DISEASES OF WOMEN

Chapter 1

ANATOMY AND PHYSIOLOGY of the Genital Tract

The genital tract in the female is a constantly changing structure, from the time it starts to develop until its functions end. This fact is emphasized in Fig. 1 (frontispiece), and it must be kept in mind in all considerations of anatomy, physiology, and pathology. We must remember not only the striking normal changes which take place every few weeks in connection with ovulation and the still greater changes due to pregnancy, but also the structural changes during development to the point of function and during subsidence after the menopause. A practical approach, however, to the problem of describing the anatomy is to divide the structural features of each organ into those which are relatively constant throughout the childbearing period and those which change with functional activity. The first may be considered as the anatomy of the organ and the second as part of the physiology.

Before describing the anatomy and physiology of the individual organs, it is well to call attention to certain general features. The situation of these organs in the bony pelvis gives them excellent protection from accidental injury. Even in crushing injuries, which have increased so much with the extended use of the automobile and airplane, this strong protecting box of bone usually prevents serious damage to the contained organs.

This rigid framework of the pelvis, through which the child must pass in labor, requires special study and detailed measurements in obstetrics, but for gynecologic work general consideration will suffice. The pelvis is formed by four bones: the two innominate bones, the sacrum, and the coccyx. Each innominate bone consists of three parts: the ilium, ischium, and pubis. These are separate bones in early life, but there is gradual ossification of the cartilaginous junctions so that by the twentieth year the three parts are fused, forming the remarkable os innominatum, which bears the weight of the body and furnishes specially shaped surfaces for the attachment of the complicated muscular mechanism which operates the lower extremity. In early life these functions of weight-bearing and muscular activity put strain on the extensive cartilaginous parts, hence the importance of maintaining the nutritional integrity of cartilage in early years in order to avoid the pelvic deformities which are so serious in childbearing.

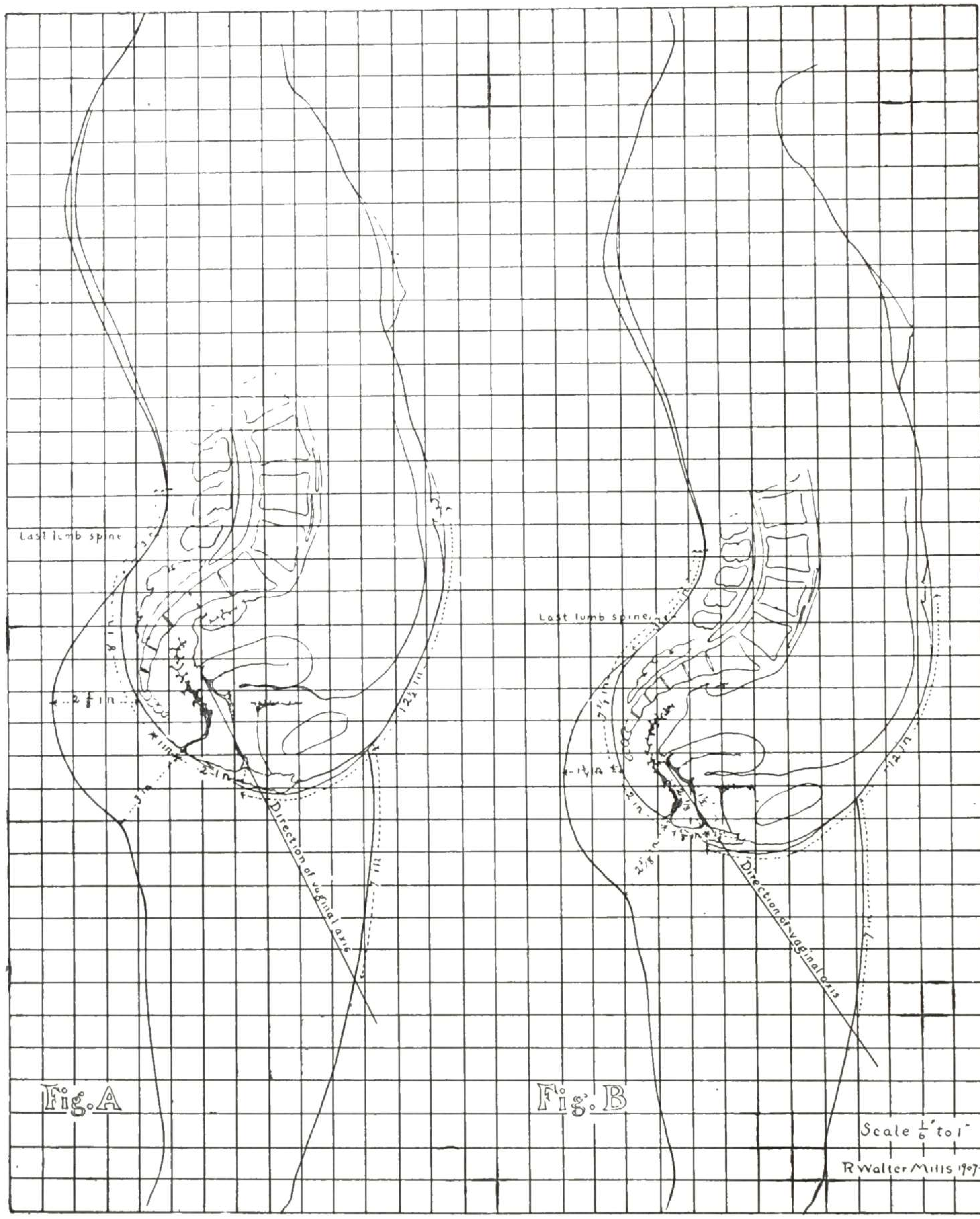


Fig. 2.—*A*, Exact contour and measurements of the woman selected for Fig. 3. *B*, Exact contour and measurements of another model, presenting a more pronounced lumbar and abdominal curve. The small squares represent one-inch squares at life size. (R. Walter Mills.)

A, Artist's model, aged twenty-eight years, mother of two children (six and eight years old respectively), has worn corset practically none, is in good health and fairly muscular. Height 5 ft. 7 in., weight 140 lb., bust measure 36 in., waist 27 in. (2 in. above umbilicus), circumference at umbilicus 30 in., hips 39 in., thigh 22½ in. (2 in. below gluteal crease), anteroposterior diameter of body at waist 6¾ in., anteroposterior diameter of thigh (2 in. below gluteal crease) 6⅝ in. The other data are given on the outline. To conform to the so-called "perfect form" the hips should be a trifle larger and the weight somewhat more.

B, Young woman, aged twenty-seven years, never pregnant, has worn corset very little, is in good health and muscular. Height 5 ft. 4 in., weight 114 lb., bust measure 32 in., waist 24 in. (2 in. above umbilicus), hips 38 in., thigh 22. (2 in. below gluteal crease), anteroposterior diameter of body at waist 6½ in., anteroposterior diameter of thigh (2 in. below gluteal crease) 6⅝ in. The other data are given on the outline. The lumbar and abdominal curves are more pronounced than in *A*.

The numerous exact measurements here given constitute valuable data to guide in medical drawings of this character.

Fig. 3.—Anteroposterior section of pelvis (semidiagrammatic). In order to show the structures and relations exactly as they are in what may be considered a typical woman in the erect posture, a detailed study was made of many drawings from frozen sections for the internal relations, and of several well-formed women in the normal standing posture for the contour and external relations. This gave a result differing considerably from the usual representation of a patient standing, made by taking a drawing of a section of a flattened cadaver and turning it upright. The lumbar curve is more marked, the lower abdominal wall and the buttocks are more prominent, and there is a change of the relations of the internal organs to the external landmarks.

For the internal relations the admirable frozen sections of Sellheim were principally followed, and the exactness with which the pelvis and contents of the actual sections fitted into the contours of the living models was most pleasing and instructive. (Redrawn and colored from original drawing by Dr. R. Walter Mills.)

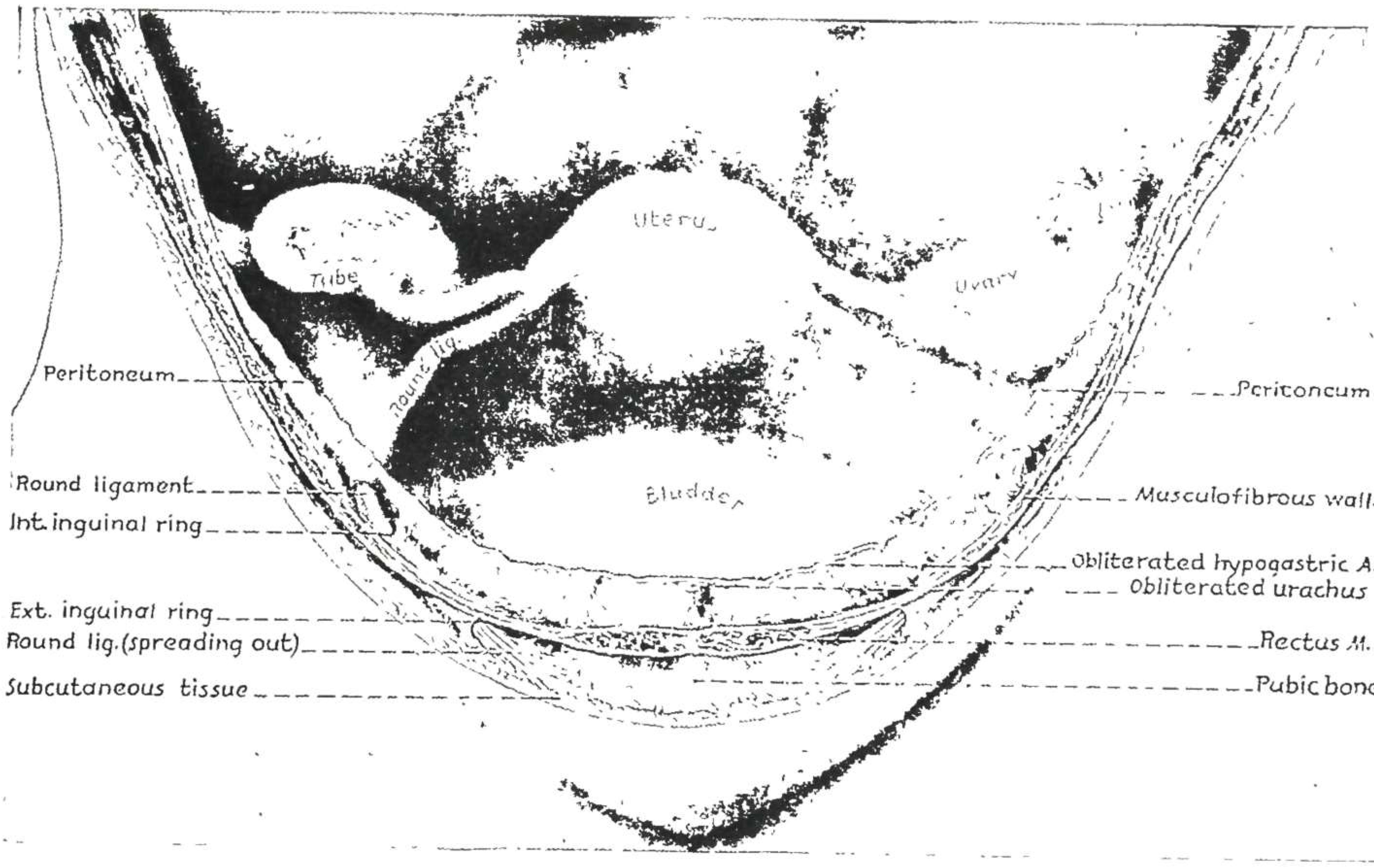


Fig. 4.—View of pelvic organs from in front, showing the relations of various structures to each other and to the abdominal wall.

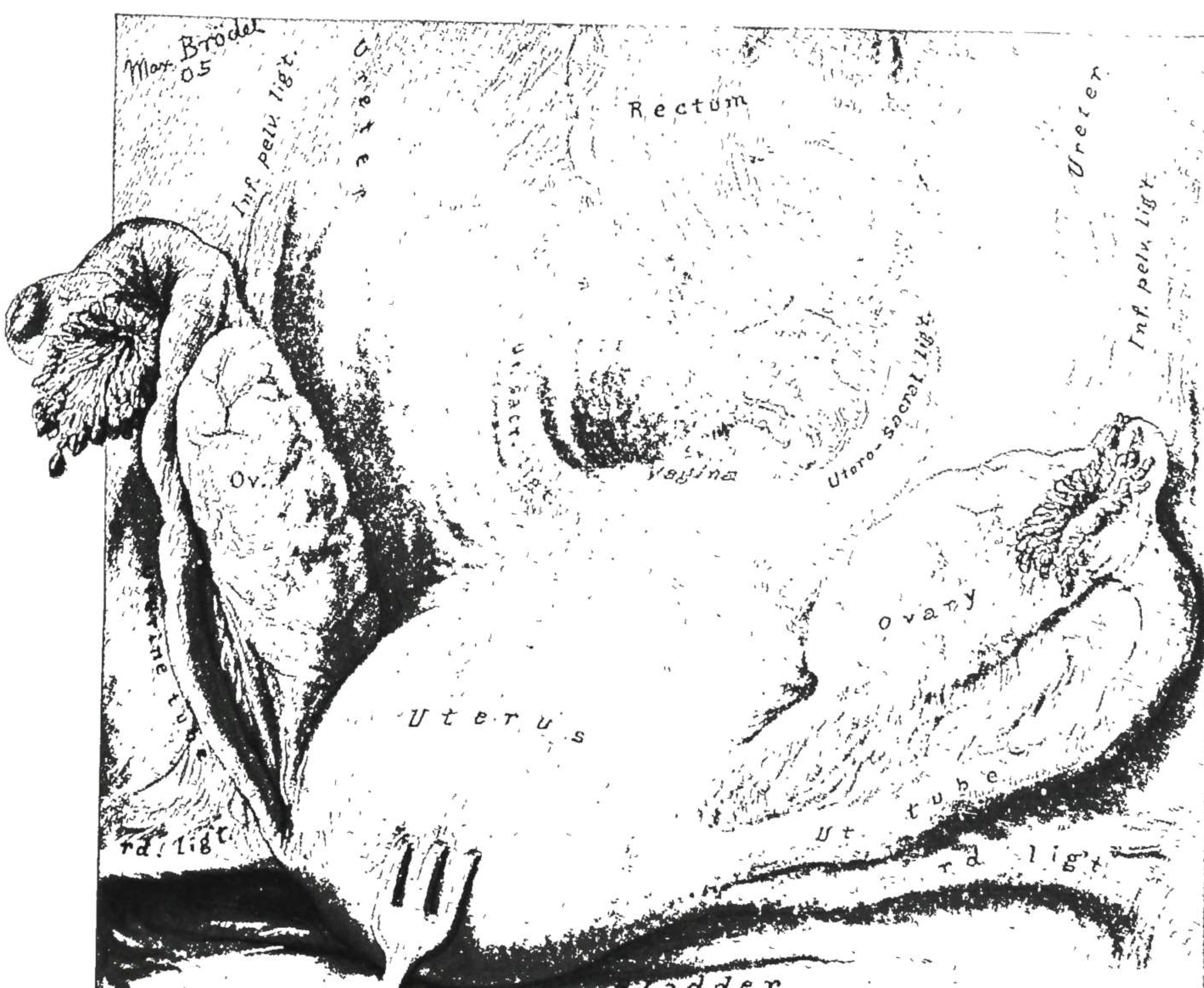


Fig. 5.—View of the pelvic structures back of the uterus and broad ligaments. (From Kelly: Gynecology, D. Appleton-Century Co.)

It is well to call attention to the fact that the anatomical "perineum" includes all the area of the pelvic outlet, extending medially from the pubic arch to the coccyx and laterally to the ischial tuberosity of each side. The wedge of soft tissues lying between the rectum and vagina at their lower ends is the "perineal body." In gynecological writings, however, the perineal body is usually referred to as the "perineum," that being a shorter and more convenient term, to which long usage has given a specific meaning in connection with the soft tissues closing the pelvic outlet in the female.

The female generative organs are located in intimate contact with the bladder and rectum. Consequently bladder and rectal diseases are often mistaken for disease of the genital tract, and vice versa. This fact must be kept in mind, particularly in obscure or chronic disturbances, and special examinations resorted to as necessary to insure differentiation.

