several small branches. The uterine artery helps to supply the tube in some cases. The veins open into the pampiniform or ovarian plexus and pass into the broad ligament. The lymphatics join with those from the ovary. The nerve supply comes from the pelvic plexus of each side.

PHYSIOLOGY OF THE TUBES

The primary function of the fallopian tube of each side is to convey ova from the corresponding ovary to the uterus. It is supposed to require several days for the ovum to pass the length of the tube. In addition to this, the tube conveys spermatozoa in the opposite direction, and it is usually in the tube that the union of the ovum and the spermatozoon takes place.

The mechanism by which the ovum is carried from the ovary into the tube is complicated. The many factors involved in mammals and in the human being have recently been reviewed by Bruni.

Just prior to ovulation, through contraction in the supporting structure of the ovary and muscular contraction of the tube and its ligaments, the fimbriated end of the tube covers over the surface of the ovary. Westman proved this by injecting a drop of Lipiodol under the peritoneal sheath of the end of the tube and then tracing its movements by x-ray film. Direct observation by peritoneoscope and at laparotomy have since confirmed this. At about the time of ovulation by means of the hoop of erectile tissue, described by Ginfellt, the end of the tube is held wide open.

With ovulation the liquor folliculi causes the ovum to adhere slightly to the surface of the ovary until it is transported into the tube partially by the

cilia and partly by the current created by ciliary movement toward the uterus. The transport of the ovum through the ampullar portion of the tube is due to the peristaltic contractions of the tube toward the uterus. At the isthmus of the tube the progress of the ovum is delayed since the isthmic segment remains contracted for three or four days after ovulation has occurred. The annular sphincter also remains contracted. At about the seventh postovulation day or later, the isthmus and sphincter relax and strong peristaltic contractions occur in the remainder of the tube, forcing the ovum through the isthmial and interstitial portion of the tube and into the uterine cavity.

The developmental adaptation of epithelium to the particular function it is to perform is well seen in the tubal fimbriae, in which practically all the cells are ciliated (Fig. 95) instead of being of the mixed variety seen in the intratubal mucosa. Besides this action of the cilia directly on the ovum, the constant movement of all the cilia causes a slight current of peritoneal fluid toward the interior of the tube from all directions. This helps to carry the ovum or any other particles into the tube. The fact that there is such a current toward the interior of the tube has been demonstrated in animals by the injection into the pelvic peritoneal cavity of numerous small insoluble particles, which were found later in the tubes.

Fig. 95.—Fimbriated end of the tube. Showing the epithelium consisting almost entirely of ciliated columnar cells. (From Novak: Am. J. Obst. & Gynec.)

Cyclic variations in the intratubal pressure, interpreted as periastaltic contractions, have been shown experimentally in a sow's fallopian tube. These are controlled by estrin and progestin in the blood.

Kymographic records of Rubin tests made on human beings show similar variations, which are interpreted by Rubin as evidence of peristaltic contractions of the tube. We have observed what appeared to be peristalsis under the fluoroscope during a hysterosalpingogram. The rate of contractions varies at different times in the cycle, contractions being most frequent just before and after ovulation and least frequent about the time of menstruation.

Normal Changes in the Tubal Epithelium

In studying the physiology of the uterus it was found that this organ, particularly the mucosa, was subjected to normal changes under three conditions: menstruation, pregnancy, and the menopause. Now, in the fallopian

tube also, we find normal changes, due to menstruation, to pregnancy, and to the menopause. Speaking generally, it may be said that these changes are like those occurring in the uterus but are less marked.

During **menstruation** there is congestion of the tube and possibly a slight effusion of blood into the interior of the tube. If this does take place, however, it is slight and is of no importance when considering the source of the menstrual blood. Practically all of the menstrual blood comes from the uterus.
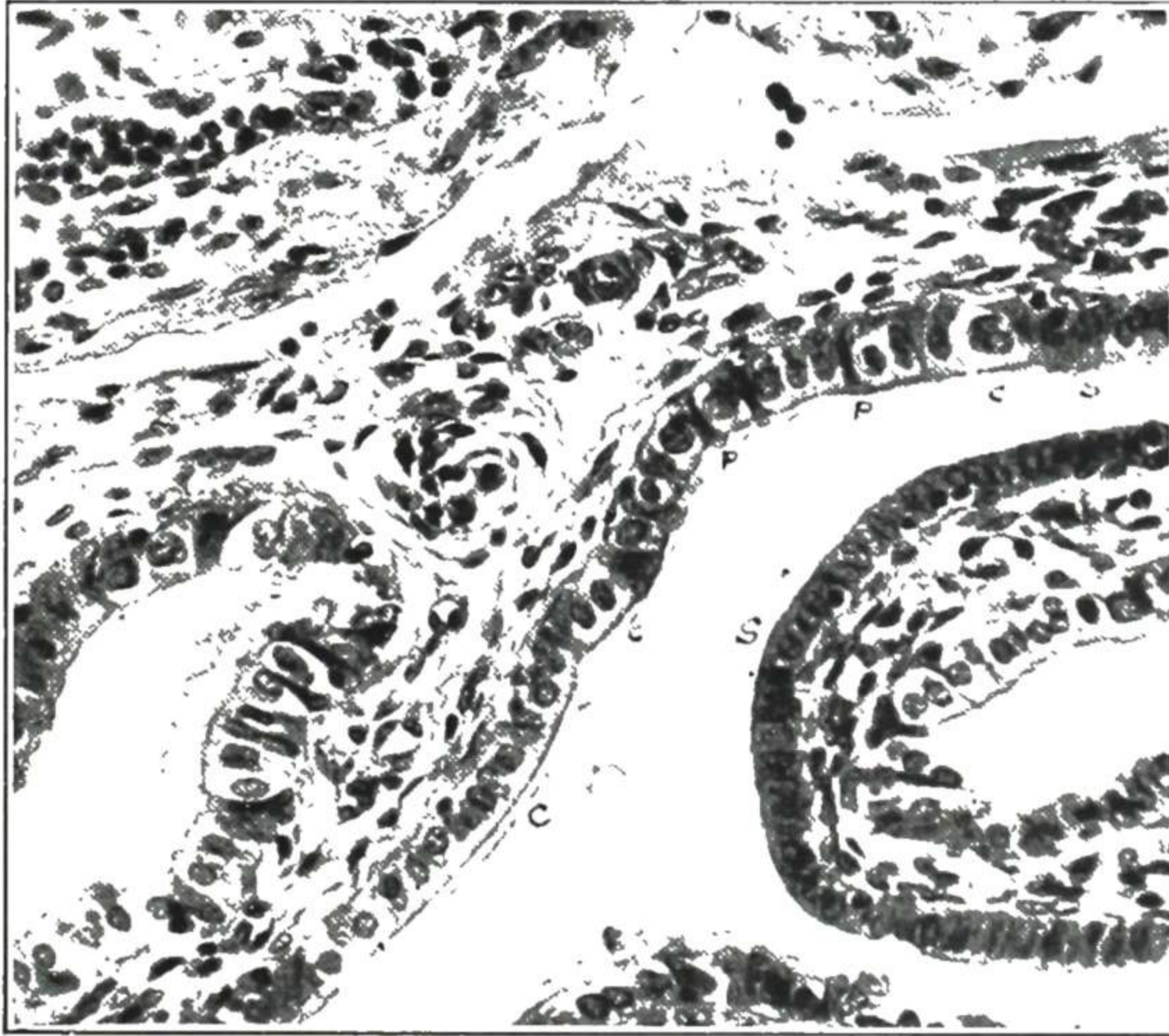

Fig. 96.—Normal postmenstrual tubal epithelium showing ciliated, nonsecretory cells (*C*), nonciliated, secretory cells (*S*), and peg cells (*P*). (From Novak: Am. J. Obst. & Gynec.)
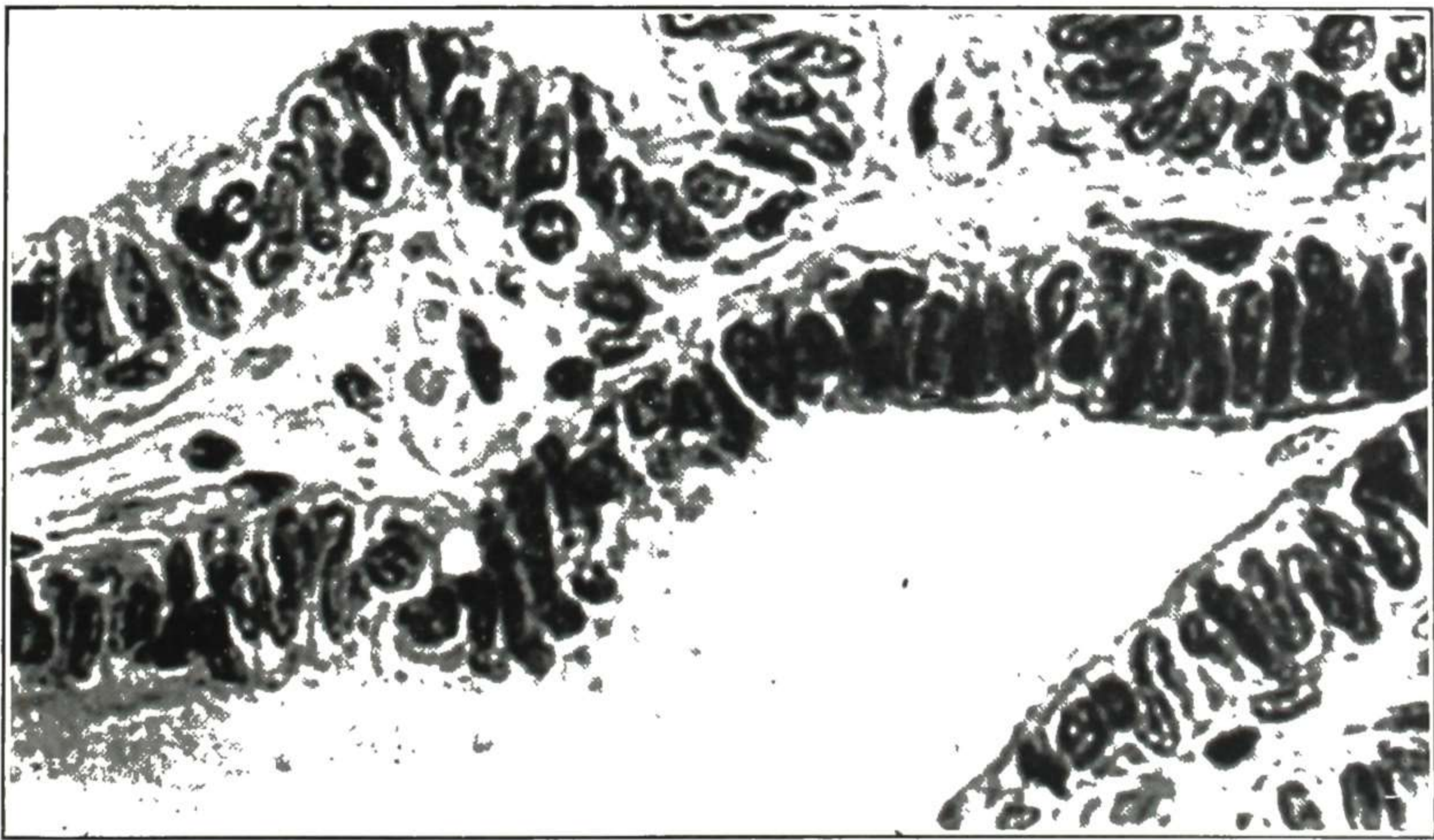

Fig. 97.—Tubal mucosa growth stage. The cells are all about the same height. Secretory cells are seen at *C*, ciliated cells at *B*, and straight rod cells at *A*. Gyn. Lab.