The bladder and rectum fill and empty at irregular intervals. This calls for considerable mobility of the uterus which lies between them. This mobility is attained and properly limited by a mechanism involving several factors, the particulars of which we shall study later when dealing with uterine displacements.

In this first chapter will be given the anatomy and physiology of the adult organs, together with the maturing to function and the changes of subsiding function. Development of the genital tract is most usefully considered in connection with developmental anomalies, and hence is given in the chapter on Malformations (Chapter 12). The anatomy and physiology (supporting action) of the pelvic floor are best discussed in connection with relaxation and other damage to those structures and will be found in Chapter 4.

The essential pelvic organs in the group of structures involved in gynecologic* diseases are shown in Figs. 2 to 6. They are as follows:

1. The **ovaries,** in which the ova are formed.
2. The **fallopian tubes,** which conduct the ova from the ovaries to the uterus.
3. The **uterus,** which receives and nourishes the fertilized ovum and expels the fetus at term.
4. The **vagina,** which is the connecting link between the uterus and the outside world.

There are also several accessory structures: namely, the external genitals, the perineum, the pelvic floor, the pelvic connective tissue, and the pelvic peritoneum. In addition, there are certain distant structures connected with the endocrine system which have a special and marked influence on the pelvic organs. These will be mentioned in their proper connections.

OVARY

The ovary is a temporary organ with an active life span of about thirty-five years. It is a remarkable organ in that its product is not simply some special secretion, to complement the many other secretions in rounding out

*As to the pronunciation of "gynecology," the weight of authority is decidedly in favor of soft g, short y and the accent on the third syllable—jin e kol′ o je (Webster's Unabridged Dictionary, Century Dictionary, Standard Dictionary, and the following medical dictionaries—Dorland's, New Gould's, Stedman's). A few authorities give it as second choice, some favoring soft g and long y, and others favoring hard g and long y.

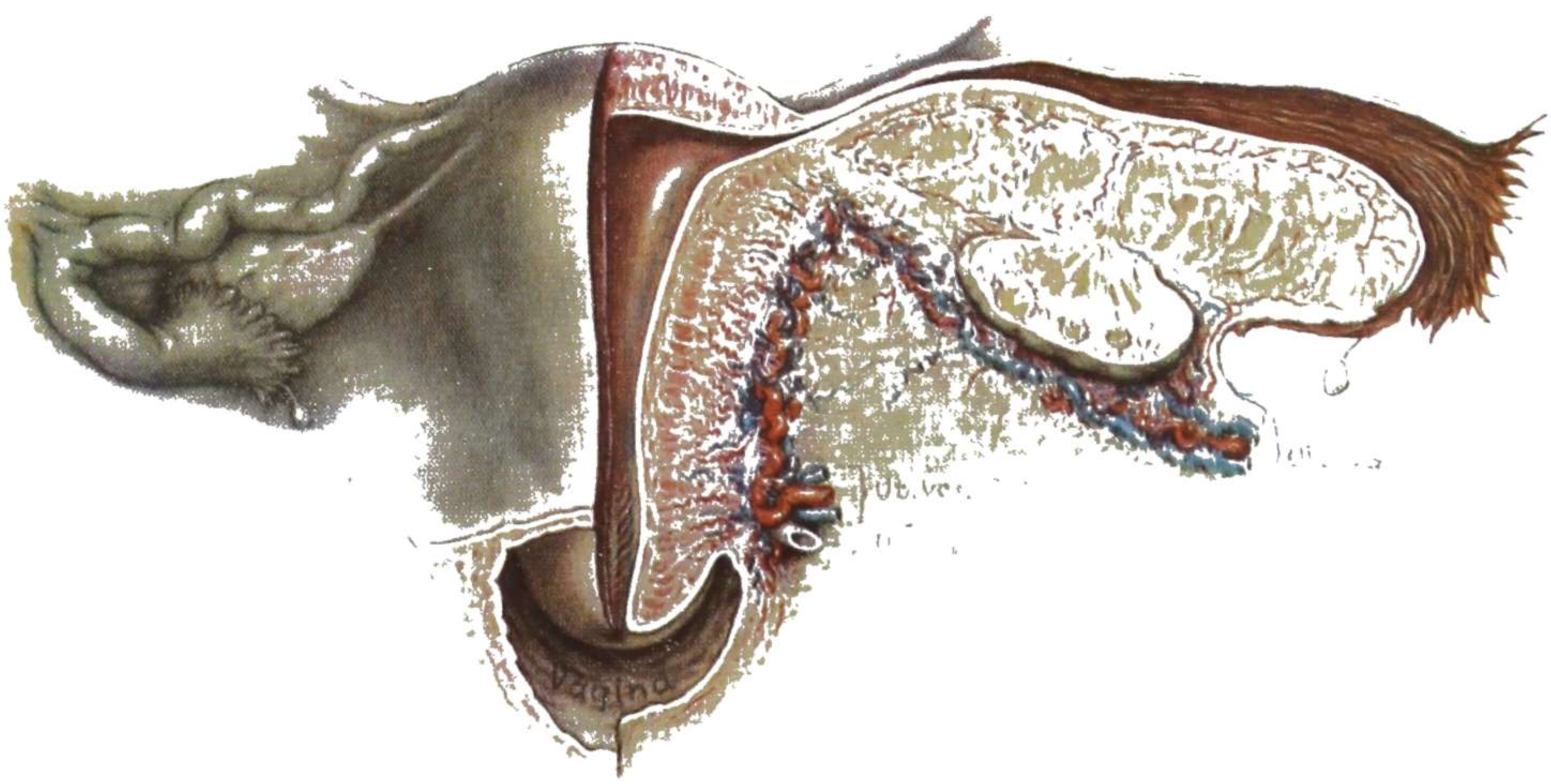


Fig. 6.—View from behind, showing on the left the relations of ovary and fallopian tube and posterior surface of uterus. On the right is a section of the uterus, tube, ovary, and broad ligament, showing the relations of these various structures and their blood supply.

The sectioned ovary shows its connection with the broad ligament at the hilum, where the blood vessels and lymphatics and nerves enter. The utero-ovarian vascular arc gives free blood supply to the ovary, tube, and uterus. The ureter, on its way from the bladder to the kidney, is cut across just posterior to the uterine vessels under which it passes in the broad ligament. Notice the gradual but marked enlargement of the tubal cavity from the very narrow uterine portion to the outer portion (ampulla).

the physiology of daily activities, but a special cell for originating another individual. This special cell carries the spark of a separate life, and also within its small compass there exists something which later flowers into the characteristics of the donor and of her ancestors for generations back. In addition to producing this potent cell, the ovary controls the development and functioning of the organs which receive and nourish the fertilized ovum and expel the separate individual at the proper stage of development. With these important and mysterious functions, it is little wonder that there are two ovaries, to double safeguard this heritage, and that the more we learn about ovarian physiology the wider become the dim horizons of the unknown.

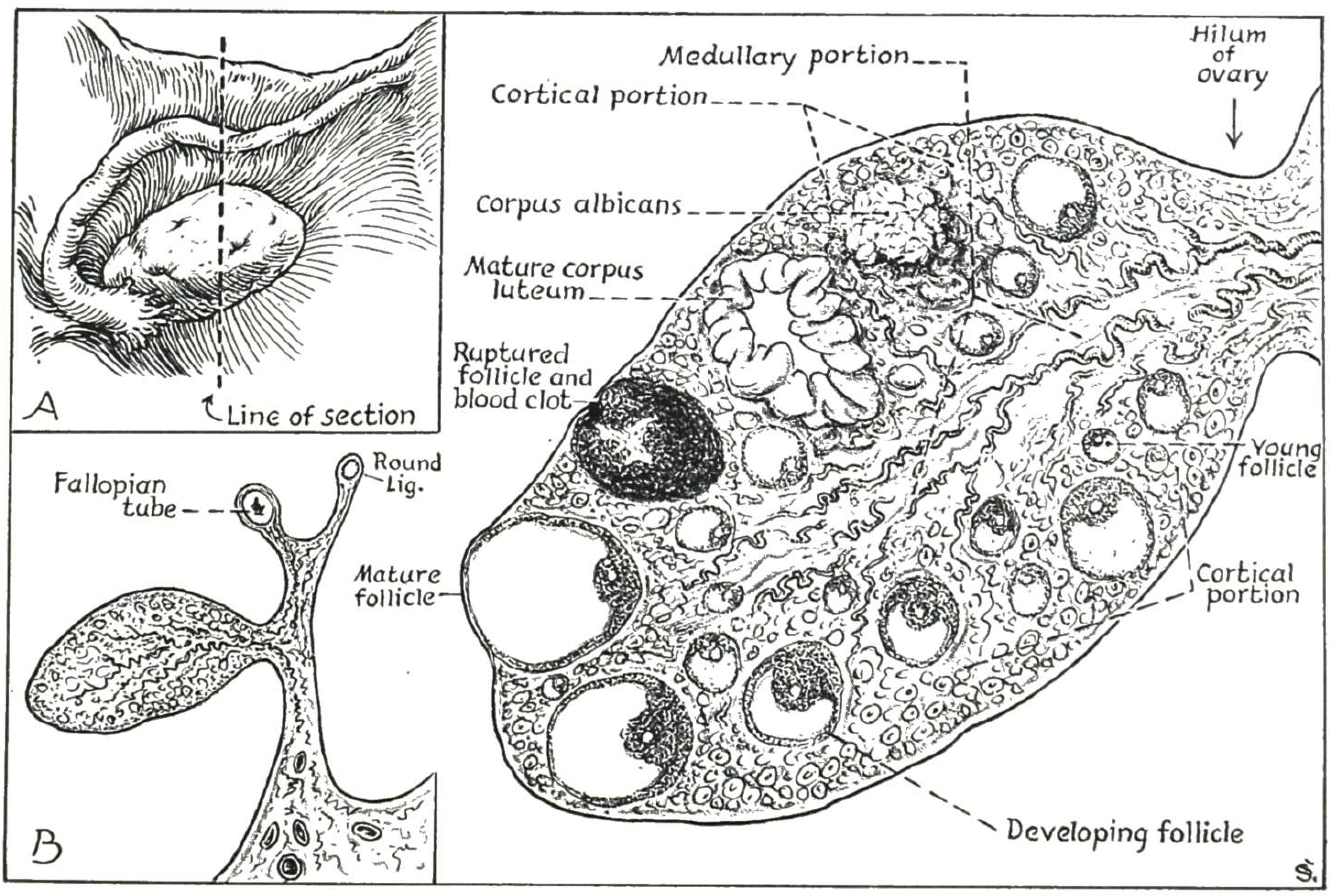


Fig. 7. Fig. 8.

Fig. 7.—Ovarian structures and relations. *A*, Showing surface relations of ovary, tube, and round ligament, and the line of section for *B*. *B*, Showing the attachment of the ovary to the broad ligament at the hilum, and incidentally the relative locations of the tube and round ligament.

Fig. 8.—Diagrammatic representation of the details of ovarian structure. The blood vessels, lymphatics, and nerves enter at the hilum and, with their connective tissue supports, extend through the center of the ovary, forming the medullary portion. From this central location nutrition and drainage and nerve control are supplied to the cortical portion, which is the special functioning part of the ovary.

Structure.—The human ovary is approximately one and a half inches long by one inch wide and half an inch thick, though the ovaries vary much in size in different persons and even in the same individual the two ovaries may differ considerably. The ovaries are situated one on each side of the uterus near the pelvic brim and close to the outer end of the fallopian tube (Fig. 6). Each ovary projects from the posterior wall of the broad ligament of its respective side, as shown in Fig. 7, and the peritoneal fold thus formed is called the "mesovarium." It is through this attachment to the broad ligament that the ovary receives its blood supply. The area where the vessels and nerves find entrance and exit is called the hilum of the ovary (Fig. 8). Immediately about the hilum, and extending some little distance into the ovary, is the area known as the medulla or **medullary portion**. This is occupied by the blood vessels, lymph vessels, the nerves, and supporting tissue. It contains no follicles, but it contains remnants of the tubular structure which in the male develops into the testicle.

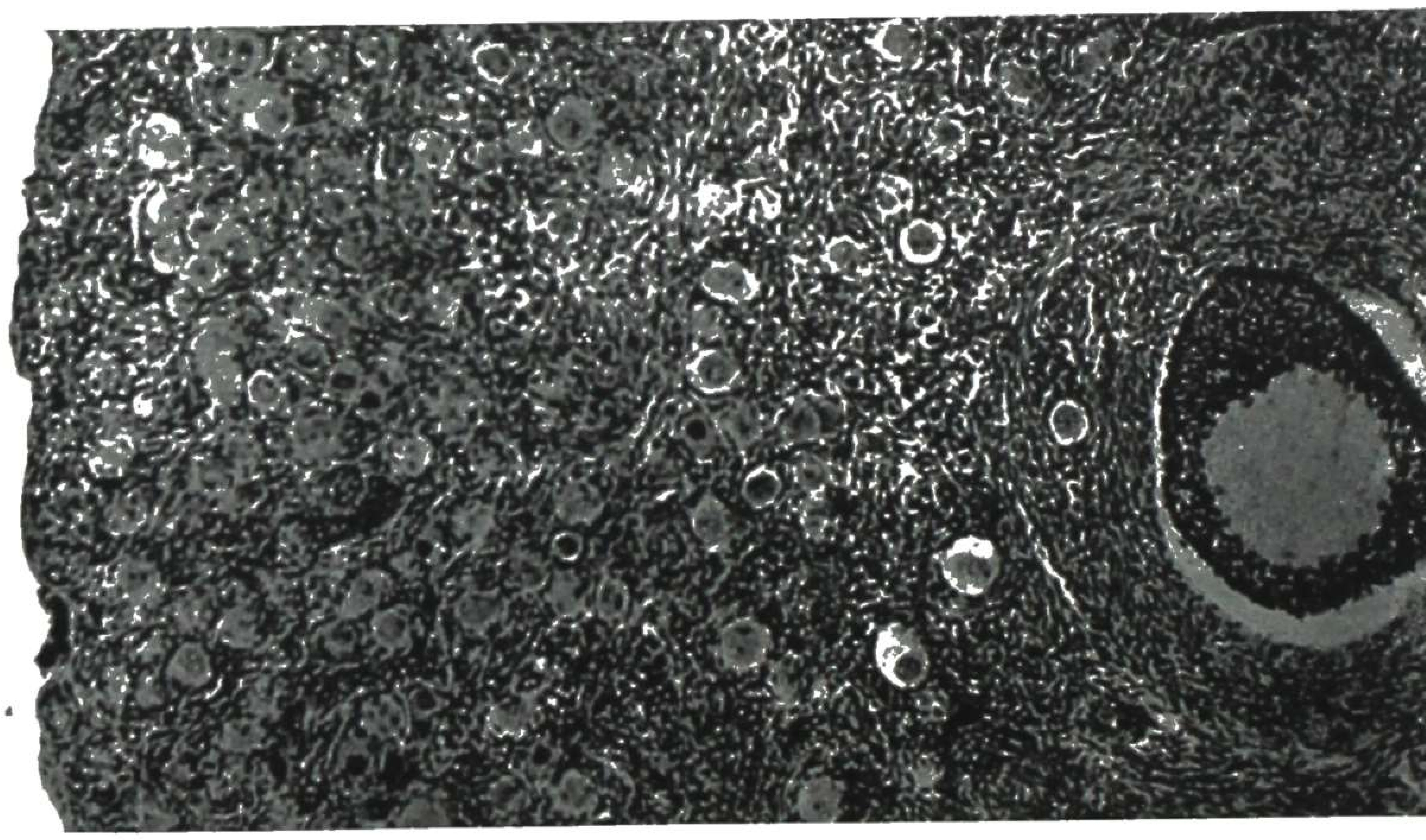


Fig. 9.—Photomicrograph of the cortical portion of ovary of a two-year-old child. Notice the large number of primordial follicles, embedded in a stroma which is characteristically ovarian. Note the large developing follicles in the deeper portion of the section. Gyn. Lab.

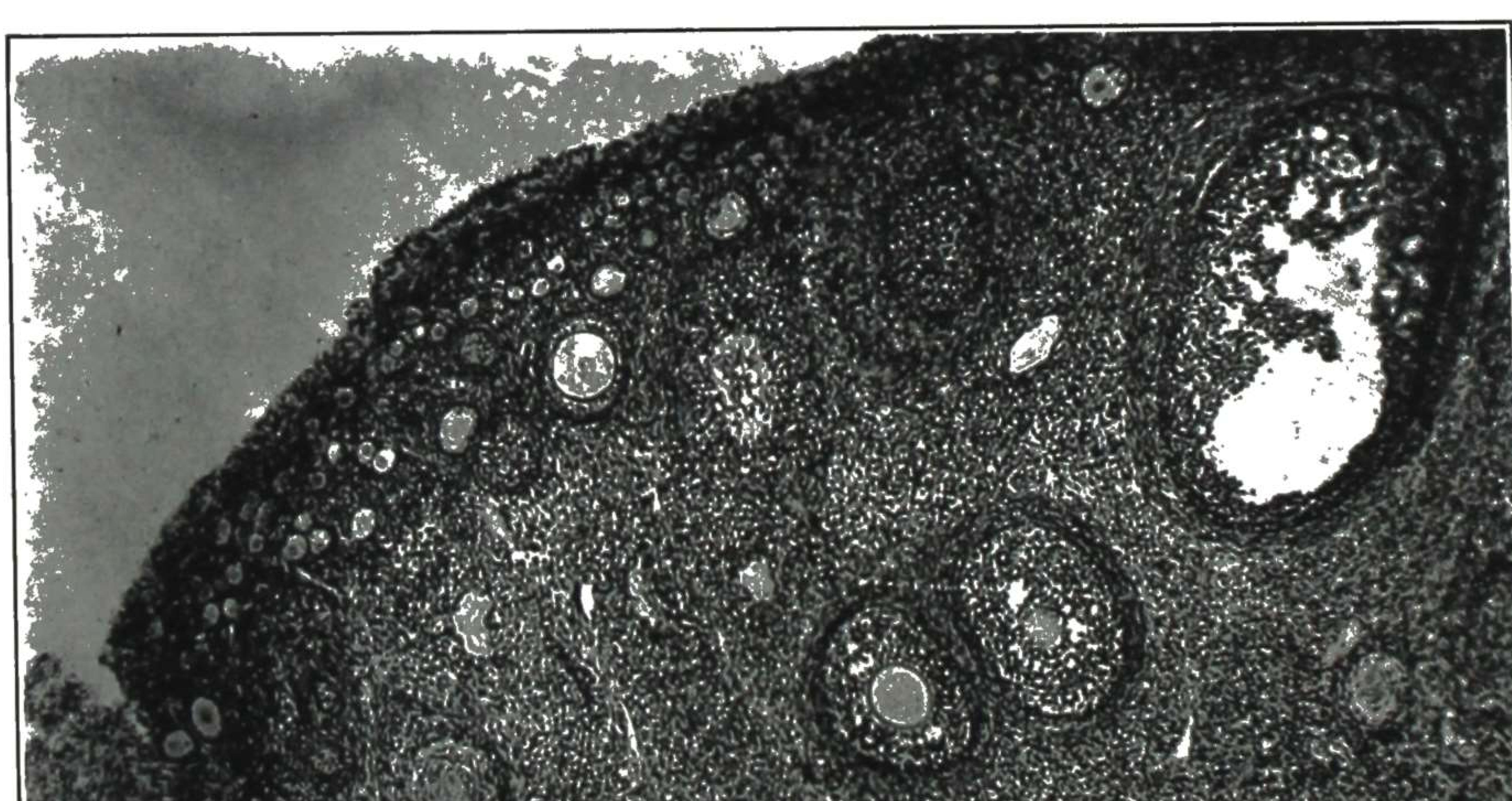


Fig. 10.—Photomicrograph of ovary of rabbit, showing follicles in various stages of development. Notice the primordial follicles in the cortex and the developing follicles in the deeper portion of the ovary. Gyn. Lab.

The remaining part of the ovary contains the graafian follicles, and is called the cortex or **cortical portion** (Fig. 8). The free surface of the cortical portion (that is, the peritoneal surface of the ovary) is covered with cylindrical epithelium. The term germinal epithelium was given to this epithelium by Waldeyer because he thought that the sex cells were derived from it. As will be seen later, many embryologists now feel that the sex cells are derived from the cells lining the hind-gut in man, and this has led Schiller to suggest changing the name of germinal epithelium to surface epithelium. The circular line at the base of the ovary, where this differentiated surface epithelium meets the peritoneum, is called the linea alba.

In structure the adult ovary is simply a collection of ova, or microscopic eggs, supported and held together by tissue which forms the framework. Each ovum is contained within a minute sac called the ovisac or graafian follicle, and a section of an ovary shows graafian follicles in various stages of development. This characteristic structure of the human ovary is shown diagrammatically in Fig. 8.

The supporting tissue extends between the follicles in all directions and, in addition to supporting and protecting them, carries the blood vessels which nourish them and also the lymph vessels and nerves. It forms the theca interna and externa of the follicles. Schwarz and Young in a detailed study of the stromal blood vessels conclude that there are smooth muscle fibers in the cortex which are derived from the smooth muscle of the vessel wall. Near the periphery of the ovary the fibers form a rather dense capsule which is known as the "tunica albuginea."

The **graafian follicles** are very numerous and of different sizes, as shown in Figs. 9 and 10. The small young follicles (primordial follicles) lie near the surface and number thousands. The great number and crowded condition in the outer portion of the growing ovary are well shown in Fig. 9. As the follicle develops, the single layer of cells lining it proliferates and the lining becomes many-layered, as in the follicle on the right in Fig. 9.

The follicles formed near the surface of the ovary are very small at first but as they grow down they increase in size. When they are of medium size the direction of growth is reversed and with further enlargement they approach the surface. The pointed "theca cone" is an interesting factor in this movement toward the surface by the maturing follicle, as explained later under ovulation. Many eggs develop that one may ovulate. The less-favored ova die and their follicles become atretic.

The graafian follicle is lined with an epithelial layer several cells thick, called the "membrana granulosa," and is filled with clear viscid fluid, the "liquor folliculi." The **ovum** lies within the follicle near one side and is completely surrounded by cells of the membrana granulosa.

As the graafian follicle matures, it approaches the surface and becomes still larger. It gradually protrudes at the free surface of the ovary, and when ripe it bursts, liberating the ovum on the surface of the ovary, from where it finds its way into the fallopian tube. This ripening and bursting of the graafian follicle and liberation of the contained ovum constitutes **ovulation,** which is considered in detail under the physiology of the ovary.

New generations of eggs are continuously becoming differentiated throughout sexual maturity, hence the life span of an ovum is probably very short. With the death of the ovum the granulosa cells die and disappear. Such a degenerated atretic follicle is small, and it eventually atrophies and is obliterated through a deposit of new connective tissue elements. In some, however, the fluid increases after the ovum dies, thus forming a minute cyst. If there are many of these small follicular cysts, the condition is designated "cystic ovary." Occasionally one or more will become larger through a pathological accumulation of follicular fluid, and may become important clinically.

Edgar Allen gave this brief concept of ovarian physiology: "Since the blood stream is the common carrier for both nutritional and hormonal supplies, the matter of competition for limited quantities of these substances, amounting actually to a struggle for survival in some instances, seems most fundamental in any concept of ovarian physiology. The developing eggs in the mammalian ovary might truly be considered a crowded population in a life and death struggle for limited amounts of vital necessities, a struggle so severe that only 400 human eggs, of hundreds of thousands, may reach maturity and be ovulated during the reproducive life of the average woman."

Fig. 11.

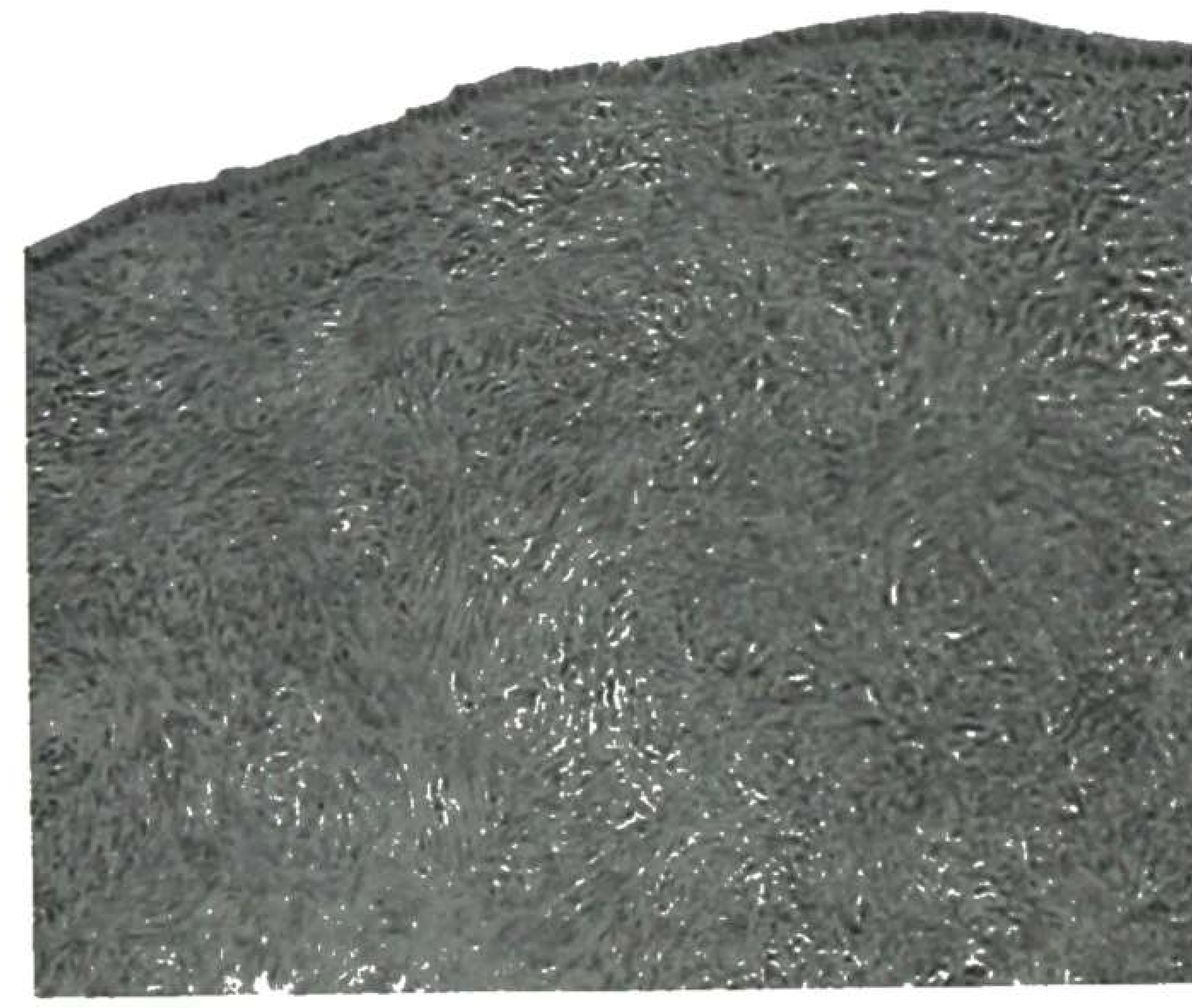


Fig. 12.

Fig. 11.—Ovary with recent corpus luteum at left end. Gyn. Lab.

Fig. 12.—High-power photomicrograph from the margin. Notice the entire absence of follicles and the change in the stroma, so that it resembles fibrous tissue. Gyn. Lab.

After the ripened ovum is discharged, the ruptured follicle fills with serum which clots, and the rent in the follicular wall soon heals. In a few days pigment appears in certain cells about the periphery. These cells increase rapidly in size and form a thick wavy wall in the outer portion of the broken follicle. Since the pigment in the cells is yellow, the cells are called "lutein" cells, and the mass formed by them is, of course, also yellow and hence is called the **corpus luteum** (yellow body). A section of a corpus luteum shows this wavy yellow outer portion formed by the lutein cells. Under high power the secreting cells are seen in typical gland formation.

The recent corpus luteum is a prominent structure in the ovary, as shown in Fig. 11. On account of its size and vascularity and hemorrhagic appearance it may be mistaken for a hemorrhagic cyst of the ovary. Such normal corpora lutea constitute some of the so-called "blood cysts" removed by operators not familiar with pelvic physiology. The various changes in the corpus luteum are described and illustrated in detail under Physiology of the Ovary.

The lutea cells gradually disappear, and after a time the area of the ruptured follicle is occupied only by hyaline material and scar tissue. The area is then no longer yellow, but white, and consequently is called the **corpus albicans** (Fig. 8). The corpus albicans represents the final stage of the ruptured follicle. After many follicles have ruptured, the surface of the ovary often becomes very uneven on account of the number of these depressed scars (Figs. 5 and 7, *A*).

Ordinarily the corpus luteum passes through the described changes in a short time. If, however, pregnancy follows ovulation, the corpus luteum of that ovulation grows very large and remains throughout the pregnancy although functionally it is not essential after the third month.

The senile ovary is made up largely of old corpora lutea resulting in many hyaline areas. The follicles disappear and the stroma becomes more or less fibrous (Fig. 12).

In the histologic study of the ovary, certain remnants are found which do not conform to the characteristics of the ordinary elements. These consist of invaginations or islands of germinal epithelium which have some of the characteristics of the epithelium of other localities, for example, tubal or endometrial. Such a remnant of erratic development (embryological "rest") may remain simply as a part of the histologic picture of that ovary or it may develop into a definite pathological structure, e.g., a serous or pseudomucinous or endometrial cyst.

Ligaments.—The ovary lies in the pelvis obliquely and its inner end is about one inch from the uterus. Extending from this end of the ovary to the uterus is a small fibromuscular cord, the "utero-ovarian ligament," which joins the uterus just below the fallopian tube. The suspensory ligament of the ovary, the "ligamentum suspensorium ovarii," is the thickened edge of the broad ligament connecting the ovary and tube with the side of the pelvis. The "infundibulo-ovarian ligament" extends from the ovary to the outer end of the fallopian tube and usually carries an elongated fimbria.

The ligaments of the ovary contain smooth muscle cells, and these contractile elements cause various movements of the ovary in relation to the uterus and the adjacent tube. The importance of these movements in pelvic function is discussed under Physiology of the Tubes. At the hilum of the ovary these smooth muscle fibers extend into the medulla, blending with the ovarian stroma.

Vessels and Nerves.—The ovary is supplied with blood by several branches of the ovarian artery, which corresponds to the spermatic artery in the male. The ovarian artery arises directly from the abdominal aorta and, passing downward to the side of the pelvis, enters the broad ligament and sends branches to the ovary and uterus and tube. The terminal portion of the uterine artery connects with the ovarian, thus forming an arterial arch which supplies the ovary and tube, and this uterine portion is sometimes of major importance. This arterial arch is shown fairly well in Fig. 6. The venous supply of the ovary corresponds to the arterial supply. They form a plexus in the broad ligament near the hilum of the ovary which is known as the pampiniform plexus or the ovarian plexus.

The main artery as it enters the hilus of the ovary is undulant, tortuous, and somewhat flattened. The spiral arrangement of the arteries within the ovary was mentioned by Farre in 1858. In 1934 Belou demonstrated them by radiographic study and since that time these arteries have been investigated by Delson, Lubin, and Reynolds. In the hilus of the ovary primary, secondary, and tertiary branches arise from the main artery. Though the primary and secondary branches show spiraling, the tertiary branches are the only ones which show marked and consistent coillike spiral arrangement. The diameter of the vessels diminishes gradually until the tertiary branches end in the capillary bed (Fig. 13). Delson et al. concluded that the pattern of the vessels varied with the hormone activity and with the presence and size of the various components of the ovary.

The lymphatic spaces surround the graafian follicles and ramify throughout the connective tissue of the ovary. They pass out at the hilum and anastomose with the uterine lymphatics in the broad ligament and empty into the lumbar glands. The distribution of the lymphatic vessels and glands is shown in Fig. 59 along with the uterine lymphatics.

The nerves come from the renal and spermatic ganglia of the autonomic nervous system, and entering the hilum they ramify throughout the ovary. As with the blood vessels and the lymphatics, the nerve supply of the pelvis including the ovary is best taken up for illustration as a unit, and these general illustrations accompany the discussion of the uterus (Figs. 60 to 65).