In a case of removal of the uterus by operation and the fastening of one of the tubes in the vaginal incision, a slight bloody flow was noticed at the menstrual periods for a few months. But such tubes are pathologic, and it is an open question whether or not bloody flow would take place from a normal tube.

The tubal epithelium contains two types of cells: the ciliated or nonsecretory, and the nonciliated or secretory.

The epithelium of the tubes also goes through cyclic changes during the menstrual cycle. The following stages have been described by Novak and Everett:

1. Postmenstrual stage (Fig. 96) in which the epithelium is low at first but rapidly increases in height, so that by the third or fourth day after menstruation it is almost as tall as during the interval. The cells are narrow, closely packed, and, after the first day or so, of uniform height.

2. In the growth phase (Fig. 97) the epithelium is uniformly tall, the ciliated cells being broad, with rounded nuclei near the free margin. The nonciliated cells are narrower and the nuclei are deeply placed.

3. In the premenstrual phase (Fig. 98) the ciliated cells become lower, so that the secretory cells project beyond them, giving the margin a ragged appearance. The secretory cells show a bulbous herniation into the lumen of the tube, often carrying the nucleus with it. Mitoses are rarely seen.
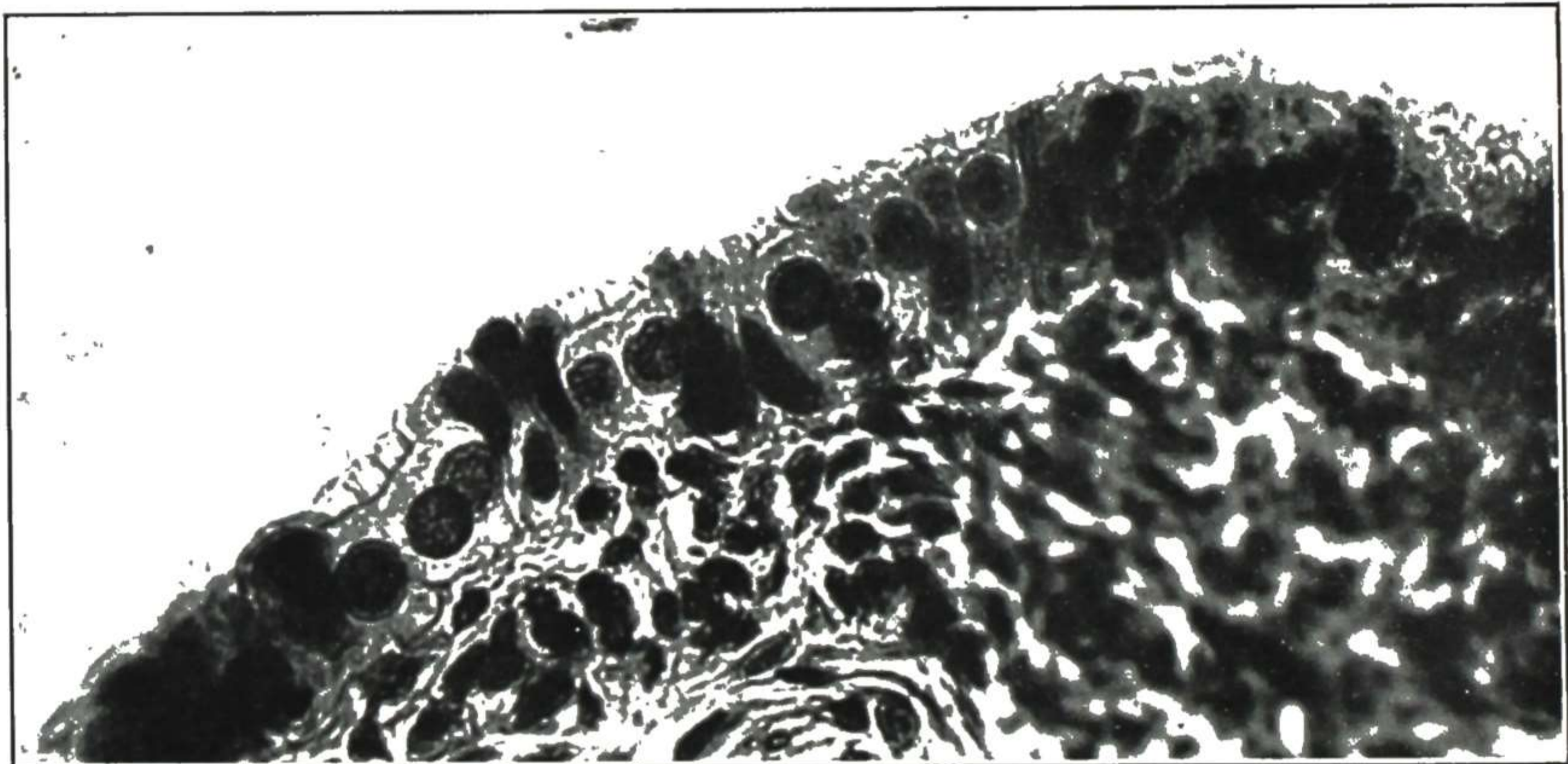

Fig. 98.—Tubal mucosa, premenstrual phase. The marked irregularity in height is clearly seen; the nonciliated secretory cells, seen at *A*, are much higher than the ciliated nonsecretory cells seen at *B*. The three secretory cells clustered together at *A* show partially extruded nuclei with their rounded surface toward the tubal lumen. Gyn. Lab.

4. During the stage of menstruation the epithelium becomes quite low. The secretory cells, having emptied out into the lumen, are very low, and frequently the nucleus is quite bare of cytoplasm.

Novak, in an instructive article on the different types of genital epithelium and their occasional variability, emphasizes the strategic position of the fallopian tube in this segmental development of the original coelomic epithelium to different functions in the different parts of the tract.

PELVIC PERITONEUM

The pelvic peritoneum is that portion of the wall of the peritoneal sac which lies in the pelvis. It is attached more or less closely to the pelvic organs, and its free surface comes in contact with the peritoneal surface of the intestines as they move about in the lower abdomen. To get an idea of the

distribution of the peritoneum in the pelvis, imagine a piece of thin cloth laid over the pelvic organs and tucked down firmly around them (Fig. 57).

Starting from the abdominal wall, the peritoneum passes on to the bladder, and from the posterior surface of the bladder to the uterus. The height of the abdominovesical fold of peritoneum varies much with the varying size of the bladder, which fact is of great importance in surgical work. The distance to which the peritoneum extends down the anterior surface of the uterus varies considerably in different persons. Usually it extends to the level of the internal os and is about an inch above the anterior vaginal fornix. When the bladder is distended, the peritoneum is drawn upward somewhat. This vesico-uterine fold of peritoneum forms the two so-called "vesico-uterine ligaments."

The peritoneum then folds over the uterus and tubes and round ligaments, covering these structures and forming the "broad ligament" of each side. All the posterior surface of the uterus is covered with peritoneum except that portion lying within the vagina. The fold of peritoneum extends a considerable distance below the point of attachment of the vagina to the uterus (Figs. 2 and 51) before being reflected on to the rectum. The deep pouch of peritoneum thus formed is called the "cul-de-sac of Douglas." It is known also as the "posterior cul-de-sac" and as the "posterior peritoneal pouch" and as the "recto-uterine pouch." This posterior cul-de-sac is very important surgically. A collection of exudate or a tumor in this situation can be easily felt from the posterior vaginal fornix. This is the point of incision in posterior vaginal section.

The peritoneum, as it is reflected from the uterus to the rectum, helps to form the "sacro-uterine ligaments." The sacro-uterine ligaments, two in number, one on each side, extend backward from the lower part of the uterus around the rectum to the sacrum. They are composed of connective tissue, a few muscular fibers, and peritoneum. The cul-de-sac of Douglas dips down between them for a considerable distance (Fig. 57). The expanse of peritoneum extending from the sacroiliac ligament to the broad ligament of each side forms a kind of shelf. The two together are sometimes called the "recto-uterine shelves." There is also a fold or shallow pouch of peritoneum on each side between the fallopian tube and the round ligament. A small portion of the uterus at the sides and in front is not covered with peritoneum (Fig. 51).

The structure of the pelvic peritoneum is much the same as of peritoneum elsewhere. It is a very thin and smooth membrane, formed of a basis of delicate fibrous and elastic tissue, supporting large endothelial cells.

PELVIC CONNECTIVE TISSUE

The anatomy of the strong fascial layers of the musculofibrous sling, or diaphragm, closing the pelvic outlet are discussed in Chapter 4. This supporting diaphragm is formed by the levator muscles and the fascia above and below, the upper being known as the pelvic fascia and the lower as the obturator fascia, as well as by other names. Between the peritoneum and the well-marked pelvic fascia there is a large amount of loose connective tissue distributed so as to fill the spaces between the organs. This connective tissue is designated as the endo-pelvic fascia. Where it is necessary for the organs to change their relations

to each other in physiologic activity, the connection is open and loose to permit of free movement. The principal collections of connective tissue are at the sides of and in front of the cervix uteri and at the base of each broad ligament. The tissue also runs up the sides of the uterus between the peritoneal layers, as shown in Fig. 99.

Fig. 99.—Diagrammatic representation of the connective tissue areas in the pelvis at different levels. Left side of pelvis—section through cervix, showing the large area of connective tissue at side of cervix. Right side of pelvis—section at higher level, showing how the broad ligament becomes thinned, leaving only a small amount of connective tissue at side of corpus uteri.