Fig. 13.—Right ovary, twentieth day of pregnancy. Arteries only injected except that the injection mass was forced into the veins draining the corpus luteum through the vascular bed of this gland. The right vein has been blocked off in the negative. One corpus luteum is supplied by three terminal branches arising from a single artery arising from the caudal (left) spiral artery. This was in the hilus of this ovary. Small arterial branches to the fimbria were cut off. (×3.) (From Reynolds: Am. J. Obst. & Gynec., February, 1947.)

DEVELOPMENT AND PHYSIOLOGY OF THE OVARY

The ovary has two functions. One is the formation and discharge of the ova, which are the essential female reproductive cells, and the other is the endocrine function. The two functions are intimately connected, each being dependent on the other.

The development of the ovary is conveniently divided into three phases: the undifferentiated or gonad-anlage stage; the formation of primary and secondary germinal cords; and the partition of these cords into separate germinal cells and the further development of the future ovarian follicle.

In both male and female the major portion of the genitourinary tract is derived from the mesonephron or wolffian body. According to Fischel, in the earliest stage there is an accumulation of mesenchymal cells on the anterior aspect of the mesonephron. These mesenchymal cells are specific for the gonad and are not found elsewhere in the body. The covering epithelium over the mass in the early stages is the same as that covering the other abdominal organs, but later it loses the characteristics of a serosa or peritoneum

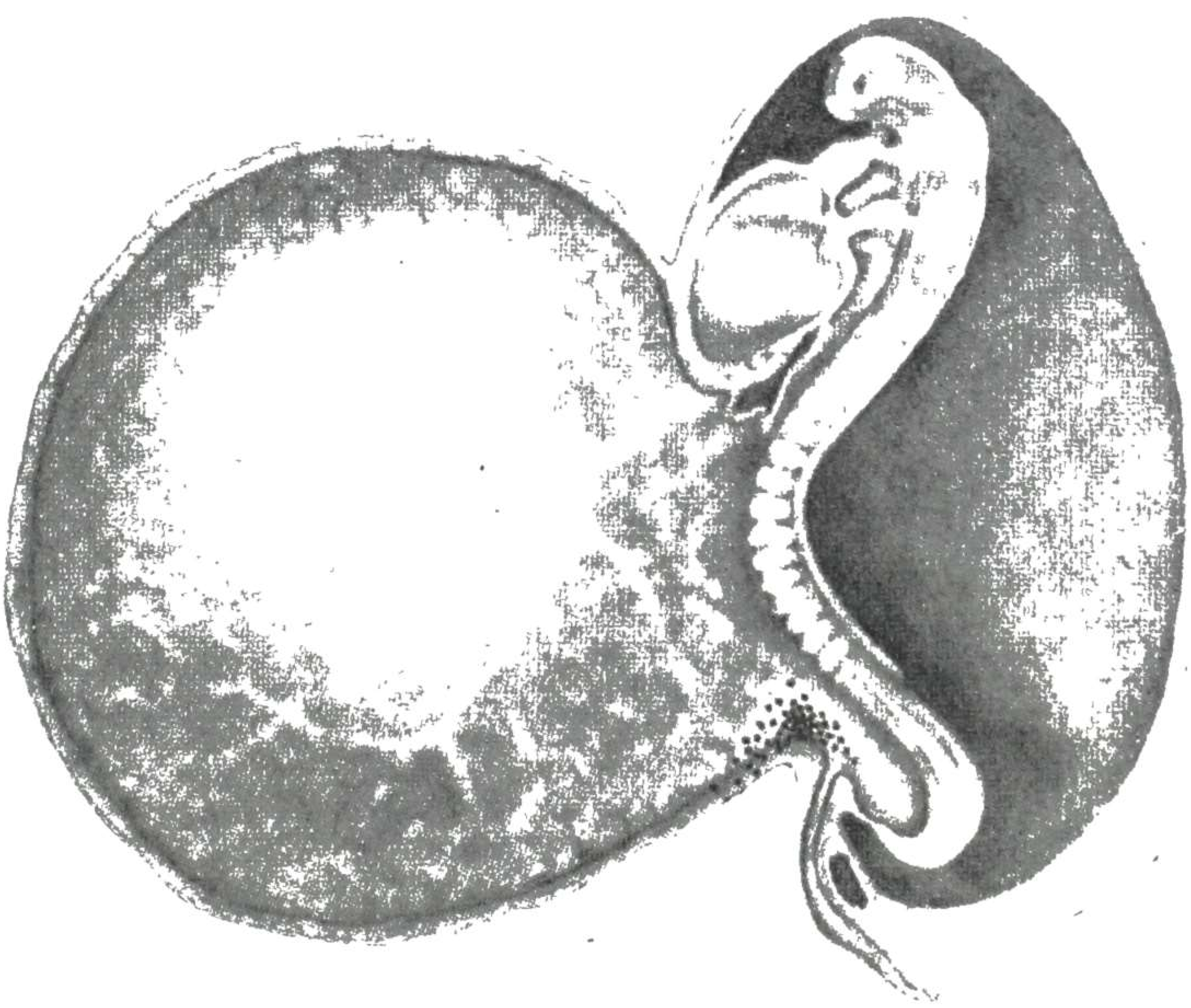
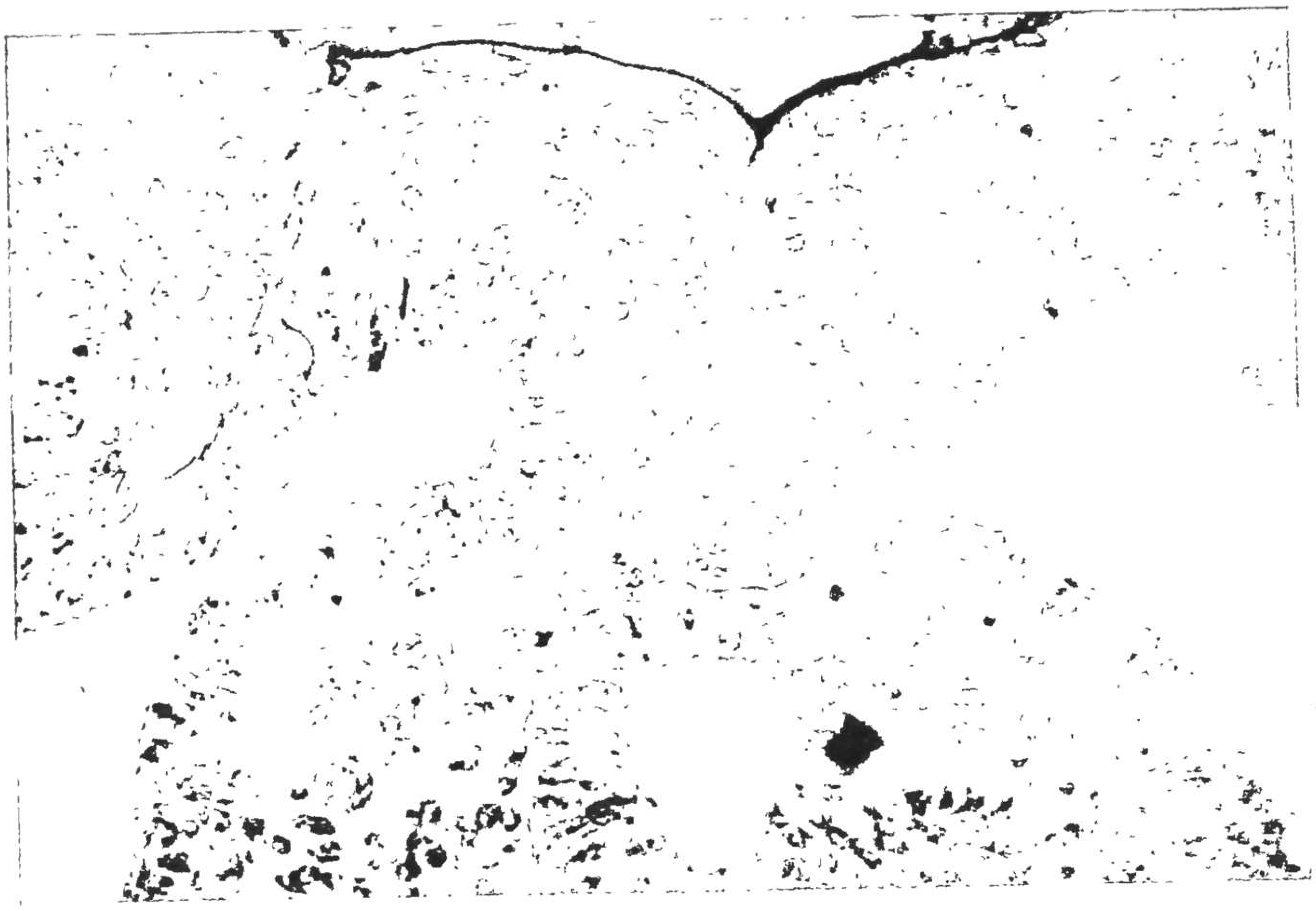
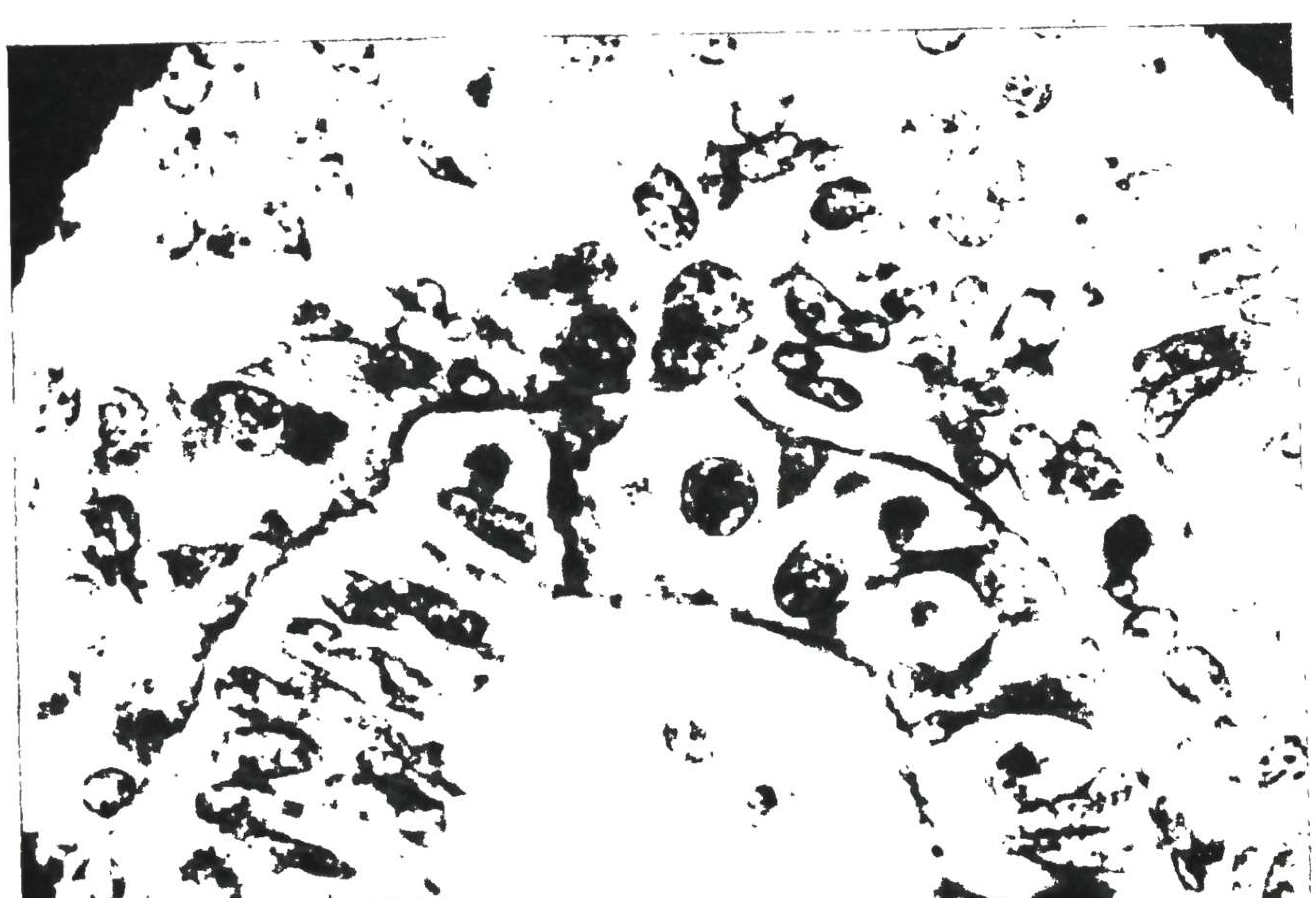


Fig. 14.—Reconstruction of embryo, amnion, yolk sac, and body stalk, based on photographs of the specimen and on serial sections. The germ cells (black dots) are located in the ventral wall of the hindgut and also in the adjoining region of the yolk sac. (×22.) (From Witschi: Carnegie Institution of Washington, Publication 575, Contrib. Embryol., 1948.)

and becomes a single layer of epithelial cells. Waldeyer and other early anatomists believed that this differentiated celomic epithelium, which they designated as germinal epithelium, was the progenitor of the germ cells. According to this theory the so-called primordial germ cells in the overlying epithelium of the gonad invade the underlying ovarian mesenchyme forming the germinal cords. Many of the modern embryologists have discarded this explanation since it has been found that the germinal cells are derived from the dorsal part of the endothelium of the hind-gut. Politzer found that these cells differ from the usual lining cells in that they possess the ability to move by ameboid motility. They can also be distinguished from the usual epithelial cells because they are larger and take a paler stain than the surrounding cells (Figs. 14 to 16).



A.



B.

Fig. 15.—*A*, Showing early stage of emigration of germ cells from the endoderm of the gut into the mesentery and into the peritoneum over it. The germ cells are the prominent large clear cells. *B*, Details of *A*, showing two of the germ cells penetrating the basal layer of the endoderm of the gut. (From Witschi: Carnegie Institution of Washington, Publication 575, Contrib. Embryol., 1948.)

In the first phase these germinal cells, by amoebic movements, migrate through the dorsal mesenteric epithelium into the epithelium of the genital fold which is the future hilus of the ovary. The invasion continues into the central mesenchyme of the future ovary where some of the germinal cells reach but do not penetrate the surface epithelium; others stop in the thickened mesenchyme in the outer portion of the ovary which later becomes the albuginea, and still others locate in the central portion of the ovary. The fact that the primordial germ cells in mice originate in the manner described above was conclusively proved by Everett. He transplanted the genital ridge tissue to the kidney prior to the time that the sex cells had migrated into it, and found that, although the genitourinary ducts develop, the ridge fails to develop sex cells. When the genital ridge was transplanted after the migration of the sex cell into the central mesenchyme, typical ovarian tissue was

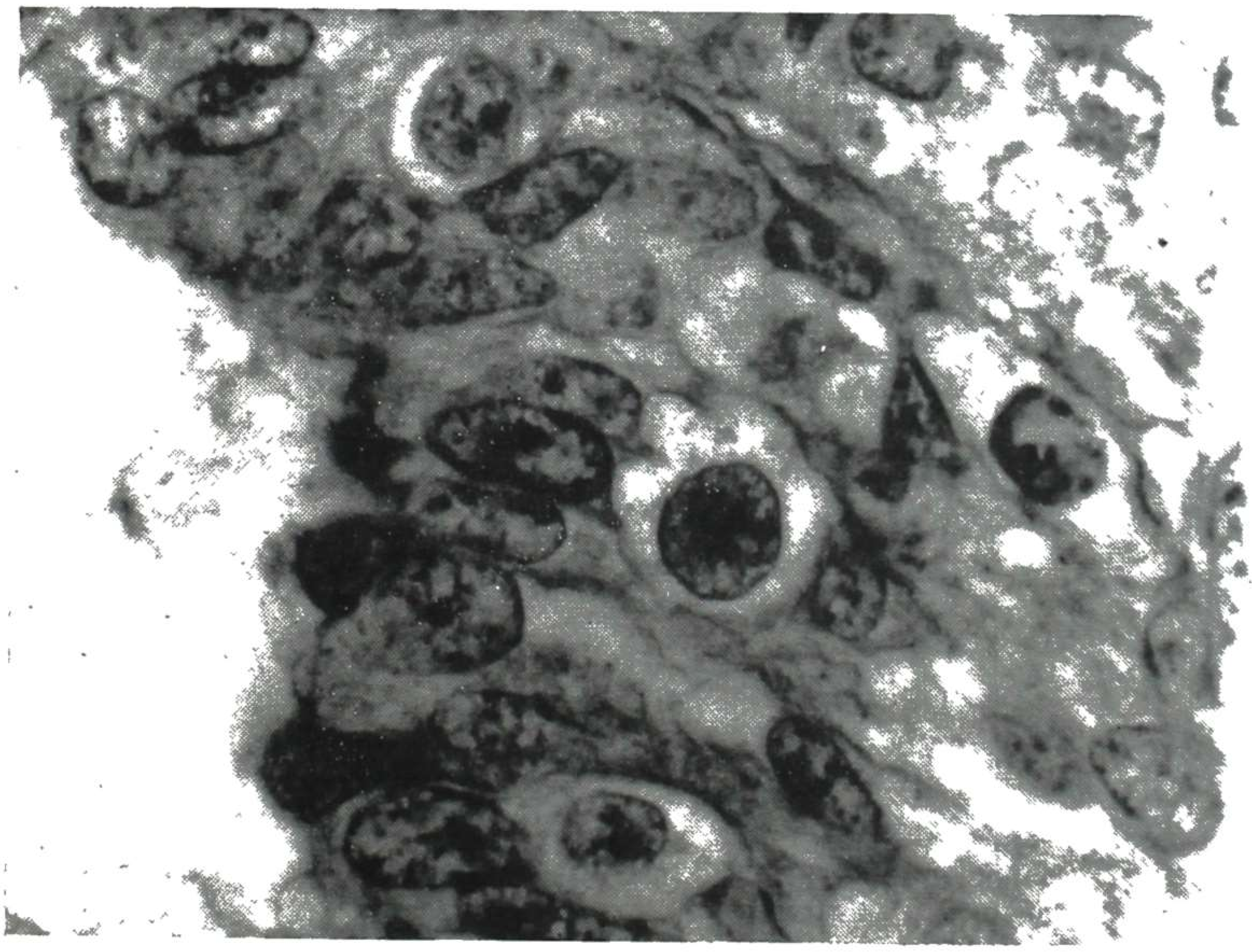


Fig. 16.—An amoeboid germ cell with projecting pseudopodia can be seen moving toward the peritoneum of the coelomic cavity. (From Witschi: Carnegie Institution of Washington, Publication 575, Contrib. Embryol., 1948.)

formed containing sex cells. In the first phase of differentiation cells of the gonad arrange themselves in cords which converge toward the hilus of the ovary. These solid cords in the female form the rete ovarii and serve no purpose, but in the male they acquire a lumen and persist as an anastomosis between the seminiferous tubules and the wolffian duct or the future vas deferens. In the female these columns usually disappear rapidly, though occasionally portions persist and are found in the fully developed ovary. The ovarian rete was also supposed to be the result of downgrowth of the surface epithelium, but Fischel found that they developed in situ. Forbes studied serial sections of ovaries in 44 human fetuses and 11 infants from six weeks to three and a half years of age to determine the time and mode of disappearance of the medullary (primary sex) cords. He found that these begin to regress in the fetus of about 150 mm. crown rump length (C.R.L.), show progressive reduction in size and number, and usually disappear at 280 mm. C.R.L.; occasionally they were found in larger fetuses. They are absent from all of the infants' and children's ovaries examined. The lumina do not normally develop in ovarian medullary cords.

The second phase of ovarian development is marked by the formation of the germinal cords containing the primordial egg cells and other small round cells which later are converted into the granulosa cells. These cords are called Waldeyer or Pflüger tubules and were formerly thought to be derived from ingrowth of the surface epithelium of the ovary. Fischel has shown that they arise from the mesenchyme in situ and that the egg cell itself acts on the surrounding tissue, organizing it into cords and, eventually, with the aid of the granulosa organizing ability, into follicles. The terminal cords formed locally are called the primary sex cords. Another cordlike projection which is derived from the surface epithelium was described by Grunewald. He designates these as the secondary sex cords and found that they fuse with the primary sex cords. The function of these secondary cords is not known; they usually disappear during the course of normal development as do the primary cords. It is thought that serosal cysts known as Walthard inclusions and Brenner tumors may develop from remnants of these secondary cords. Also some of the granulosa cells develop from these secondary cords.

The final phase in the development of the ovary is the division of the germinal cords into islands of germinal cells by ingrowth of the surrounding stroma cells. This process is complete when each sex cell is surrounded by its future granulosa cell layer; these latter cells, as previously mentioned, are present in the primary and the secondary sex cords. At this stage the egg surrounded by a single layer of granulosa is called a primordial follicle. Schiller objects to this designation for there is no cavity at this stage and the term follicle means a cavity or bag filled with fluid. Next, the granulosa cells proliferate, and this growth is most marked in the area where the ovum is located. Later, liquefaction occurs, forming a cavity filled with fluid. The cavity is lined by a single layer of granulosa cells except at the point where the egg is located, and here it is many layers thick. This mass of granulosa cells surrounding the ovum is called the cumulus oophorus or discus proligerus.

When the granulosa cells begin to proliferate, the surrounding ovarian stroma becomes arranged in a concentric framework around the developing follicle. These peripheral ovarian stromal cells, which are derived from the same embryonal mesenchyme as the granulosa cells, form a loose inner layer containing the blood vessels and a compact outer layer. The inner layer is called the theca interna and the outer layer is the theca externa. Separating the theca interna from the granulosa is a clear membrane called the hyaloid membrane or membrana propria. The granulosa layer contains no vessels and it derives its nutrition from the capillaries of the theca interna. Until the formation of the cavity and the collection of follicular fluid, the development of the follicle is carried on by a self-contained organizing power. The egg stimulates the organization of the granulosa, which in turn stimulates the formation of the theca. After the follicular cavity is formed, the further development of the egg, theca interna, and granulosa is controlled by the anterior pituitary hormones. This organizing power not only holds true for the normal granulosa but is seen also in granulosa cell tumors where the neoplastic granulosa stimulates ovarian stroma to an overproduction of thecal tissue.

Since there is still a question as to whether some of the sex cells may not be derived from the germinal epithelium, as advocated by Waldeyer, a brief summary of this theory together with some of the more recent work supporting it is in order. As embryonic development progresses, there are periods in which these so-called primordial germ cells in the overlying germinal epithelium of the gonad invade the underlying ovarian mesenchyme. The first period of invasion occurs before sex differentiation is evident. During this period tubules are formed by the epithelial downgrowths. If the gonad subsequently becomes an ovary, they remain in the medulla of the ovary as the medullary tubules. If a testicle is formed, they become the seminiferous tubules containing sex cells. With the next period of invasion into the ovary, according to the theory of Waldeyer, of Felix, and of Winiwarter, ova and follicles are formed from ingrowths of the germinal epithelium. Their idea is that all the ova that a woman is to have during her life are formed at birth or shortly thereafter. The work of Allen in 1922 and the work of Swezy and Evans on ovogenesis in the mammalia throw doubt on this idea. Swezy and Evans summarized their findings as follows:

"Ovogenesis occurs throughout adult life in the guinea pig, cat, dog, and man, as a rhythmical process, during which thousands of ova are produced de novo, followed by the degeneration of all but a few which mature. In the guinea pig, cat, and dog this rhythm of ovogenesis coincides with the rhythm of the estrus cycle, beginning at ovulation and reaching its peak at anoestrum, with wholesale degeneration occurring at late prooestrum. Ovogenesis was proven in adult mice by Allen and Creadick. Using colchicine to arrest the cells in mitosis, they were able to demonstrate mitoses in the general epithelium of an adult mouse ovary. Lack of knowledge of a definite estrus cycle in man weakens the correlation here, but the rhythm of ovogenesis is as striking in the number of ova produced and destroyed as in the other animals.

"New sex cells are produced by proliferations from the germinal epithelium in the form of invaginations and ingrowths of epithelial cords. These become separated from the germinal epithelium, pass through the tunica albuginea and form a more or less continuous layer underneath the tunica. From one to many cells in each group may develop into ova, the remainder forming the follicle cells.

"Contrary to the concept involved in the germ plasm theory, the mammalian ova (excepting those that mature and are fertilized) have a shorter life span than any other group of cells in the body outside of the reproductive tract."

Simkins, in 1932, concluded that new ova after birth are formed from certain cells in the ovarian mesenchyme which are induced to develop into germ cells through the influence of the anterior pituitary hormones. Schwarz, Young, and Crouse, in a recent study of ovogenesis in the adult human ovary, concluded that "the development of new ova after birth and in active adult life can be definitely accepted." They feel that the main source of the ova is the germinal epithelium but that their mesenchymal origin cannot be discarded.

OVULATION

Ovulation is the term applied to the maturation and discharge of an ovum. The progressive stages in ovulation together with associated changes in the uterus and in hormone levels are shown in Fig. 1.

gressive reduction in size and number, and usually disappear at 280 mm. C.R.L.; occasionally they were found in larger fetuses. They are absent from all of the infants' and children's ovaries examined. The lumina do not normally develop in ovarian medullary cords.

The second phase of ovarian development is marked by the formation of the germinal cords containing the primordial egg cells and other small round cells which later are converted into the granulosa cells. These cords are called Waldeyer or Pflüger tubules and were formerly thought to be derived from ingrowth of the surface epithelium of the ovary. Fischel has shown that they arise from the mesenchyme in situ and that the egg cell itself acts on the surrounding tissue, organizing it into cords and, eventually, with the aid of the granulosa organizing ability, into follicles. The terminal cords formed locally are called the primary sex cords. Another cordlike projection which is derived from the surface epithelium was described by Grunewald. He designates these as the secondary sex cords and found that they fuse with the primary sex cords. The function of these secondary cords is not known; they usually disappear during the course of normal development as do the primary cords. It is thought that serosal cysts known as Walthard inclusions and Brenner tumors may develop from remnants of these secondary cords. Also some of the granulosa cells develop from these secondary cords.

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OVULATION

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development and degeneration of the ovum and follicle by means of intravital staining, concluded that the liquor folliculi is a secretory product from the blood vessels and lymphatics which is possibly modified by the influence of the granulosa cells. At one point the granulosa cells are heaped up into a mass which surrounds the ovum, as shown in Figs. 18 to 20. This projection is spoken of as the cumulus oophorus or discus proligerus.

Fig. 19.—Photomicrograph of a follicle which is nearly mature, as indicated by the size of the cavity compared to the ovum. Gyn. Lab.

Surrounding the follicle, even in the early stages, is a sheath composed of the surrounding stroma cells, called the theca folliculi. As the graafian follicle forms, the theca becomes divided into two layers. The outer layer,

theca externa, does not differ from the surrounding stroma. The inner layer, **theca interna,** shows some differentiation of its cells, which become oval in shape and closely packed. This layer becomes also more vascular.

In the fully developed graafian follicle, the ovum is surrounded by a layer of radially placed cells of the granulosa, called the "corona radiata." Between the latter and the ovum is a transparent zone called the "zona pellucida." The perivitelline space lies betwen the zona pellucida and the ovum.

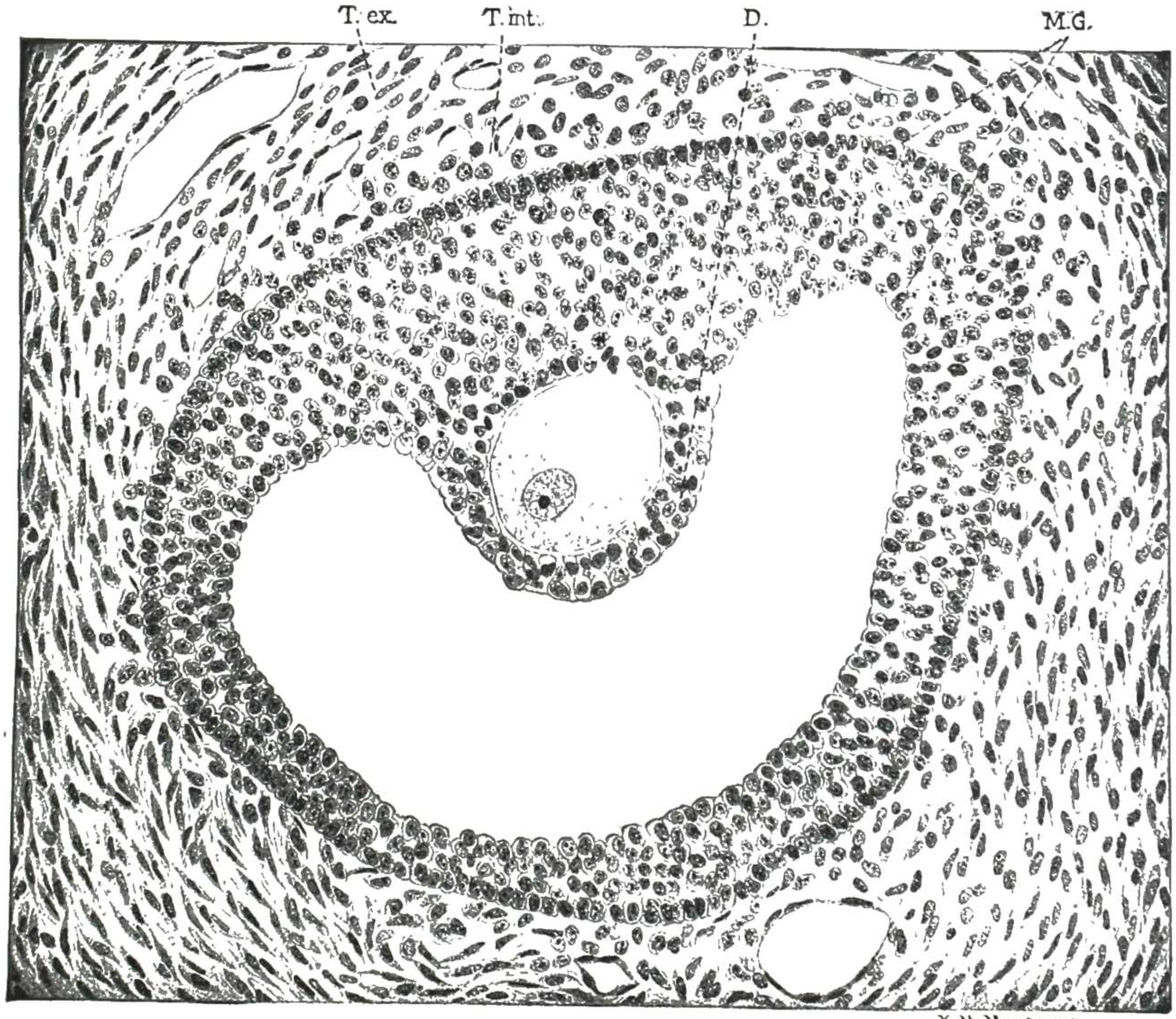


Fig. 20.—Drawing of a somewhat older follicle and contained ovum, to show the details of the follicular epithelium (membrana granulosa) and of the ovarian stroma, which is very rich in cells. The follicular cavity has begun to form. *M.G.*, membrana granulosa; *D*, discus proligerus; *T.int.*, theca interna; *T.ex.*, theca externa. (From Williams: Obstetrics, D. Appleton-Century Co.)

The **ovum,** which is the most important structure in the ovary, is a single cell composed of four parts, as follows:

a. A limiting membrane called the "vitelline membrane."
b. The cell substance or protoplasm, the inner portion of which is deutoplasm and is known as the yolk.
c. The nucleus or "germinal vesicle."
d. The nucleolus or "germinal spot."