The areas of connective tissue are exceedingly rich in lymphatics and veins. Inflammation taking place in this connective tissue is called "pelvic cellulitis." The connective tissue about the uterus is often spoken of as the "parametrium" or parametrial tissue, and inflammation of it is accordingly called "parametritis." In the beginning of gynecologic work it was supposed that nearly all inflammation in the pelvis outside the uterus was inflammation of the connective tisue (i.e., pelvic cellulitis), but it was soon found that in the majority of cases of an inflammatory mass in the pelvis (particularly in gonorrheal inflammation) the process extended from the uterine cavity to the tube and then to the peritoneum. In such cases, if there is connective tissue involvement at all, it is usually a late development and of only secondary importance. There are exceptions to this rule; for example, those inflammatory conditions resulting from tears of the cervix or from operation on the cervix, or from puerperal in-

fection (staphylococcic, steptococcic). In such cases the inflammation extends directly through the wall of the uterus into the pelvic connective tissue.

The connective tissue between the pelvic organs has been the subject of considerable controversy among those who have specially investigated it, the difference being as to whether it normally presents condensations forming distinct fascial sheets between the organs or only loose areolar connective tissue. Evidence pro and con will be found in the articles by Goff, by Curtis, Anson, and Beaton, and those by Koster, Hurd, Hornaday, Sears. The matter is not so easy to settle as might appear at first thought. The following factors complicate the problem of deciding what is normal anatomy in this respect: (1) Prolapse cases, on which most operative work involving these tissues is carried out, are not normal but pathological, and the tendency of the prolapse drag on areas of loose connective tissue would seem to be to produce lines of tension and condensation resulting in the condensed sheets or fascial planes so often found in such cases. (2) As will be seen in the literature mentioned, careful investigation of normal pelves by microscopic study of cross sections of the urethrovaginal and vesicovaginal and rectovaginal septa failed to show evidence of such sheet-like condensations. (3) In the dissection of loose connective tissue it is difficult to avoid artifacts giving the impression of such sheetlike planes of condensed tissue. Demonstration of microscopic cross sections of undisturbed portions of the septa, along with regular dissections of other portions of the same septa, would assist in arriving at a decision in the matter. (4) The difficulty in securing employment of uniform and clearly understood terms for the different portions of the pelvic connective tissue is aggravated by a secondary meaning attached to the word "fascia."

As ordinarily understood, a fascia or fascial layer is a firm, condensed sheet of connective tissue, in contradistinction to the other kind which is loose areolar connective tissue. In addition to this primary and well-understood meaning of the word, the term is used by anatomists to designate also loose areolar connective tissue. This secondary use of the term leads to misunderstanding and confusion, as may be seen by perusal of the literature of this controversy, and there seems little chance of a clarification of the matter as long as this term is used to designate two diametrically opposed types of structure. For anatomical knowledge and nomenclature we naturally depend on the anatomists, who make a lifetime study of the subject. A welcome aid toward uniform and generally understood designations in this matter would be to limit the term fascia to a condensed sheet of connective tissue, and designate loose areolar connective tissue as areolar connective tissue.

VAGINA

The vagina is a musculomembranous canal extending from the vulva to the neck of the uterus, around which it is attached. It lies between the bladder and the rectum as shown in Fig. 2.

Its **size** and **shape** are variable and it is capable of great distention, as is seen when the child passes through it in labor. The length of the vagina is ordinarily three to four inches along its anterior wall, and five to six inches

along its posterior wall (Fig. 100). It is constricted at its lower end, where it is partially closed by the hymen, and it becomes dilated toward the uterine extremity.

Normally, the anterior and posterior vaginal walls lie in contact, and on cross-section the **cavity** is represented by a slit having somewhat the shape of the letter H (Fig. 101). The wide diameter of the vagina, some distance up the canal, is the transverse diameter, but the wide diameter of the vulvar cleft is the anteroposterior diameter. Furthermore, the anterior end of the vagina lies so far up in the narrow part of the pubic arch (in patients where the perineum has not been damaged) that there is not much room laterally. Consequently, in introducing the speculum, the preferable way is to introduce one finger into the vaginal opening and press the perineum well back, so that the vaginal opening is stretched anteroposteriorly and made to correspond in a measure with the vulvar cleft, and then to introduce the speculum obliquely as shown in Chapter 2. When the speculum is well past the entrance, so that it may be used to depress the perineum, it is then turned with its width in the transverse diameter of the vaginal canal and introduced all the way.
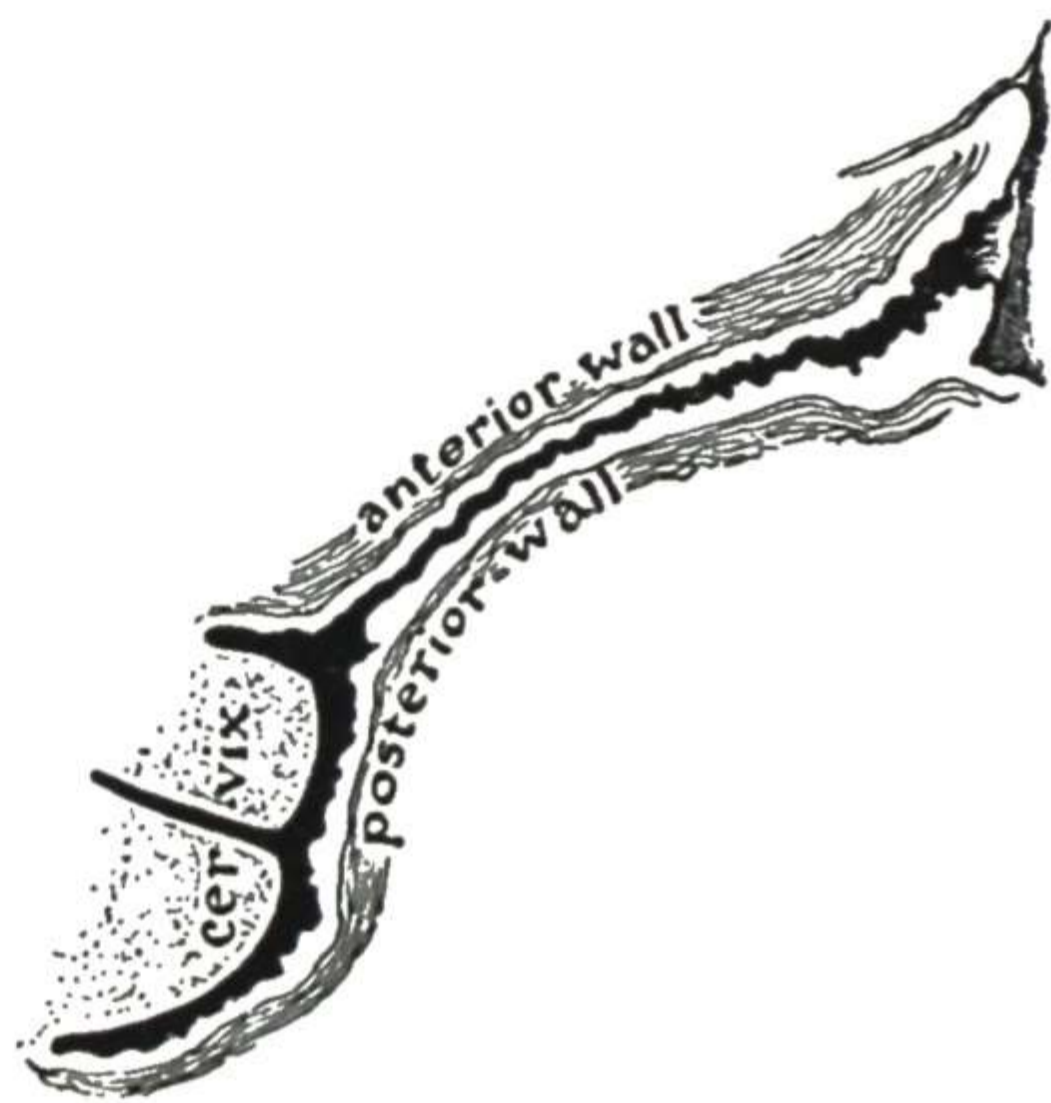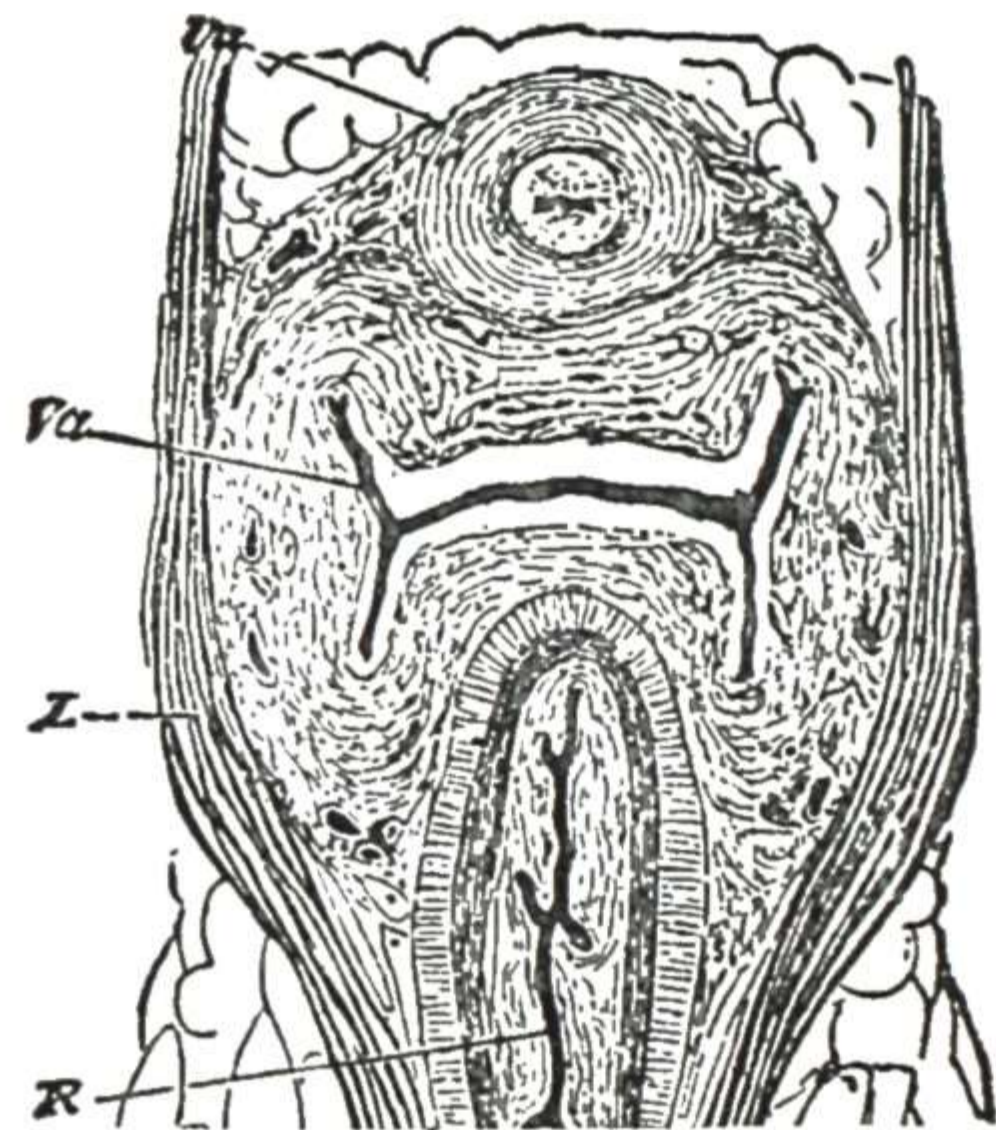

Fig. 100.   Fig. 101.

Fig. 100.—Longitudinal section of vagina. (From Skene: Diseases of Women, D. Appleton-Century Co.)

Fig. 101.—Cross section of the pelvic structures, showing the relations of the urethra, vagina, rectum, and levator ani muscles. Notice how the vaginal walls fold so that the shape of the cavity approximates the letter H. *Ur*, Urethra; *Va*, vagina; *R*, rectum; *L*, levator ani muscle. (From Savage: Anatomy of Pelvic Organs.)

Relations.—Fig. 100 shows the angle which the axis of the uterus normally bears to the axis of the vagina. The upper end of the vagina surrounds the lower end of the uterus. That portion of the cervix uteri projecting into the vagina is known as the vaginal portion (portio vaginalis). The attachment of the vagina extends higher on the posterior wall of the cervix than on the anterior. The vaginal mucosa is continued on the cervix as far as the external os.

The upper end of the vagina is termed the "vaginal vault." The term "fornix" is also much used, the anterior fornix being that portion of the vault in front of the cervix, and the posterior fornix being that portion lying behind the cervix, and the right and left lateral fornices lying to the right and left, respectively. With the uterus in normal position, the posterior fornix is much deeper than the anterior, for the vaginal wall is attached higher on the posterior surface of the cervix than on the anterior.

The vagina is surrounded by important structures. The anterior wall is in contact with the urethra and the base of the bladder. The vaginal wall and bladder wall and the tissue lying between them constitute the vesicovaginal septum. The posterior wall for the lower three-fourths of its extent is attached to the anterior wall of the rectum, except for the very lowest portion, which is separated from the rectal wall by the perineum. The vaginal and rectal walls and the tissue lying between them constitute the rectovaginal septum. The upper fourth of the posterior wall is separated from the rectum by the recto-uterine pouch of peritoneum, known as the "cul-de-sac of Douglas." The sides of the vagina give attachment to fibers from the levator ani muscles and the rectovesical fascia.

The wall of the vagina presents three layers: an external connective tissue layer, a middle muscular layer, and an inner mucous layer.

The CONNECTIVE TISSUE layer serves to attach the vagina to the adjacent organs. It contains the external plexus of veins, and is composed of connective tissue filled with lymphatics and blood vessels, the veins being especially numerous. The attachment of the vagina anteriorly is firm in the lower third where it is attached to the urethra. It is more loosely attached to the bladder in the middle and upper third, particularly the latter, and is easily separated in operating.

The MUSCULAR LAYER contains involuntary muscle fibers arranged in bundles without distinct strata. Some of the bundles are longitudinal, some transverse, and some oblique. The muscular layer is thicker at the lower than at the upper end.

The MUCOUS LAYER, or lining of the vagina, presents on the surface a thick squamous epithelium of many layers (Fig. 102), with the usual basal layer just above the connective tissue. The vagina normally contains no glands. The secretion found in the vagina comes from the cervix and the endometrium, principally the former. The vaginal walls are kept constantly moist with the secretion, and consequently the epithelium desquamates before it advances so far in the process of cornification as is seen in integument. In cases of prolapse, where the vagina is turned outside the vulva and is subjected to friction of the clothing and is kept dry by contact with them, it becomes more like ordinary epidermis and shows well-marked keratin changes. The mucosa (epithelium and connective tissue immediately under it) is attached to the muscular coat by a submucous layer of loose connective tissue which is very rich in interlacing veins, about some of which are bundles of muscular fibers, forming a kind of cavernous tissue.

The vaginal mucosa is thrown into numerous large folds called "rugae." Extending longitudinally along both the anterior and the posterior wall of the vagina is a prominent ridge, best marked in the virgin. These ridges are known as the "columns" of the vagina, and from them the rugae extend laterally. The columns and rugae become more or less obliterated by childbirth, so that in many multiparae the vagina walls are almost smooth.

Vessels and Nerves.—The blood supply of the vagina comes from the anterior trunk of the internal iliac, through the vaginal, uterine, middle hemorrhoidal, and internal pubic arteries. These anastomose freely in the vaginal

wall. The veins of the vagina are arranged principally in two plexuses that form complete sheaths around the canal. One plexus is external to the muscular layer, while the other lies just beneath the mucosa. These veins form an intricate network and communicate freely with the plexus of the other organs and with the plexus of the broad ligament.

The lymphatics from the lower third of the vagina, it is generally held, join those from the external genitals and empty into the inguinal glands. But Poirier, who has made a special study of the subject, claims that all the lymphatics of the vagina empty into the pelvic glands and that when an injection of the vaginal lymphatics is made, even just within the hymen, no injection material passes to the inguinal glands except through some anastomosing channels. The lymphatics from the middle third of the vagina empty into the hypogastric glands. Those from the upper third join with the lymphatics of the cervix uteri and pass to the iliac glands.

The NERVE SUPPLY of the vagina comes from the pelvic plexus of each side.

PHYSIOLOGIC CHANGES IN THE VAGINA

Studies in the cyclic changes of the vaginal epithelium in the human being and in the monkey point to the fact that these changes are under the control of the ovarian hormones.

Dierks, from a study of vaginal biopsies in women at various times in the menstrual cycle, concluded that the relationship of the three epithelial layers of the vaginal epithelium varied at different times in the period. The vaginal epithelium is composed of three layers: a basal layer, a functional layer, and a cornification or intra-epithelial layer.

Immediately after menstruation there is an increase in the functional layer and a marked proliferation of the basal layer so that this latter becomes many layers thick. Numerous mitoses can be seen in the basal layer. Near the middle of the cycle or about the time of ovulation a layer of new cells is formed between the basal layer and the functional layer. This layer was described by Dierks as the intra-epithelial cornified zone. The cells in this layer contain granules and the nuclei are small and dark staining. With the onset of the menses the functional and the intra-epithelial layers are destroyed and cast off, leaving the basalis layer completely denuded at the end of menstruation. There are some dissenting views as to the presence of this cycle, but this work has been confirmed by Geist, Papanicolaou, and others. Papanicolaou has followed the cyclic changes by the vaginal smear technique and can tell the time of ovulation and diagnose early pregnancy with a high degree of accuracy.

In young girls before puberty the vaginal epithelium consists of an inactive basal layer three or four cells deep. There is no glycogen in these cells during this period. With the onset of puberty the three layers are promptly established, and glycogen appears in the cells. After the menopause the vaginal epithelium returns to the prepuberty state with no glycogen in the cells and a basal layer of only two or three layers. In the newborn child some of the maternal estrin is still present and, as would be expected, glycogen is found in the vaginal epithelial cells for three or four weeks after birth. The mature epithelium can be produced in the prepuberty girls by theelin administration.

The variations in the mucosa of the vagina at different ages were studied by Davis and Pearl, and Fig. 102, presenting these changes from birth to old age, is from their article.
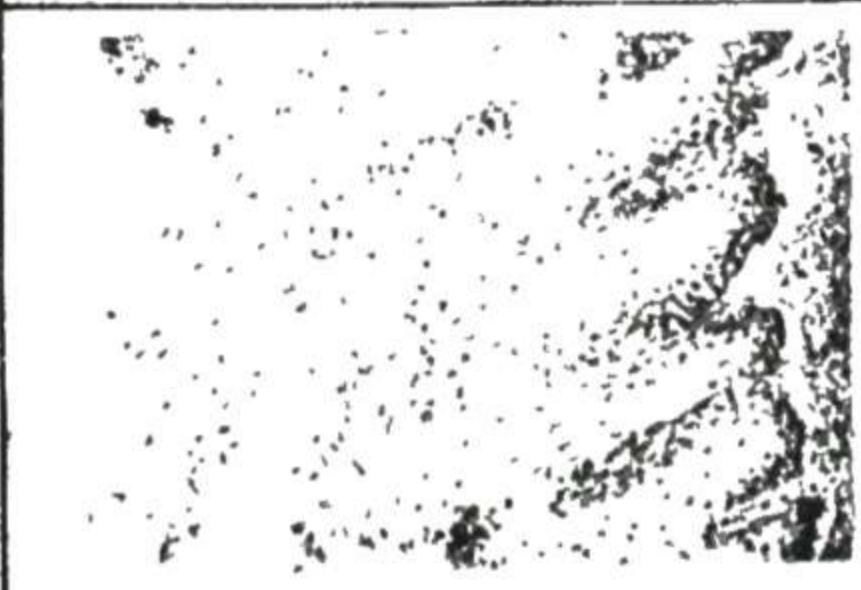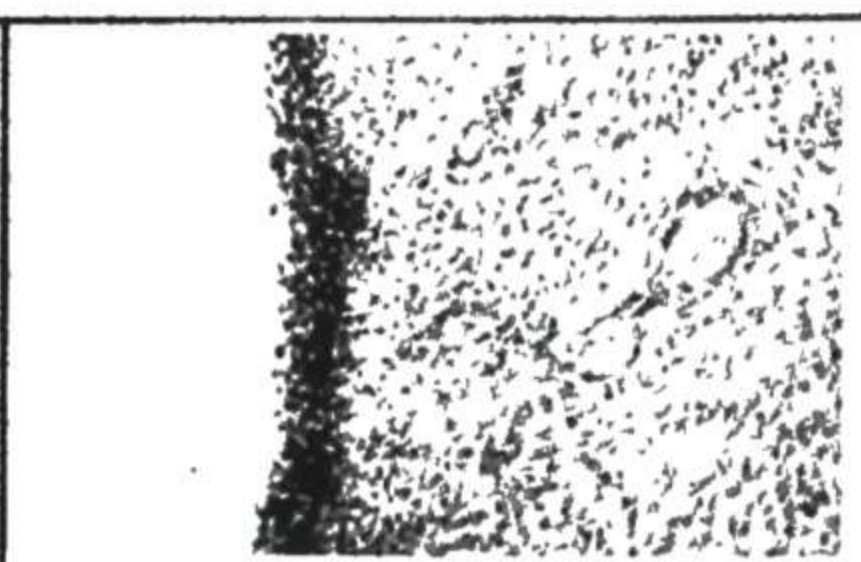
	Newborn	Month old Child	Puberty	Sex-Mature	Post-Menopause
Estrogenic hormone →	+	−	appears	+	−
Epithelium →					
Glycogen →	+	−	− to +	+	−
Acidity →	acid pH 4-5	alkaline pH 7	alkaline ↓ acid	acid pH 4-5	neutral or alkaline pH 6-7
Flora	sterile ⟋ Döderlein's bac. (secretion abundant)	sparse, coccal and varied flora (secretion scant)	sparse, coccal → rich bacillary	Döderlein's bacilli (secretion abundant)	varied flora (secretion scant)

Fig. 102.—The changes in the vaginal epithelial covering at different ages, showing the dominant role of estrogen in the control of the biology of the vagina and of the character of its mucosa. (From Davis and Pearl: Am. J. Obst. & Gynec.)