The ovum is spherical, and when fully developed measures 0.2 mm. in diameter. Just before the ovum is discharged upon the surface of the ovary by the bursting of the follicle, as previously described, it goes through a process of ripening. This process is called "maturation" and consists in the karyokinetic division of the nucleus and the expulsion of a small portion of it. This occurs twice in succession. With the first division the chromosomes split so that the oocyte and the polar body each contain forty-eight chromosomes, which is the normal number in the human being. After ovulation the egg passes into the tube and the second division occurs with fertilization. With this division the chromosomes do not split but the pairs separate so that the mature ovum and the second polar body each contain one-half the normal number of chromosomes, or twenty-four. The sperms go through a like process, but the mature sperms instead of having 24 identical pairs of chromosomes have one dissimilar pair called the X and the Y chromosomes; the latter is known as the sex-determining chromosome. In the reductional division, one of the sperms gets the X and the other gets the Y chromosome. If the egg is fertilized by the one containing the Y chromosome, the fundamental sex of the resultant individual will be male; if fertilized by a sperm containing the X chromosome, the individual will be a female. Hence the fundamental sex of the body cells is determined at fertilization, and up to the indifferent stage both develop alike; further sex differentiation to maturity is stimulated by the sex hormones. The cast-off portions have been named "polar bodies." The polar bodies are apparently of no further use, as they soon disappear. It may be remarked here that certain tumors (teratomas) are supposed to originate from these polar bodies.

The endocrine mechanism of ovulation has long been the subject of investigation. Frank noted an increase of prolan secretion around the tenth to the twelfth day of the cycle, and later Kurzrok demonstrated an increase in the FSH at this same period. Hoffman feels that LH acts synergistically with FSH to cause ovulation.

Recently in an excellent summary on the mechanism and control of primate ovulation Sturgis gives the following explanation: From the ingenuous intrasplenic ovarian transplant experiments of Lipschutz et al., it is apparent that LH is necessary for ovulation and that under certain quantitative conditions estrogen stimulates the pituitary to produce LH. From a study of primary follicles and follicles of "second rank," which are destined to become atretic, Sturgis found that just before ovulation the granulosa cells of the primary follicle were separated by edema, while in the secondary follicles early dissolution of the granulosa cells was occurring, a sign of beginning atresia. In contrast, the theca interna of the primary follicle was thin and inactive, whereas that of the secondary follicle was thick and hypertrophied. A study of these secondary follicles shortly after ovulation demonstrated that this hypertrophy was transient, for in this follicle which is now atretic the theca interna is collapsed in folds around the shrinking cavity of the follicle. As noted later in this chapter, Corner has shown that the theca interna and not the granulosa is the principal source of estrogen. From the available evidence Sturgis concludes that the extra spurt of estrogen just prior to ovulation comes from the theca interna of these secondary follicles and that this in turn stimulates the pituitary to secrete LH which is the factor initiating ovulation. In support of this concept Sturgis mentions the work of Westman, who cauterized all of the secondary follicles in the rabbit ovary shortly before ovulation and found that the maturing primary follicle failed to ripen. Lipschutz feels that after ovulation the progesterone produced by the corpus luteum inhibits the production of LH and "holds luteinization in abeyance." Though it is known that the luteotrophic hormone (LTH) is important in the maintenance of the corpus luteum, its blood levels are not sufficiently defined to include them in the illustration in Fig. 21.

Ovulation occurs most frequently between the eleventh and fourteenth days of the cycle. The limits of the period of fertile coitus are ordinarily from the tenth to the eighteenth day after the first day of menstruation. In women with long or short menstrual cycles the time of ovulation is best estimated by subtracting two weeks from the onset of the flow. Figs. 22, *A* and *B*, shows human twin ova recovered from the tubes on the fifteenth day of the cycle, apparently within twenty-four hours after rupture of the follicles. One ovum was found in each tube and a fresh corpus luteum in each ovary, showing simultaneous ovulation in each ovary. Tubal eggs removed by Rock and Hertig on the second to third postovulatory day is shown in Fig. 23.

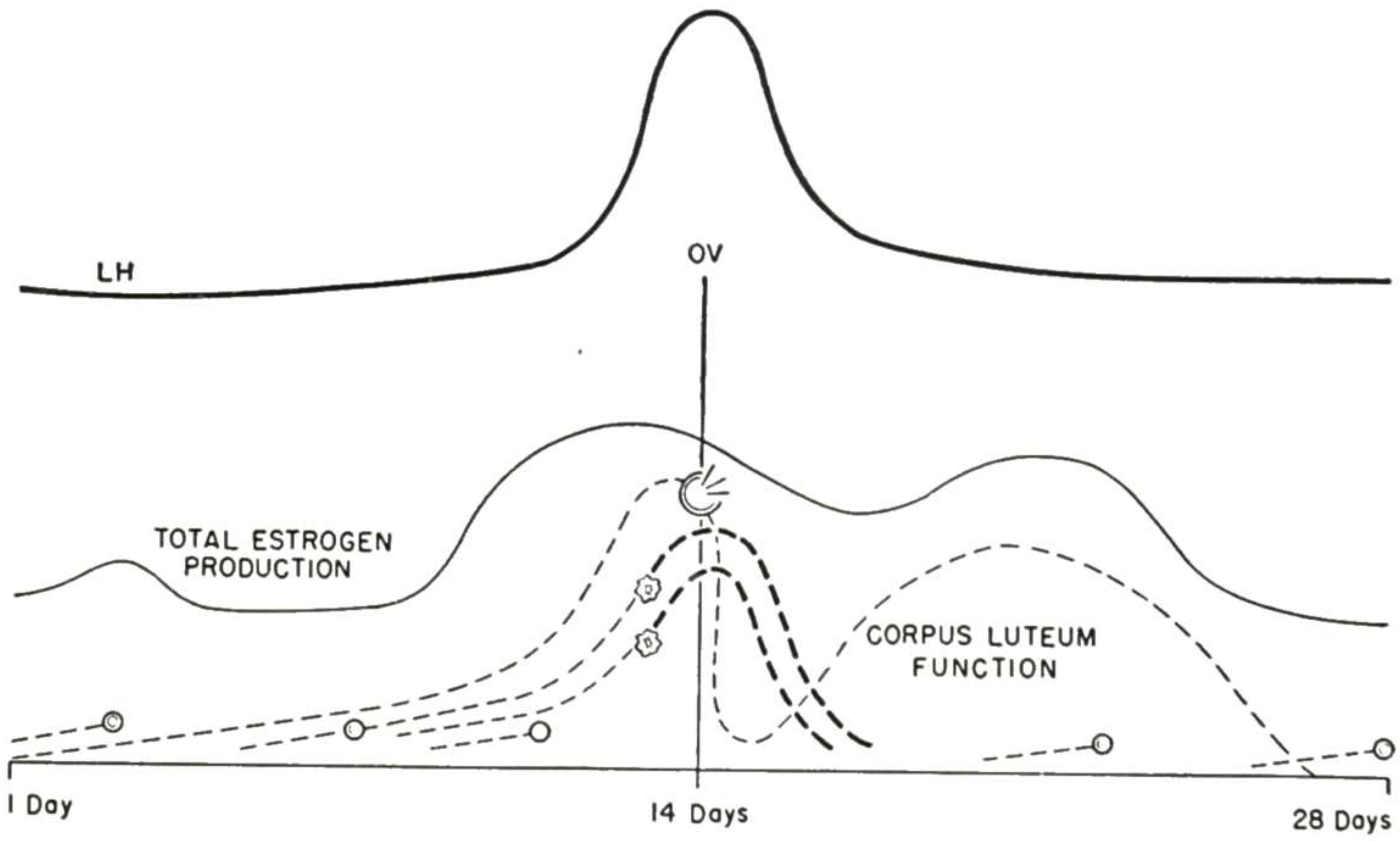
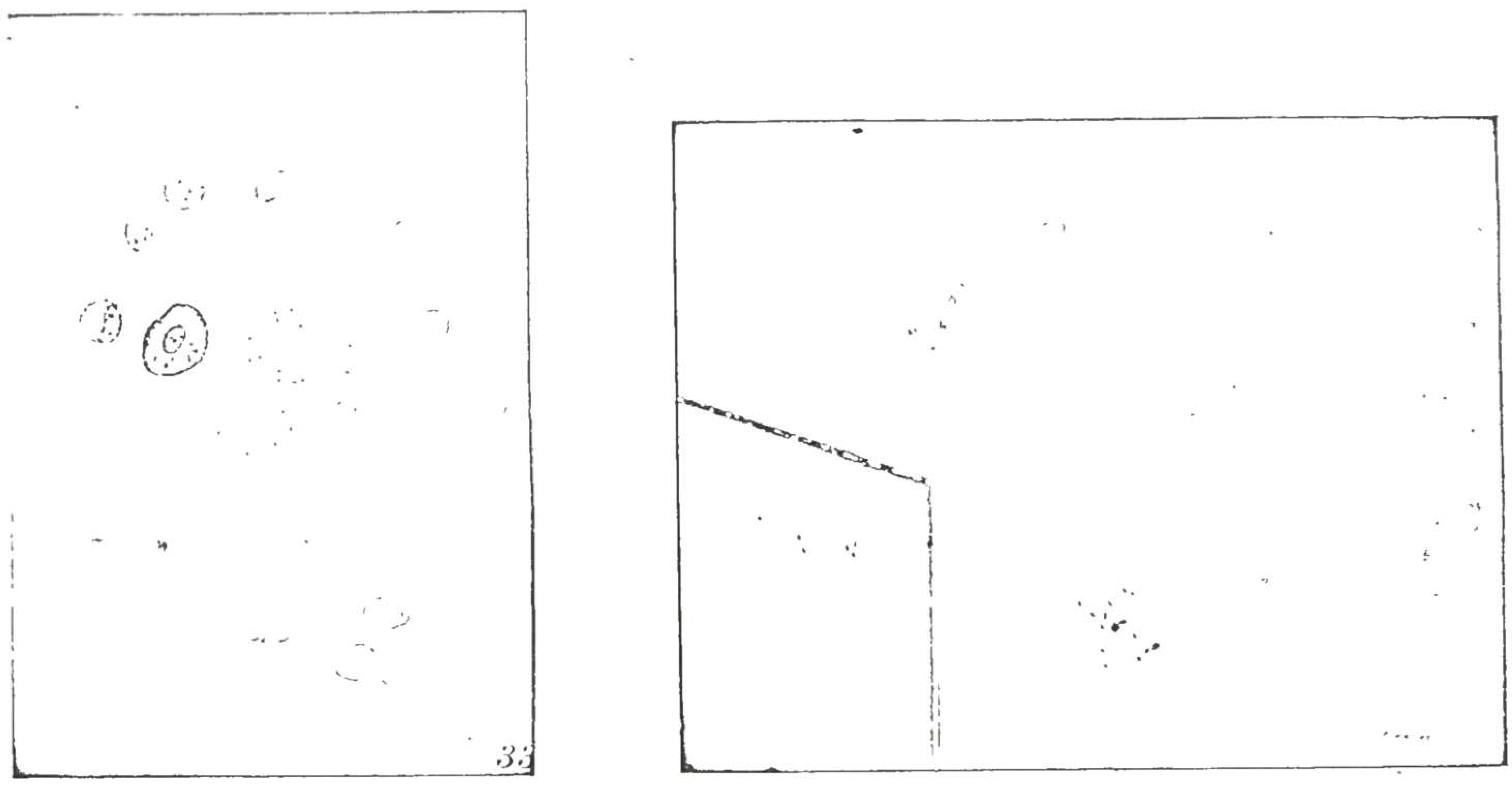


Fig. 21.—Relation of theca interna activity in atretic follicles at time of ovulation to estrogen and LH levels—Macacus Rhesus. (From Sturgis: Fertil. & Steril., January, 1950, Paul B. Hoeber, Inc.)

Preceding the rupture of the follicle, certain changes are noted in its wall—changes which are indicative of maturation of the follicle. The cells of the theca interna become larger and clearer, gradually losing their connective tissue characteristics. All grades of transition may be noted between the spindle cells of the theca externa and the polygonal cells of the theca interna.

The theca interna separates itself from the membrana granulosa, which becomes increased in thickness. According to Strassmann, who studied 18,000 serial sections of ovaries of humans and animals, ovulation is a mechanical process stimulated by the endocrine glands, and the follicles reach the surface of the ovary by the following mechanism: Through a one-sided proliferation of the theca interna on the side of the follicle nearest the surface of the ovary, a cone is formed which penetrates the surrounding tissue, thus opening a way for the developing follicle. The growing follicle ascends to the ovarian surface by following the line of least resistance provided by the cone of the theca interna. Figs. 24 to 26 show the steps in the process.

The actual cause of the rupture of the follicle has been the subject of considerable speculation, and the following theories have been proposed: (a) Smooth muscle fibers in the ovarian stroma contract rhythmically and eventually cause the follicle to rupture. There is little evidence to support this idea. (b) An enzyme digests the internal lining of the follicle until it is too weak to withstand the intrafollicular pressure. No such enzyme has been found.



A. *B.*

Fig. 22.—*A*, Twin human ovum recovered on the fifteenth day of the menstrual cycle. Ovulation probably occurred on the preceding day. This ovum was recovered from the left tube. Camera lucida drawing. Note the polar body at ten o'clock. *B*, Twin ovum to that shown in *A*, recovered from the right tube. Chromosomes of the second maturation spindle were located at eight o'clock. Camera lucida drawing. (From a monograph by Edgar Allen, J. P. Pratt, Q. U. Newell, and J. L. Bland, published by The Carnegie Institution.)

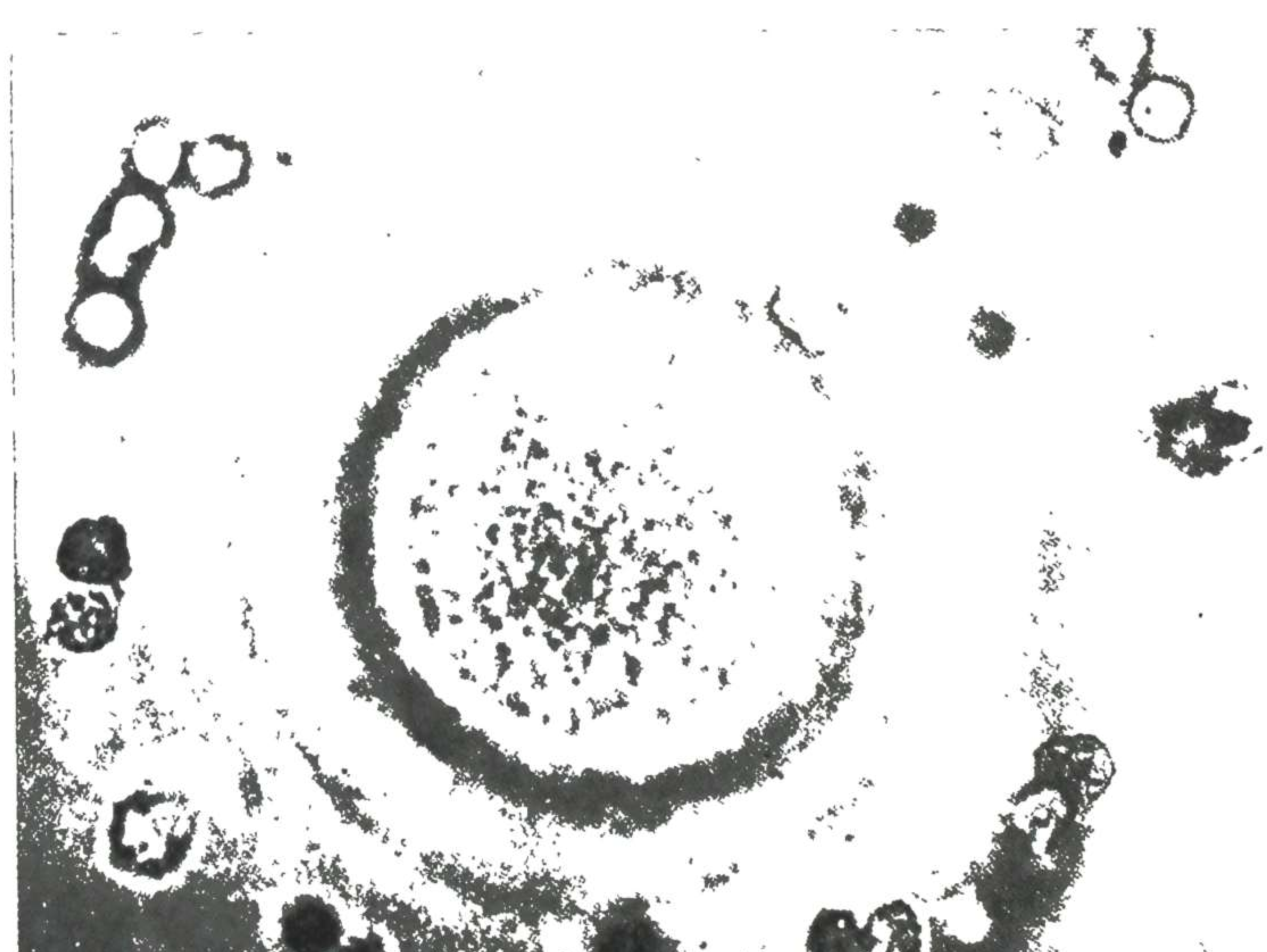


Fig. 23.—A tubal egg (dated 2 to 3 days postovulatory). The ovum was photographed before fixation in a hanging-drop of saline solution about 36 hours after it had been washed out of the tube. Note object suggestive of the polar body outside of the vitellus. (×450.) (From Rock and Hertig: Am. J. Obst. & Gynec., March, 1944.)