Davis and Hartman summarize the similar changes found in the monkey as follows:

"The cyclic changes in the vaginal epithelium were studied in a large group of female monkeys at the Carnegie Monkey Colony by means of frequent biopsies. These rhythmic changes were coordinated with ovarian activity and ovulation.
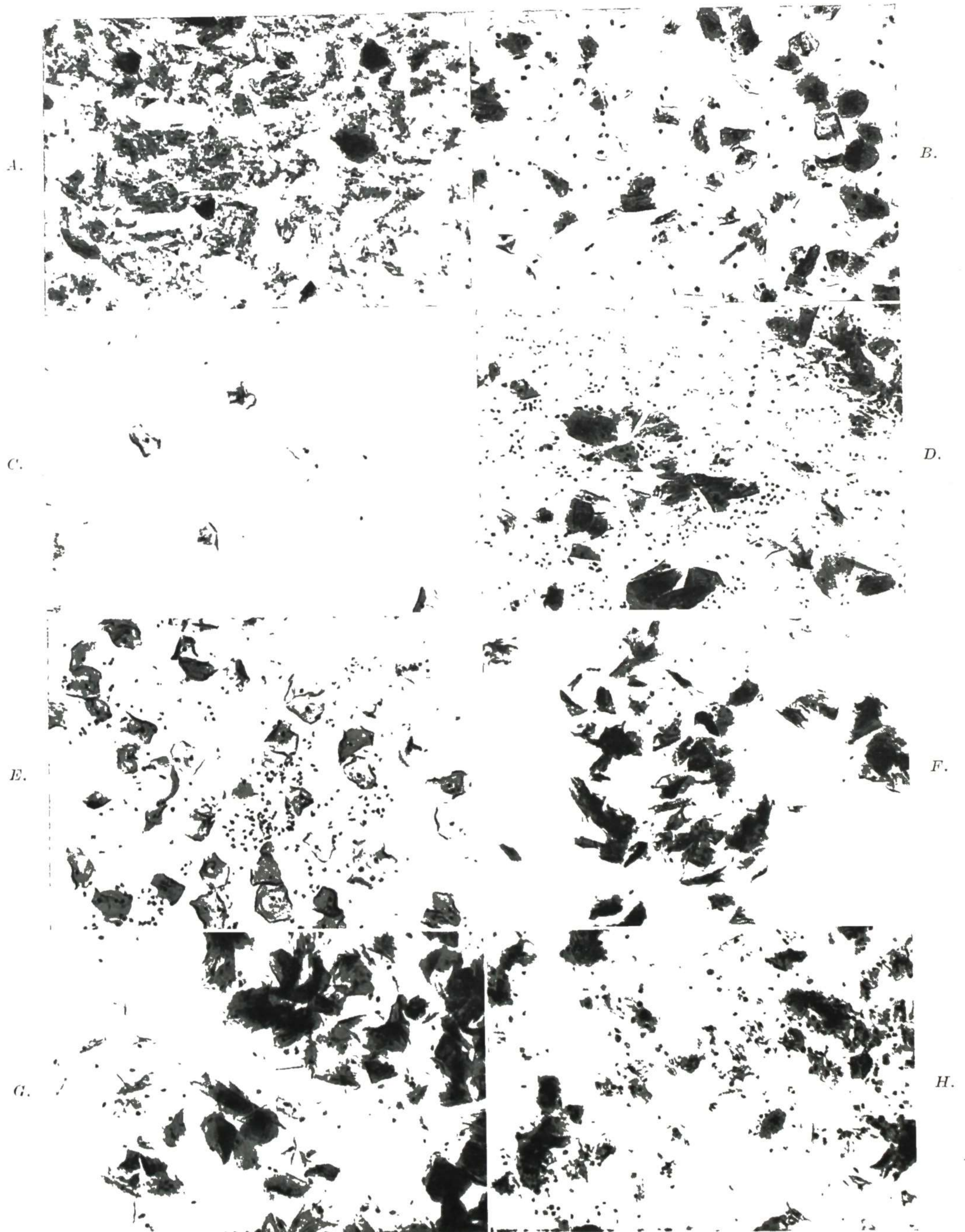
Fig. 103.—Vaginal smears during normal menstrual cycle (Papanicolaou's stain). (×165.) *A*, Postmenstrual phase: early estrogen effect (cornified cells appear darker). *B*, Late proliferative phase: good estrogen effect. *C*, Preovulatory phase: marked clearing of cells. *D*, Preovulatory phase: marked mucus and leukocytic flush. *E*, Ovulatory phase: mature cells with curling and wrinkling. *F*, Postovulatory phase: extensive clumping, marked drop in cornification. *G*, Mid-progestational phase: large pale cells, envelope-type folding, and moderate cytolysis. *H*, Premenstrual phase: free nuclei, leukocytes, bacteria, and cellular debris. (From Goldhar, Grody, and Masters: Fertil. & Steril., 1952, Paul B. Hoeber, Inc.)

"We found that the epithelium attains its greatest thickness in the mid-interval, 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 we call Dierk's layer. Following ovulation, desquamation begins and proceeds by a crumbling away of the functionalis, which is usually not completely destroyed. Mitosis begins in the basalis on the first day of menstruation, becoming most marked near the time of ovulation, and then gradually subsides.

"A cessation of ovarian activity, such as is seen at the menopause, or an abnormal ovarian activity, definitely alters these physiologic changes.

"Early in pregnancy the epithelium remains in the same state as is seen during ovulation, consisting of the typical three layers.

"Desquamation of the functional layer continues throughout pregnancy but is increased progressively following the middle of pregnancy.

"At the end of pregnancy only the basalis remains and is of irregular thickness, in many places of only three or four cells."

The vaginal epithelium in the human being undergoes changes similar to those described by Davis and Hartman in the monkey. These changes were also described in detail by Rubenstein in the human being. The changes are shown in Fig. 103, taken from an article by Goldbar, Grody, and Masters.

Estrogen stimulates proliferation of the vaginal epithelium so that it becomes many layers thick, and as the thickness increases the superficial cells are pushed farther and farther from their blood supply and hence they degenerate and become cornified. At various stages of this process typical cells appear in the vaginal smears, as described in the legends of the above-mentioned illustrations. Diagnostic use of the vaginal smear is discussed in Chapter 2.

In 1947, Rakoff, Feo, and Goldstein reviewed the physiology of the vagina. They found that, in addition to the above-described changes, there were cyclic biochemical changes. Glycogen was present in the superficial vaginal epithelium throughout the cycle until the late premenstrual phase when there was a sharp drop in the amount. The pH falls gradually from the onset of the period to ovulation, then gradually rises, reaching its highest point prior to the onset of the menses.

Cruickshank and Sharman found that the appearance of the Döderlein bacillus and an acid vaginal secretion were coincident in time with the presence of glycogen in the vaginal epithelium, and they believe that the production of the acid reaction is a defense mechanism against harmful bacteria. Early in pregnancy this reaction is absent, but it develops in the later months.

The normal vaginal discharge contains large nonpathogenic bacilli (Döderlein bacilli) which live on the glycogen contents of the exfoliated epithelial cells, and in so doing form acid which maintains the normal acidity. Any considerable diminution of the normal vaginal acidity favors the growth of pathogenic bacteria and protozoa which flourish in alkaline or less acid media. The reaction of the vaginal contents, as to acidity or tendency toward alkalinity, may be taken as a fair index as to normal or pathological character, and as a rule the greater the progress toward alkalinity the more marked the pathological disturbance. Progress toward alkalinity is measured in terms of the chemical symbol pH, which signifies a certain hydrogen-ion concentration, and increasing pH means increasing alkalinity. Extensive studies have shown that with nor-

mal contents the range of reaction is pH 3.8 to 4.4. Beyond that the discharge becomes pathological, different levels favoring the growth of different organisms as shown in the illustration.

EXTERNAL GENITALS

The external genitals (Figs. 104 to 106), called also the vulva and the pudenda, include the following structures:

Mons Veneris	Vestibule
Labia Majora	Vulvovaginal Glands
Labia Minora	Hymen
Clitoris	

The **mons veneris** is simply a pad of subcutaneous fat lying over the symphysis pubis. The triangular area which it forms is covered with hair after puberty. The upper margin is the base of the triangle and is often marked by a slight transverse crease due to bending of the abdominal wall in exercise. The sides are formed by the inguinal creases, which run downward and inward toward the pubes, making the lower pointed portion of the triangle, which is continuous with the labia majora. Examination of a microscopic section through this region shows the usual characteristics of skin, i.e., many layers of squamous epithelial cells (the deepest being cubical and the most superficial being flattened and horny) placed on loose connective tissue, and presenting hairs, sebaceous glands and sweat glands. A little deeper there is much fat, which is penetrated and held together by fibrous septa that divide it into lobules. There are also many elastic fibers.

The **labia majora** (Fig. 105) are two cutaneous folds which extend, one on each side, around the vaginal opening. They are apparently continuations of the mons veneris and, passing backward, end by joining the perineum. The external surface of each labium majus presents the ordinary characteristics of integument. Each labium is limited externally by the genitocrural folds and corresponds to that side of the scrotum in the male. The round ligament, coming through the inguinal canal of each side, terminates in the upper part of the labium majus of that side. Sometimes a distinct canal remains open for some distance along the round ligament. This is known as the canal of Nuck, and through it a hernia may take place into the labium, constituting a labial hernia. This is known also as a pudendal hernia. The hernial contents may be intestine or omentum or ovary or even the uterus. Occasionally the canal of Nuck is shut off from the peritoneal cavity, and the sac thus formed fills with fluid, giving rise to pudendal hydrocele or "hydrocele of the canal of Nuck." The inner surface of each labium majus is smooth and of a pinkish color. It has largely lost one of the characteristics of integument—the hairs—only a few fine hairs being found here.

In children the labia majora are very small and the labia minora project between them. As puberty is approached, the external labia become larger and meet in the median line. At puberty they, in common with the mons veneris, become covered with hair. A little later in life, particularly in married women, the labia minora become enlarged so much that they project forward, separating

Labium majus

Clitoris

Labium minus

Urethral opening

Vestibule

Hymen

Vagina

Greater vestibular
gland (Bartholin's)

Fossa navicularis

Urogenital trigone

Bulbocavernosus M.

Perineal body

Transv. perineal M.
(Superficial)

Levator ani M.

Ext. sphincter ani M.

Gluteus maximus M.

Labial artery

Vestibular bulb

Ischiocavernosus M.

Posterior labial N.

Dorsal N. of clitoris

Artery of clitoris

Posterior labial A.

Perineal branches
of Post. Fem. N.

Ischial
tuberosity

Perineal N.

Int. hemorrhoidal A.

Dorsal N. of clitoris

Pudendal N.

Int. hemorrhoidal N.

Sacrotuber. lig.
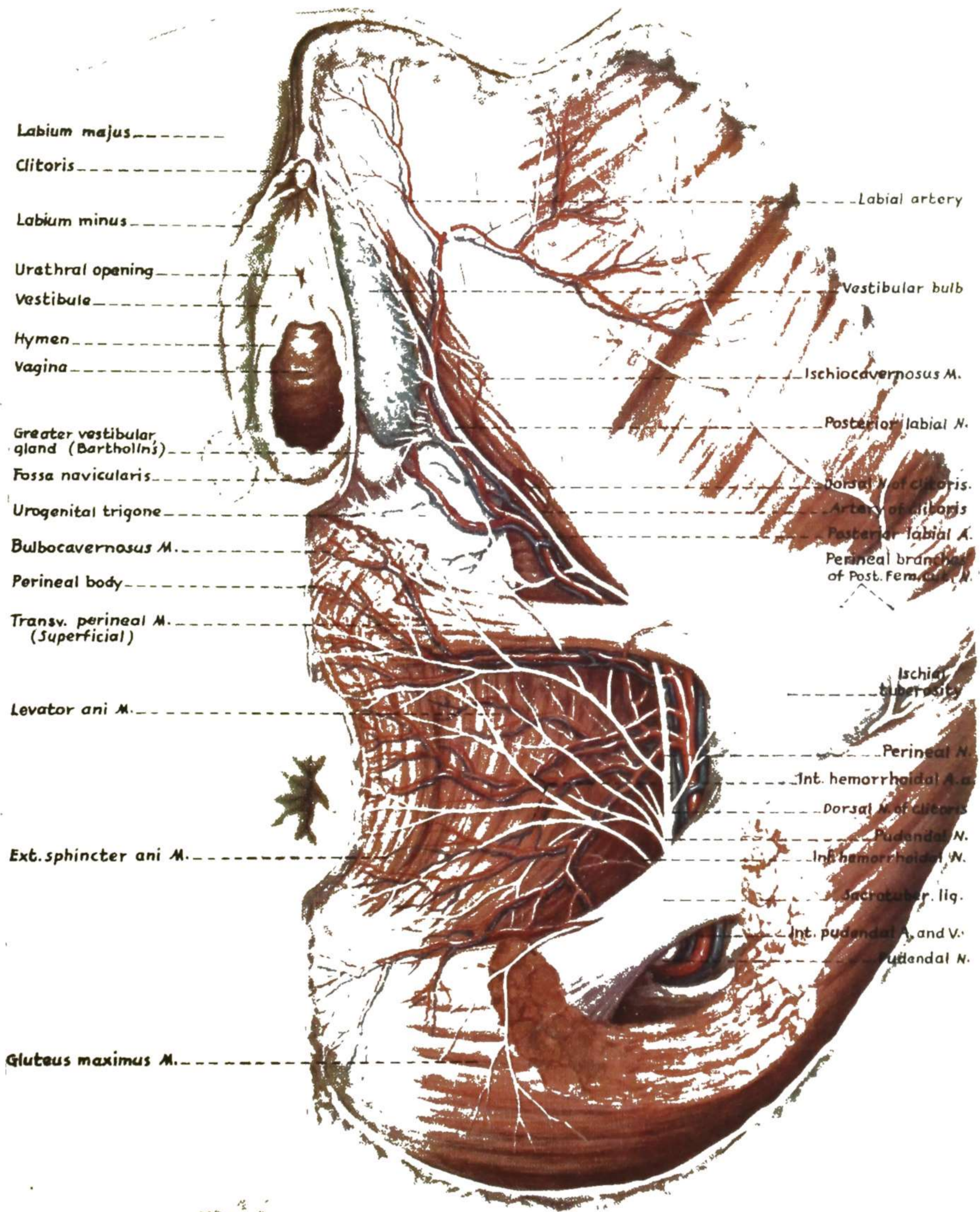
Int. pudendal A. and V.

Pudendal N.

Fig. 104.—The external genitals, with blood supply and nerve supply. (Modified from
Savage, Spalteholz, Sobotta.)

the labia majora. In old age the labia undergo marked diminution in size and prominence, the shrinking being due largely to absorption of the fat.

Microscopic examination of a section of a labium majus shows the same structures found in the mons veneris, the only difference being that on the inner surface of the labium there are only a few hairs, and they are small. There are, however, many sebaceous glands. There are also, of course, the arteries, veins, and other structures found in cutaneous and subcutaneous tissues. The connective tissue is rich in elastic fibers, and still deeper there is the thick deposit of fat that gives the labium its prominence (Fig. 106). The veins are numerous and large, and become much distended when there is intrapelvic pressure, as in pregnancy or from a tumor. Under such circumstances, a wound of the labium may lead to serious and even fatal hemorrhage.
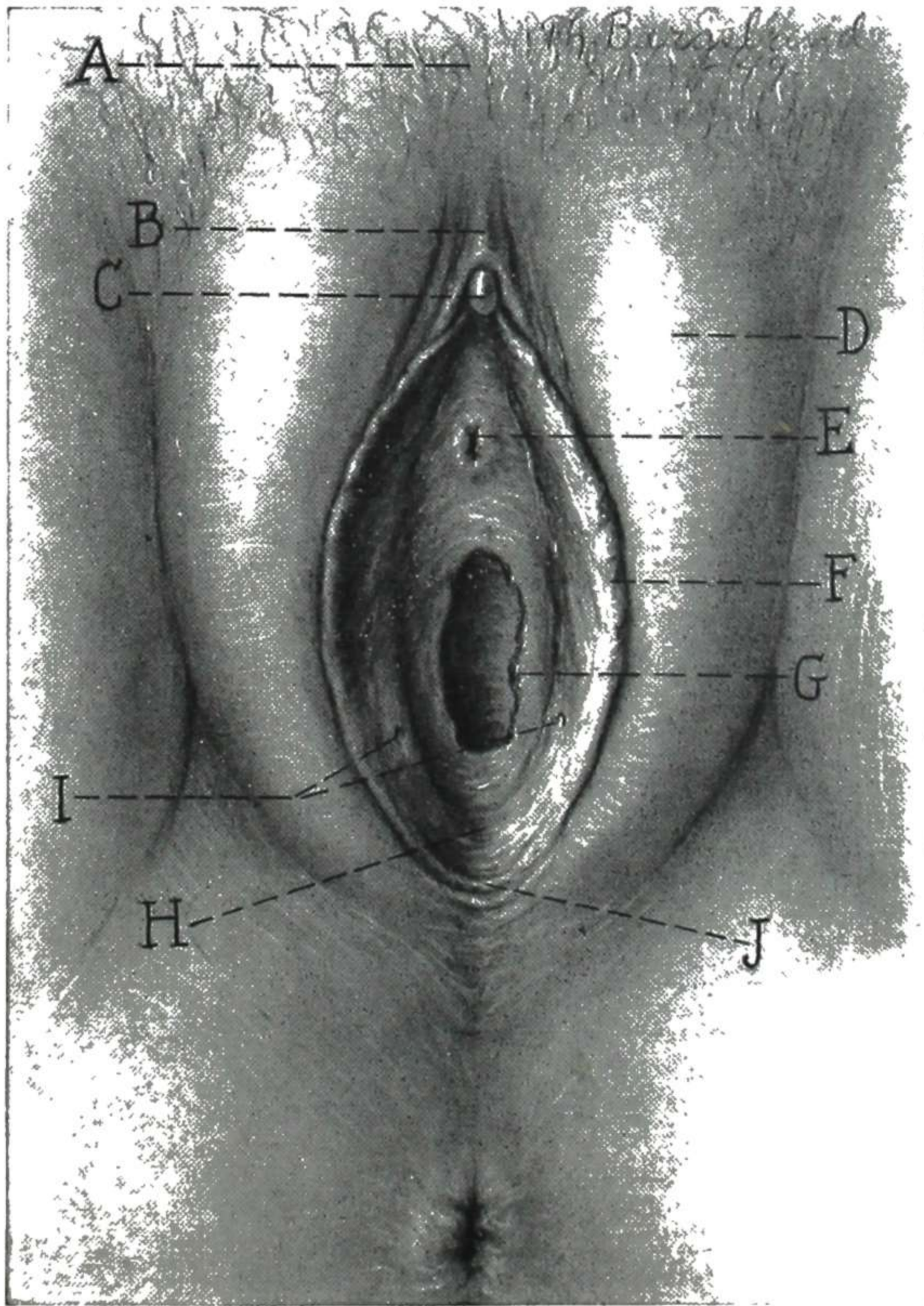

Fig. 105.—Anatomy of vulva. *A,* Mons pubis; *B,* prepuce; *C,* clitoris; *D,* labium majus; *E,* urethral meatus; *F,* labium minus; *G,* hymen; *H,* fossa navicularis; *I,* openings of Bartholin's glands; *J,* fourchette. (From Faulkner and Douglass: Essentials of Obstetrical and Gynecological Pathology, The C. V. Mosby Co.)

The **labia minora** (Fig. 105), or nymphae, are two delicate mucocutaneous folds lying between the labia majora, one on each side of the vaginal opening. Each labium minus apparently grows from, or is a secondary fold of, the upper and inner portion of the labium majus of that side. In stout women the nymphae are normally concealed by the labia majora. Ordinarily, particularly in married women, they project slightly. Frequently they are somewhat en-

larged and project half an inch or more. The enlargement is usually not exactly symmetrical, and in some cases it is confined to one labium. In a valuable article on these enlargements of the labia minora, Dickinson upholds the idea that whenever the enlargement is marked, it is proof of excessive irritation of the labium. It is stated that among the Hottentots, owing to certain treatment practiced in childhood, the labia minor often become excessively developed and hang like a thick apron between the thighs. The labia minora begin just below the anterior junction of the labia majora as double folds which pass above and below the clitoris. The folds that join above the clitoris form

Fig. 106.—Labium majus. Stratified squamous epithelium. *a*, The keratin layer with a thin eleidin layer. *b*, Mucosal cell layer with a thin layer of transitional cells and the basal germinal layer containing pigment. This specimen was obtained from a Negro woman. *c*, Connective tissue stroma. *d*, Sebaceous gland. *e*, Hair follicle. (From Douglass and Faulkner: Essentials of Obstetrical and Gynecological Pathology, The C. V. Mosby Co.)

the prepuce of the same. The labium minus of each side then descends along the inner side of the labium majus and blends with labium majus about the junction of the middle and lower third. The posterior extremities of the labia minora are united by a delicate fold which extends between them just within the posterior margin of the vulvar orifice, forming the fourchette. When the labia are separated, the fourchette is made tense, and between it and the hymen is a small depression called, from its boatlike shape, the "fossa navicularis." This delicate fourchette is, except in rare cases, torn at childbirth, and in some cases is obliterated even by sexual intercourse. It is best seen in the virgin.