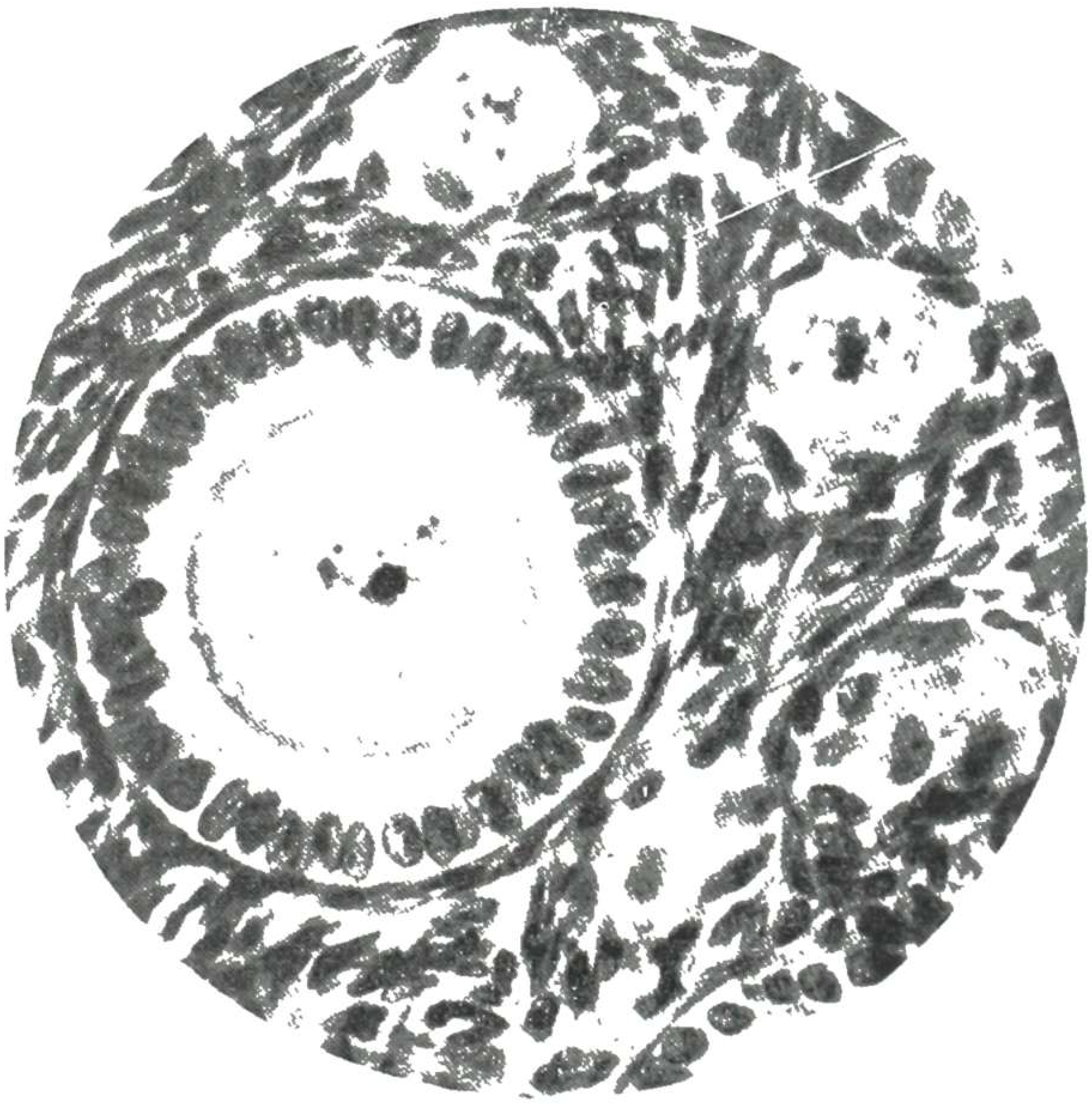


Fig. 24.—Theca interna cone, first stage. Triangular thecal wedge, indicated by line, pointing toward ovarian surface. No theca layers around follicle otherwise, one layer of granulosa cells. Small follicle of a rabbit (×325). (From Strassmann: Am. J. Obst. & Gynec.)

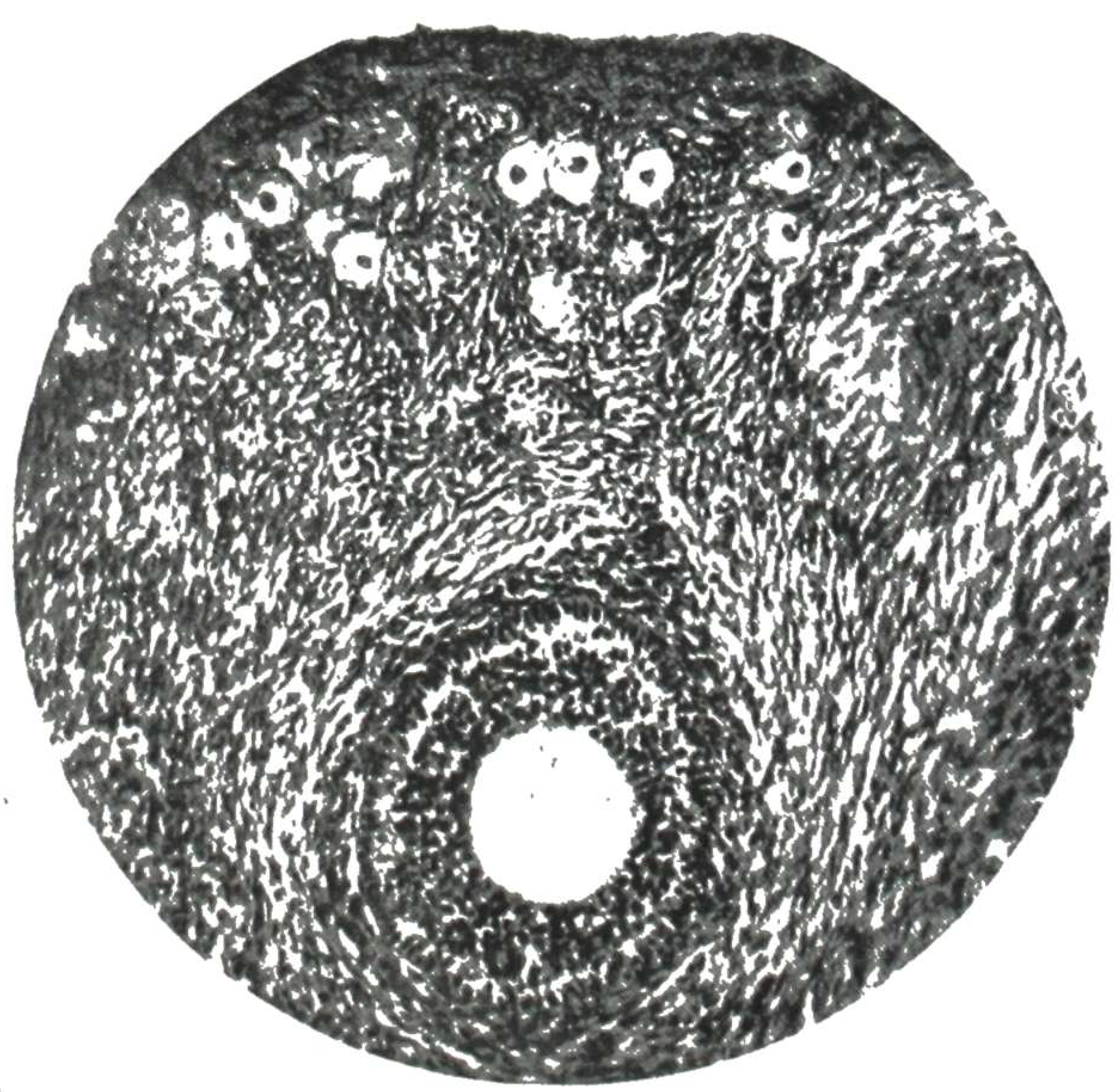


Fig. 25.—Theca interna cone, second stage, pointing toward ovarian surface. Beginning development of theca layers around follicle. Multiple layers of granulosa cells. Small follicle of a rabbit (×100). (From Strassmann: Am. J. Obst. & Gynec.)

(c) There is an increased osmotic pressure in the follicular fluid probably caused by the disintegration of the Call-Exner bodies. In rabbits J. T. Smith has shown that the Call-Exner bodies migrate into the follicular fluid and disintegrate at the time of ovulation. He feels that these bodies contribute something, probably glycogen or sugar, which raises the osmotic tension of the follicular fluid. He has shown also that in the rabbit the osmotic tension in follicles about to rupture is greater than that in unstimulated follicles.

Much study has been given to the problem of determining when a patient ovulates. The following signs and symptoms have been proposed as indicative of ovulation:

1. Séguy and Vimeux noted an increase in the quantity of the cervical mucus between the tenth and the fifteenth day of the menstrual cycle. Viergiver and Pommerenke estimated that there was four times as much cervical mucus secreted, per day, during ovulation as at other times in the cycle. The firm pattern of dried mucus and "Spinnbarkeit" are discussed in Chapter 14.

Fig. 26.—Theca interna cone, third stage, and granulosa cone, coinciding axis pointing toward ovarian surface. Streamlined adaptation of stroma. Ascending follicle of a cow (×80). (From Strassmann: Am. J. Obst. & Gynec.)

2. Uterine bleeding, frequently associated with slight pains, occurs in about 5 per cent of women. The bleeding is usually very scanty and is probably due to a temporary drop in the estrin-blood level, with withdrawal bleeding, and stops as soon as the new corpus luteum secretes enough estrogen and progesterone to correct the blood level. The pain is probably due to the rupture of the follicle and may be severe enough to cause an incorrect diagnosis of appendicitis. Some claim this is due to final spurt of growth of the follicle just before ovulation.

3. On examination of the vaginal smear Papanicolaou found erythrocytes and a sudden shower of leukocytes in 31 per cent of his series of cases. The vaginal smear is now used as an accurate test for ovulation. Zuck and Duncan found a rise in the vaginal pH at ovulation time.

4. The blood estrin rises just before ovulation and there is an increase of the gonadotrophic hormones in the urine. Farris described color changes in the ovaries of immature white rats due to hyperemia caused by these urinary hormones. By comparing the color of the ovaries in situ with the graded shades of red of the Munsell color system, he feels that he can determine the day of ovulation.

5. Premenstrual endometrial biopsy shows typical progestational effect, indicating that ovulation has occurred.

6. At operation, Cotte, Bissell, and others have noted 8 to 60 c.c. of free fluid in normally ovulating women, and it is thought that this may aid movement of the ovum. It is possible that this much fluid can be found in any abdomen. Hoyt and Meigs and also Hendrickson found some blood in the peritoneal cavity at ovulation time. It varied from a few cubic centimeters of blood to severe bleeding, causing shock.

7. Changes in electrical potential at ovulation time were noted by Burr, Hill, and Allen in 1935 in rabbits. Rock, Reboul, and Snodgrass previously felt that these same changes in the human subject indicated ovulation, but in later experiments with 10 women, only 7 of the 10 showing changes in electrical potential had ovulated.

8. Rubenstein was able to predict ovulation by a study of body temperature through the cycle. He found that there was a depression of temperature during the proliferative phase, reaching its low point just before ovulation. With ovulation the temperature rose half a degree Fahrenheit in the first twenty-four hours and exceeded one degree for the first week after ovulation. Using this test correlated with the vaginal smear technique, he was able to discover that four of his sterility patients were ovulating during menstruation. He advised coitus on the estimated day of ovulation, and succeeded in securing pregnancy in all four women. Details of vaginal changes will be given under Vagina.

A schematic sketch showing the migration of the ovum is shown in Fig. 27, microphotographs of implantation are seen in Fig. 28, and gross implantation is shown in Fig. 29.

After ovulation the **corpus luteum** is formed under the influence of the luteinizing hormone and luteïnization is maintained by a third hormone, the luteotrophic hormone. This latter is thought to be identical with the lactogenic hormone. Corner found in monkeys that there is also luteinization of some unruptured follicles, and he calls these accessory corpora lutea. The stages of change as worked out by Novak have been very helpful in correlating the histologic changes in the corpus luteum with those in the endometrium. They are as follows:

1. The stage of Proliferation (fifteenth to eighteenth day). With evacuation of the liquor folliculi, the cumulus oophorus, together with its ovum, escapes into the peritoneal cavity. The capillaries of the theca interna and externa are widely dilated. The theca interna cells increase in size due to

fatty infiltration. The granulosa cells become polygonal, take the stain less deeply, and are gradually converted into lutein cells.

Studies by J. I. Brewer indicate that the capillaries have penetrated through the granulosa into the central cavity by the end of this stage. The capillaries are distended with blood.

Grossly a very early corpus luteum appears as a thin-walled, collapsed vesicle on the surface of the ovary. The point of rupture may be evident, but hemorrhage into the lumen is not characteristic. The hyperemic wall does give the vesicle a hemorrhagic appearance. The inner surface is yellowish gray at this stage, and there is only a slight degree of undulation. Figs. 30 to 32 show corpora lutea in this early stage. Fig. 33 shows the three layers of the wall of an unruptured follicle—membrana granulosa, theca interna, theca externa in the stage of proliferation.

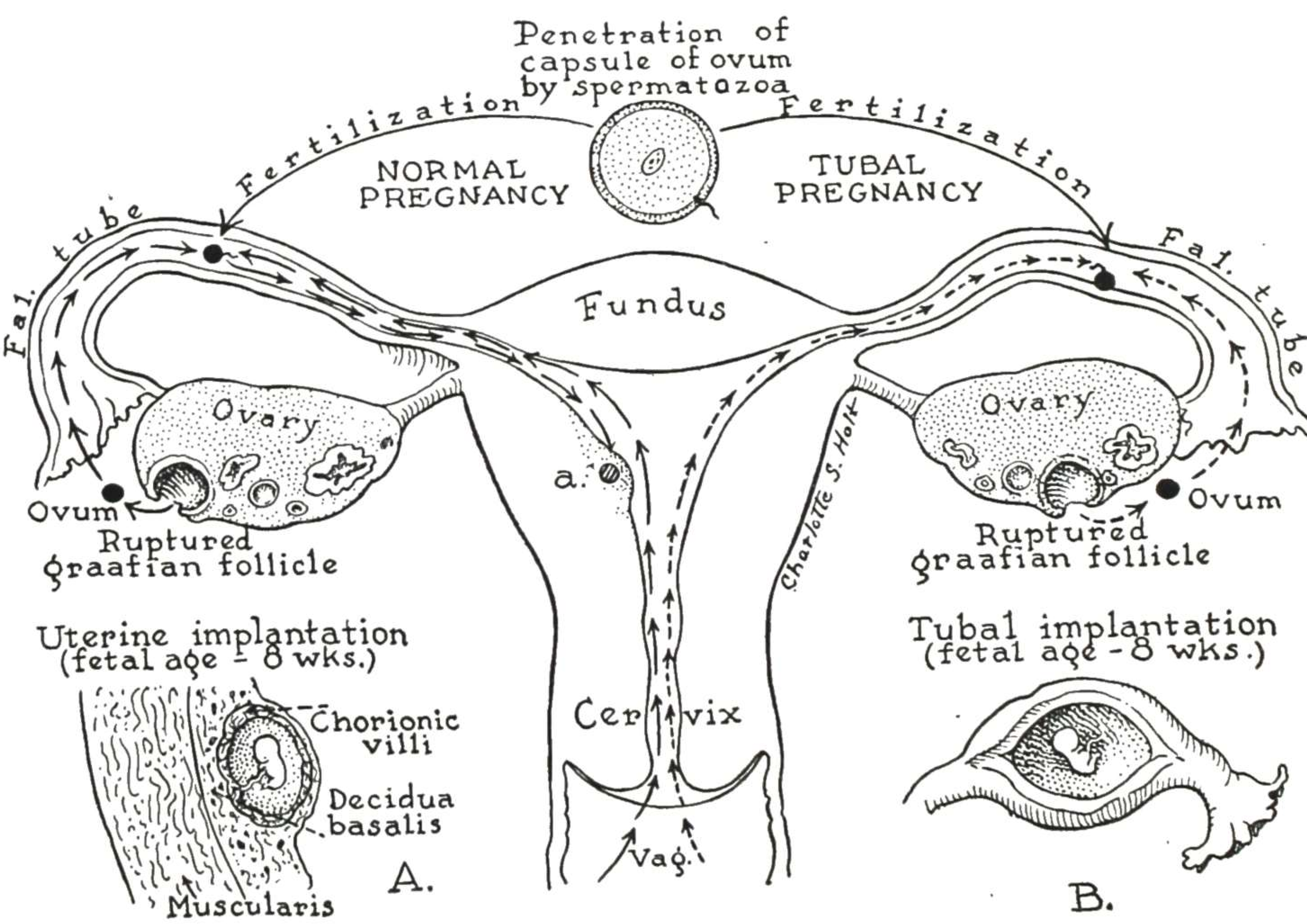


Fig. 27.—Fertilization of the ovum. Note fertilization in the tube and implantation of the fertilized ovum in the endometrium. (From Falls and McLaughlin: Obstetric and Gynecologic Nursing, The C. V. Mosby Co.)