There has been dispute as to whether the inner surfaces of the labia minora are covered by integument or mucous membrane. The covering presents some of the characteristics of each. It is a transitional form of covering and represents one step in the several changes which take place from the labia majora to the external surface of the cervix. The outer surfaces of the labia majora are ordinary integument. On the inner surfaces of the same structures, the hairs are much reduced in size and number. On the labia minora, the hairs are absent, though the sebaceous glands are still present. On the vestibule, only a few glands remain, and the thinning of the epithelium is more marked. In the vagina, all glands disappear (it being now generally held that there are

Fig. 107.—Labium minus. *a*, Stratified squamous surface epithelium with wavy outline and slight keratinization. *b*, Sebaceous glands. *c*, Stroma with venous channels. Note absence of hair follicles. (From Douglass and Faulkner: Essentials of Obstetrical and Gynecological Pathology, The C. V. Mosby Co.)

no glands in the normal vagina) and the epithelium becomes thinner and the papillae less marked. Over the vaginal portion of the cervix the papillae have almost disappeared. So there is a gradual transition from ordinary integument, with a thick epithelial layer, hairs, sebaceous glands, sweat glands, and marked papillae, to a thin epithelial layer without hairs or glands and almost without papillae. When the vaginal wall is turned out for a long time, as in prolapse, and exposed to friction by the clothing, the epithelial layer becomes much thickened, and if the surface is kept dry, it becomes horny like the external integument.

The labia minora have many small folds, giving a very uneven surface. Examination of a section of a labium minus shows numerous epithelial depressions, owing to the much folded surface. The bands and nests of epithelial cells seen in such a section are simply oblique cuts of normal folds and ingrowths. The labia minora are very rich in blood vessels, especially veins, so much so that the structure partakes of the nature of erectile tissue. They are also rich in lymphatics and nerves (Fig. 107).

The **clitoris** is the analogue of the penis in the male and is situated just below the anterior junction of the labia majora. It is a small erectile organ richly supplied with blood and nerves, and is attached to the sides of the pubic arch by its crura. In both the clitoris and the labia minora there are special nerve endings. Examination of a section of the clitoris shows the erectile nature of the structure. During sexual excitement the clitoris fills with blood and becomes swollen and firmer. It is supposed to be the most sensitive of all the genital organs to sexual contact, and on this account excision of the clitoris (clitoridectomy) was proposed and carried out for the relief of disturbances depending on sexual hyperesthesia, but the results were not such as to recommend the operation, and it is now rarely practiced.

The **vestibule** is an elliptical area situated between the labia minora. The sides are formed by the labia minora, the anterior end extends to the clitoris, and the posterior end is formed by the junction of the labia majora. Into this vestibule four canals open—the urethra, the vagina, and the duct of the vulvo-vaginal gland of each side. The urethral opening, the meatus urinarius, is situated just above the vaginal orifice. In the nullipara it is small and round. In the multipara it is larger and somewhat star-shaped, and there is often some pouting or projection of the urethral mucosa. This change is due to the swelling and distortion during labor, from which the parts never return absolutely to their former condition. The floor of the vestibule is formed of several layers of squamous epithelium and under this the subepithelial connective tissue. There are a few glands, some of which at times become enlarged.

The **hymen** is a circular or crescentic fold of mucosa and submucous connective tissue, situated at the vaginal entrance and partially closing it. The shape of the hymen and the opening in it vary greatly in different persons, some forms being given names. The crescentic hymen and the circular hymen are the usual forms. The fimbriated hymen has a dentated or fringelike margin. The cribriform hymen presents a number of small holes. In certain cases of malformation, the hymen is absent. In other cases it is closed entirely (imperforate or occluded hymen).

The hymen is usually ruptured at the first sexual intercourse. In some cases "rupture of the hymen" amounts to nothing more than stretching, with slight abrasion. In other cases there is distinct tearing, with considerable pain and some bleeding. In rare cases there may be persistent and even serious bleeding. In some cases the hymen is so rigid or tender as to prevent coitus. Long-continued sexual intercourse stretches the hymen until it is not at all prominent. Much medicolegal importance has been attached to the condition of the hymen, and, ordinarily, it is a decided help in determining whether or

not coitus has taken place. But it is a well-established fact that an intact hymen is not absolute proof of virginity, neither is an apparently ruptured or stretched hymen absolute proof of sexual intercourse.

Childbirth destroys the hymen as an intact ring. Usually after parturition there are only irregular tags of tissue left, the result of tearing and sloughing about the vaginal entrance. These irregular tags of tissue surrounding the vaginal orifice are known as "carunculae myrtiformes," and result from childbirth only, not from sexual intercourse. Coitus does not usually destroy the hymen, but simply tears it slightly and stretches it.

Fig. 108.   Fig. 109.

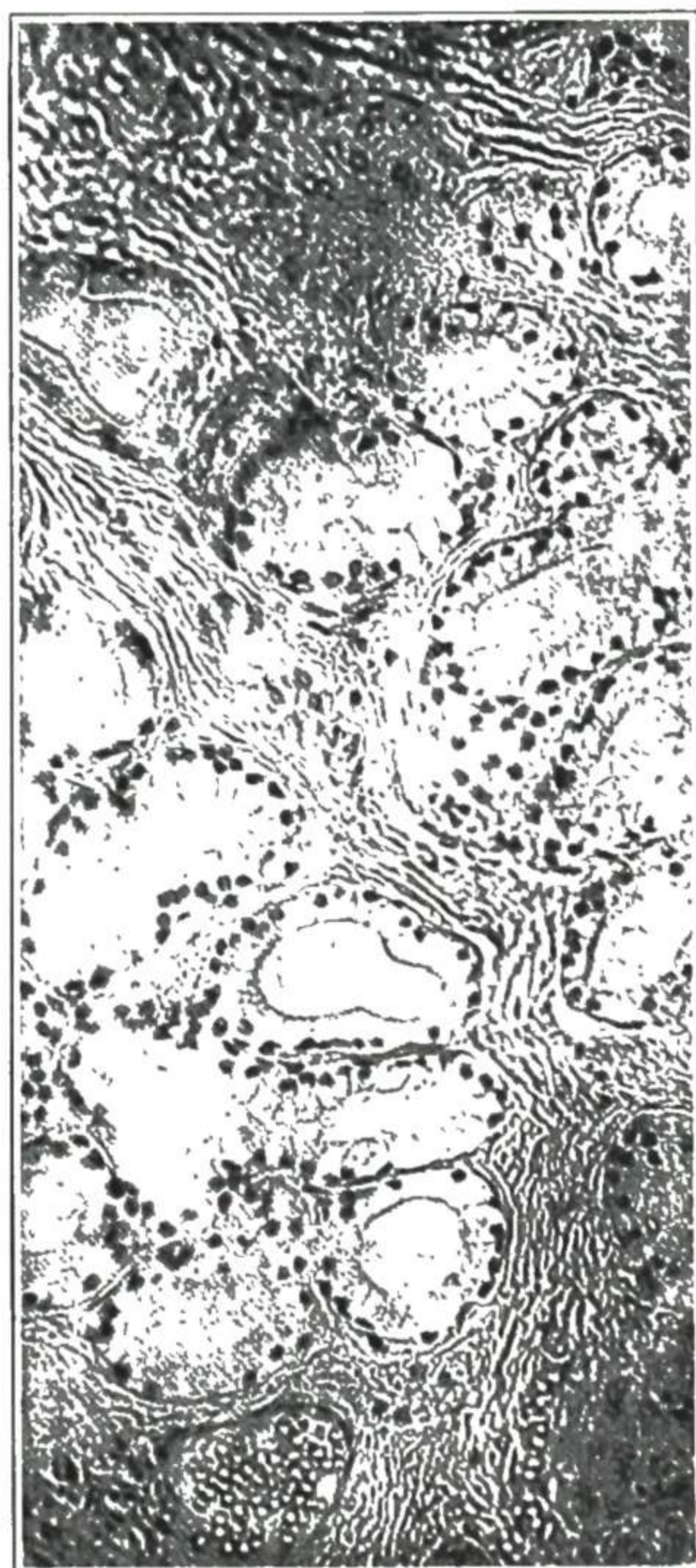Fig. 108.—Section of vulvovaginal gland showing duct and gland acini. Low power. (From Cullen: J. A. M. A.)

Fig. 109.—Section of vulvovaginal gland showing acini and lining cells. High power. Gyn. Lab.

The **vulvovaginal glands** are two glands situated beside the vaginal entrance, one on each side at the lower end of the lateral mass of veins called the vestibular bulb, as shown in Fig. 104. They correspond to Cowper's glands in the male, though their relations to the triangular ligament are not so clearly defined, apparently varying some in different cases. They lie, as a rule, behind the anterior layer of the ligament, and may lie behind or in front of the posterior layer. Each gland lies very close to the lower end of the venous bulb of that side. The gland is a small reddish body about the size of a bean, and belongs to the racemose variety of glands (Figs. 108, 109). Its secretion is discharged through a small duct which opens just in front of the hymen, about the junction of the lower with the middle third of the side of the vaginal orifice.

When the gland is normal, this opening has to be looked for rather carefully to be seen. When the gland has once become inflamed, the opening is easily seen, for it is larger and is usually surrounded by a small reddened area. The mucous secretion of the gland acts as a simple lubricant to the parts and is discharged during sexual excitement. When inflamed, the gland is felt as a hard tender mass beside the vaginal opening.

The **meatus urinarius,** as well as the urethra, is lined with stratified squamous epithelium on a basis of connective tissue rich in cells. This connective tissue of the meatus and the urethra was formerly thought to have lymph nodules of microscopic size. Ricci, Lisa, and Thom found no lymph glands in the urethra. Up until the painstaking studies of Huffman the question of the number and arrangement of the paraurethral and urethral glands was the subject of considerable controversy. Huffman states that Galen and many of the early
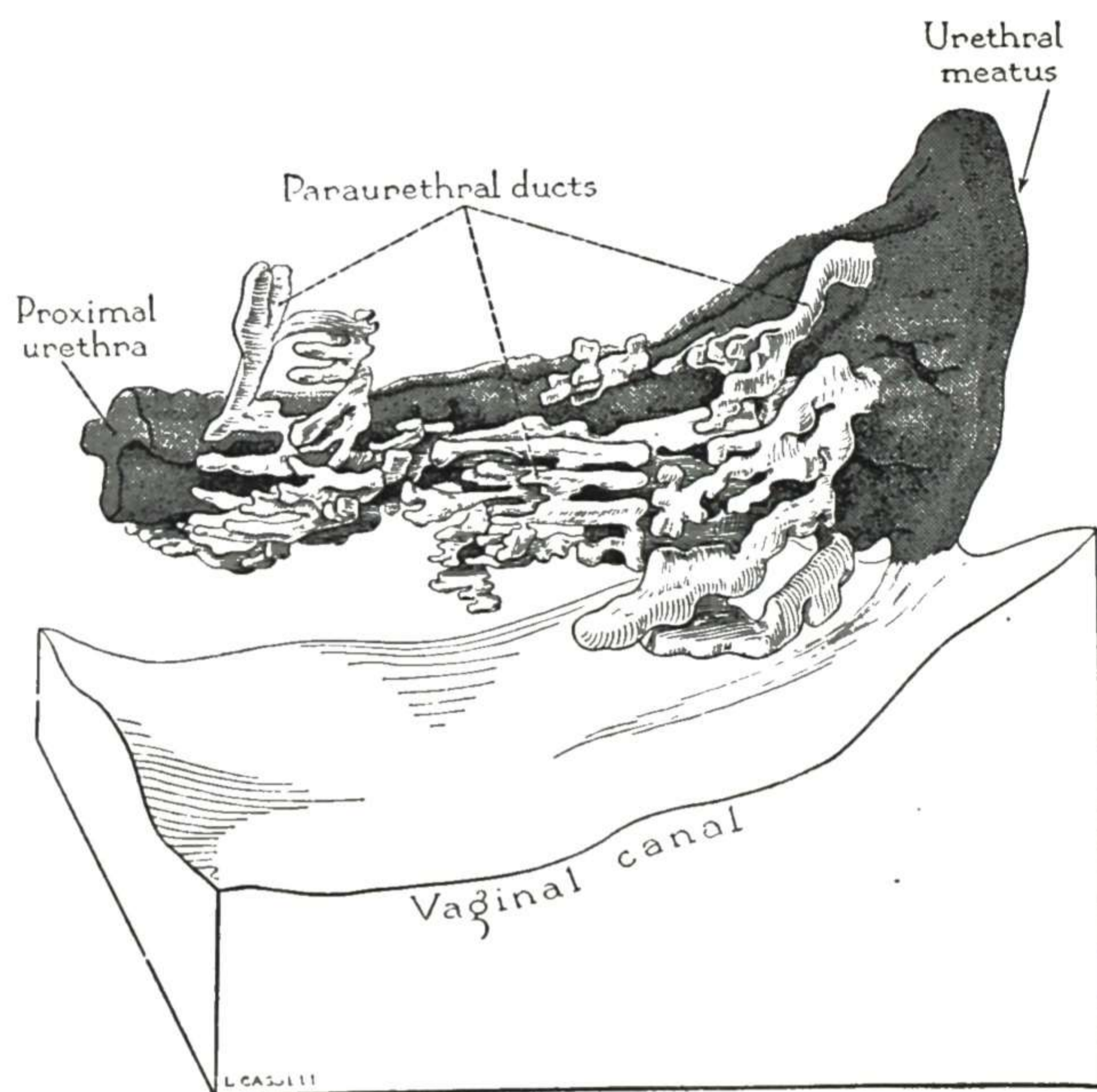

Fig. 110.—Drawing of a wax model of an adult human female urethra with its paraurethral ducts and glands as seen in right lateral view. This reconstruction is in reality a cast of the urethral canal with its outpouching ducts and glandular pockets. That portion of the model labeled "Vaginal canal" represents a cast of the vagina beneath and parallel to the urethra. Tissue from which this model was reconstructed was obtained at necropsy of a 38-year-old nullipara. This model represents the distal 2.8 cm. of a urethra measuring 3.0 cm. in total length. No ducts opened at the meatal margins. In this specimen most of the ten larger paraurethral ducts empty into the distal centimeter of the urethra through the lateral and dorsal walls. Occasional ducts empty also into the most distal portion of the middle third of the urethra. Most of the ducts and glands are noted in the lateral and dorsal periurethral tissues. About the middle third of the urethra, the paraurethral ducts and glands are found far from the urethal canal and form semicircular sheets about both the right and left sides of the urethra. (From Huffman, John W.: Am. J. Obst. & Gynec., January, 1948.)

anatomists mentioned the homology of the female genitals and described a female prostate gland. An extensive clinical study of these glands was made by Skene in 1880. He described only two tubules on each side of the floor of the urethra from three-eighths to three-quarters of an inch in length. The mouths of these tubules are in the mucous surface of the urethra just within the labia of the meatus. Huffman studied the development of these glands in the embryo

and their number and location in the adult. He found that the number and location was not constant but that these glands are numerous and they form extensive ramifications throughout the tissue about the distal urethra and may extend to within a short distance of the bladder. The numerous ducts terminate
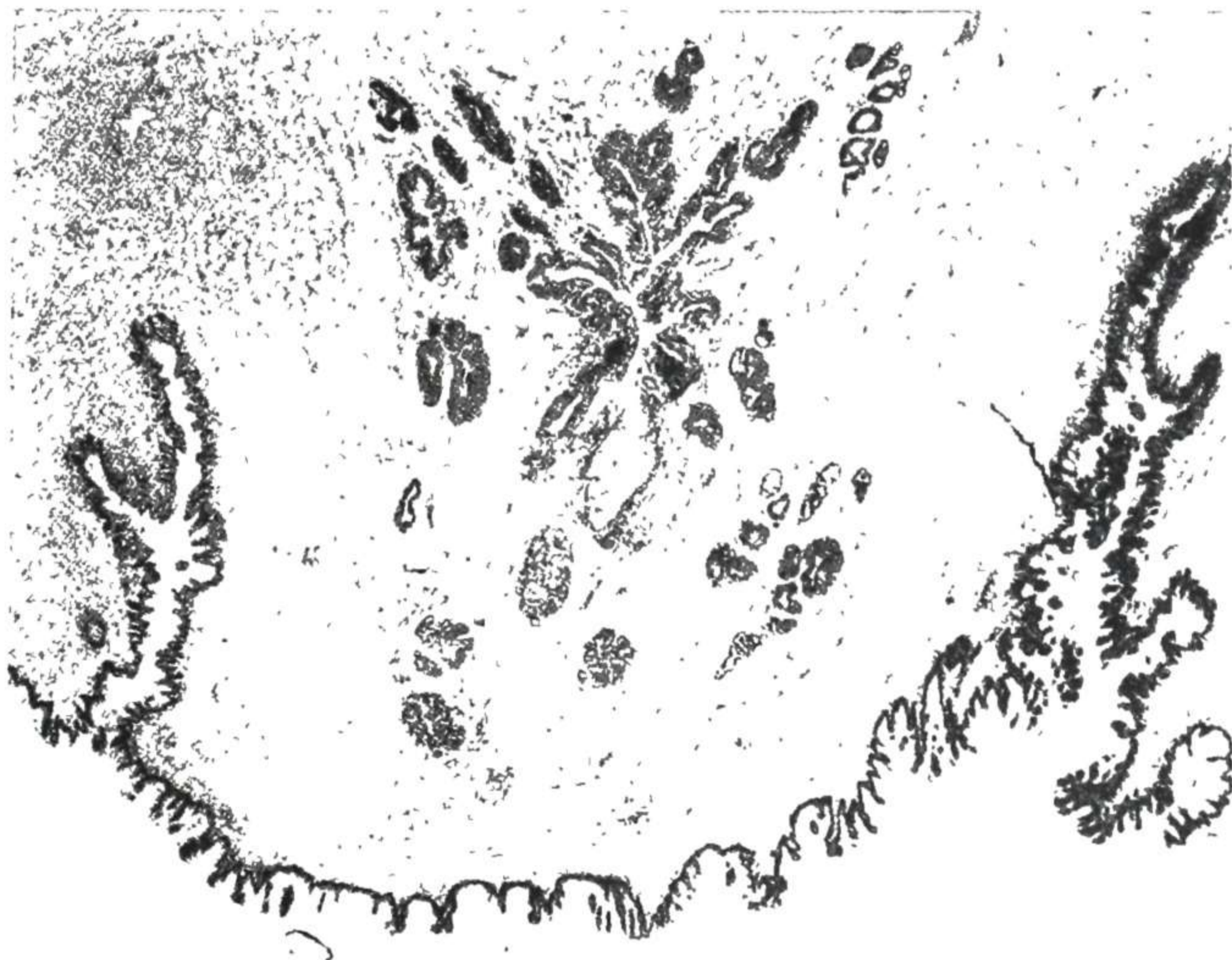

Fig. 111.—Photomicrograph of a transverse section through the urethra just within the meatus showing the urethra surrounded by many paraurethral tubules and glands. The intact vaginal mucosa borders the lower edge of the section. (From Huffman, John W.: Am. J. Obst. & Gynec., January, 1948.)

Fig. 112.—Photomicrograph. The tubular paraurethral glands are lined by low columnar epithelium with pale staining cytoplasm and have large centrally or basally placed round nuclei; some but not all of these cells take a mucicarmine stain. (From Huffman, John W.: Am. J. Obst. & Gynec., January, 1948.)

in tubular glands lined by columnar epithelium which possess limited secretory activity. He considers them to be the homologue of the prostatic glands of the male. Fig. 110, from his article, shows a wax model of a female adult urethra;

Fig. 111 is a photomicrograph of a transverse section through the urethra and vagina at a point just within the meatus; Fig. 112 shows the type of epithelium lining the tubular paraurethral glands.

The BLOOD SUPPLY of the external genitals (Fig. 104) comes principally from the internal pudic artery, one of the terminal branches of the anterior trunk of the internal iliac.

The NERVE SUPPLY (Fig. 104) comes principally from branches of the pudic and small sciatic nerves. In certain painful affections of the external genitals, the pudic nerve is sometimes divided or resected to afford relief.

The LYMPHATICS empty into the inguinal glands. Poirier calls attention to the fact that the lymphatics from the clitoris extend into the deep pelvic glands. Consequently in carcinoma of the clitoris proper (not its prepuce), the glands within the pelvis are soon involved.

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