2. The stage of Vascularization (eighteenth to twenty-third day). This second stage in the development of the corpus luteum begins with hemorrhage into the granulosa layer and lumen from the dilated capillaries of the granulosa forming extracellular lakes of blood.

While vascularization is the most conspicuous feature of this stage, changes in the epithelium are also noted. The cells take on a more luteinlike character, and the epithelial zone is quite clearly marked off from the theca interna. Endothelial cells push beyond the inner border of the lutein layer into the extravasated blood in the lumen. Connective tissue cells also penetrate the lutein layer and invade the lumen. Gradually there is developed on this inner border a layer of connective tissue cells and blood vessels, which form a sharp dividing line between the lutein layer and the blood in the lumen. At this stage the wall becomes bright yellow and takes on a wavy outline. The theca interna cells shrink toward the end of this stage. Fig. 34 shows this second stage of corpus luteum development.

There is a difference of opinion as to when the full function of the corpus luteum is established and when this function begins to wane. Brewer concluded from his studies that the peak of function occurs during the stage of vascularization, and he found definite degeneration of the lutein cells and beginning regression of the corpus luteum toward the end of this stage. In support of these conclusions he found that there was an increase in the phospholipids in the corpus luteum from the day of ovulation up to the twenty-fourth

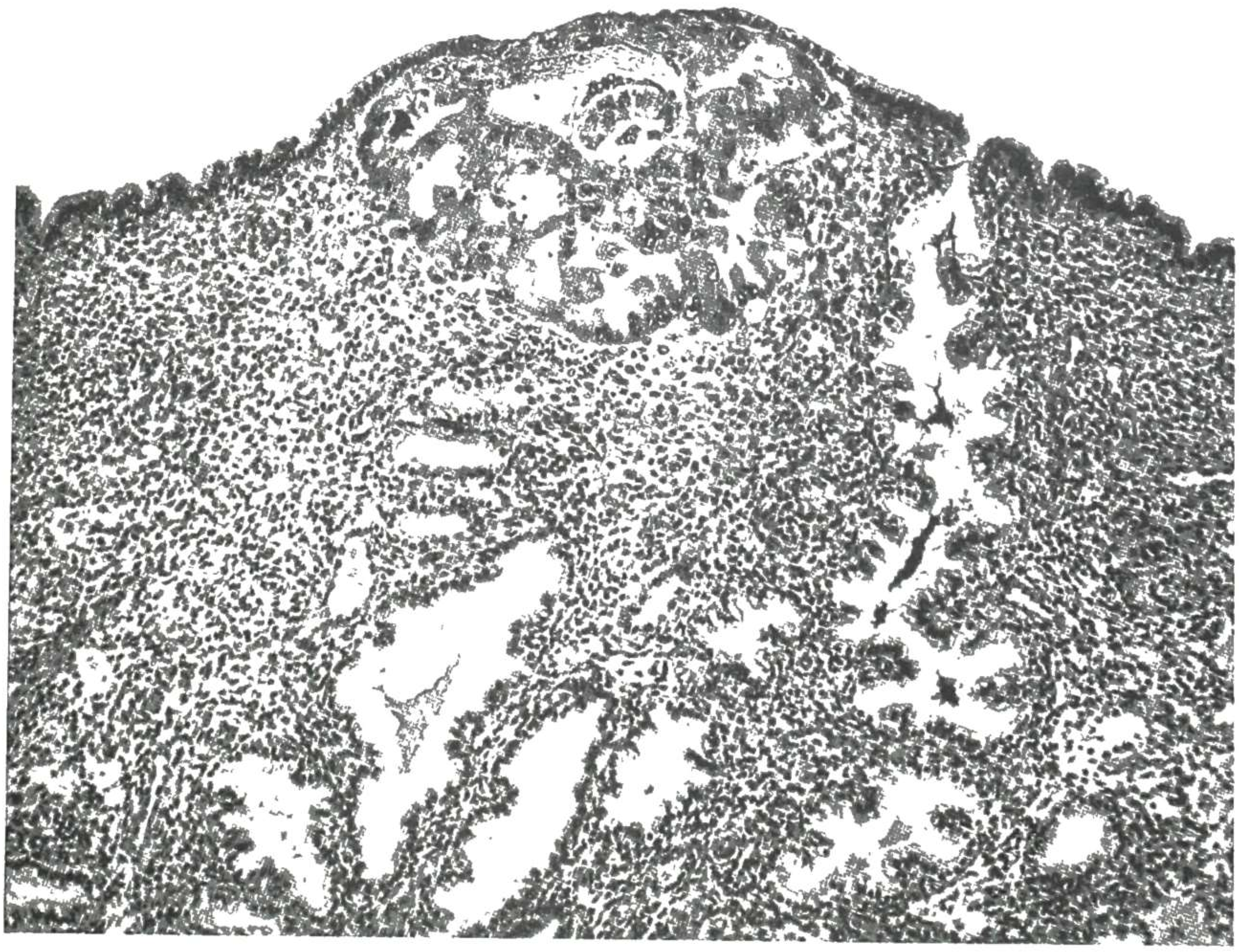


Fig. 28.—A 9.5-day human ovum implanted within the surface of 26-day secretory endometrium. The defective endometrial epithelium has been partially repaired and is in process of closing the defect created by the implanting ovum. The thick syncytiotrophoblastic plate now contains numerous coalescing lacunae for the reception of maternal blood. Some syncytiotrophoblast has formed on the abembryonic wall of the ovum, due to contact with endometrium. The embryo, a bilaminar germ disk with beginning amniotic cavity below, is composed of a thick plate of ectoderm and a thin plate of primitive entoderm. The cavity within the ovum (future chorionic cavity) contains artifactual blood. (Hematoxylin and eosin. ×100.) (Carnegie Institution of Washington, W1-8004.) (From Rock and Hertig: Am. J. Obst. & Gynec., December, 1942.)

day of the cycle. After this time there was a sharp drop in the level of the phospholipids. Coincident with this decrease of the phospholipids there was an increase in cholesterol esters, a finding indicative of degenerating tissue. Additional support for Brewer's findings is the fact that Venning and Brown and others found that the maximum secretion of sodium pregnanediol glucuronidate occurs between the nineteenth to twentieth days of the cycle with a definite fall in the level after the twenty-second day.

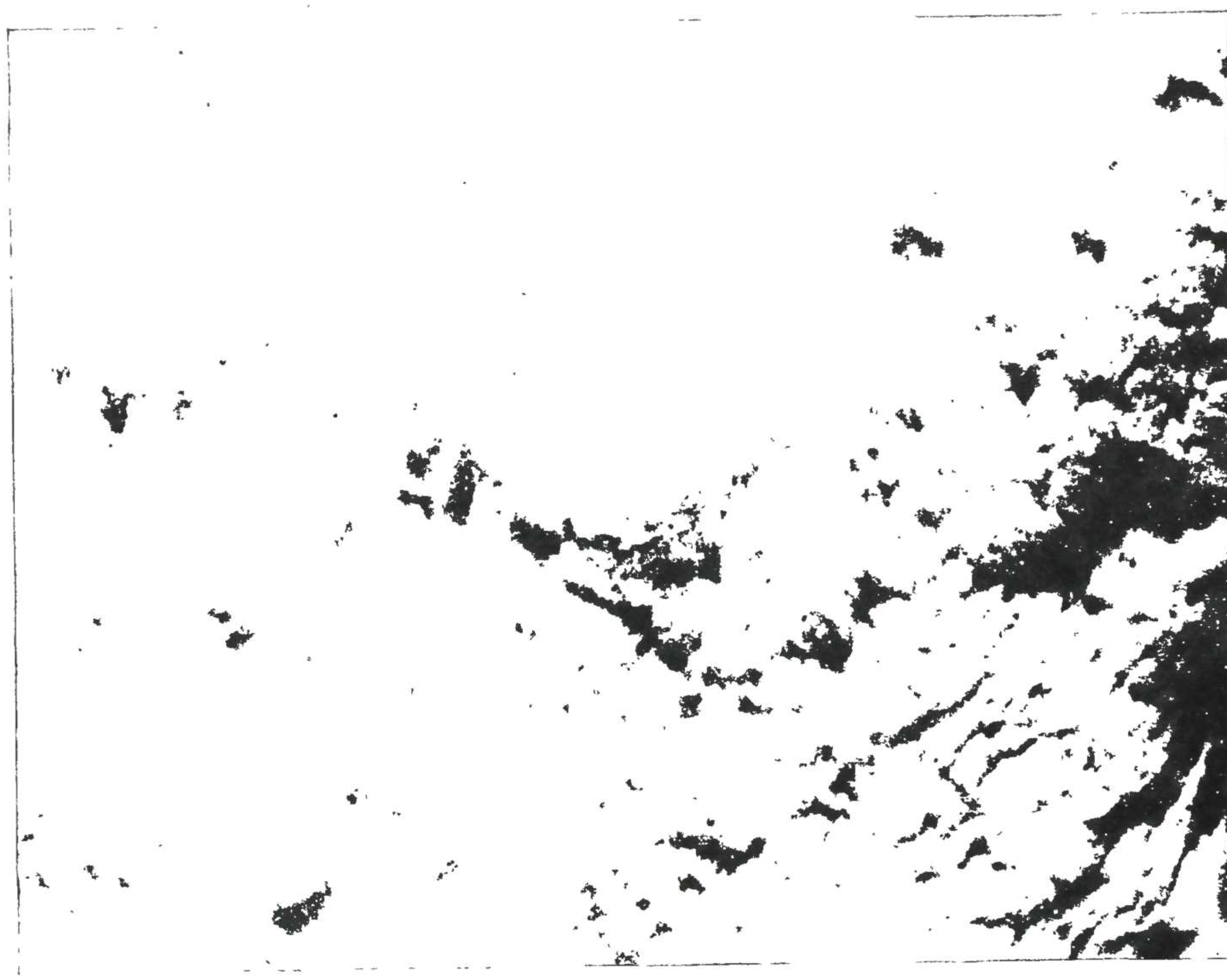


Fig. 29.—Magnified surface view of the endometrium. Notice the gland openings and the irregularity of the surface. The rounded mass in the center is a fertilized ovum, just sinking into the endometrium. (Carnegie Institution of Washington, Contrib. Embryol. 31: 65. Hertig and Rock.)

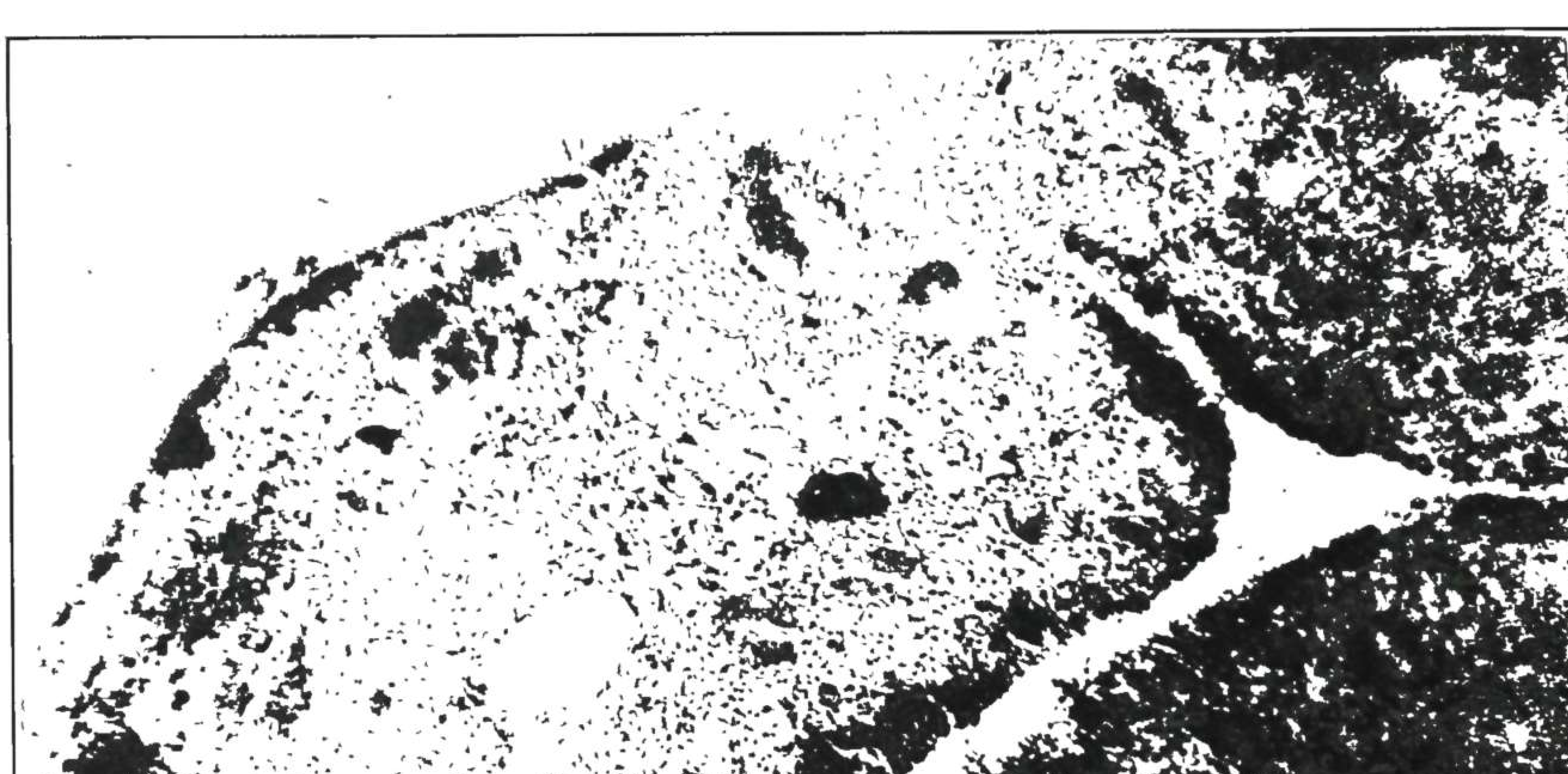


Fig. 30.—Recently ruptured follicle showing rupture point with plug already formed in the opening. This is now a corpus luteum of proliferation. Gyn. Lab.

Fig. 31.

Fig. 32.

Fig. 31.—Corpus luteum of proliferation showing the arrangement of the three layers: theca externa, theca interna, and granulosa cell layer. Gyn. Lab.

Fig. 32.—Higher power of Fig. 31, taken from an area at the extreme left end of the wall. Gyn. Lab.

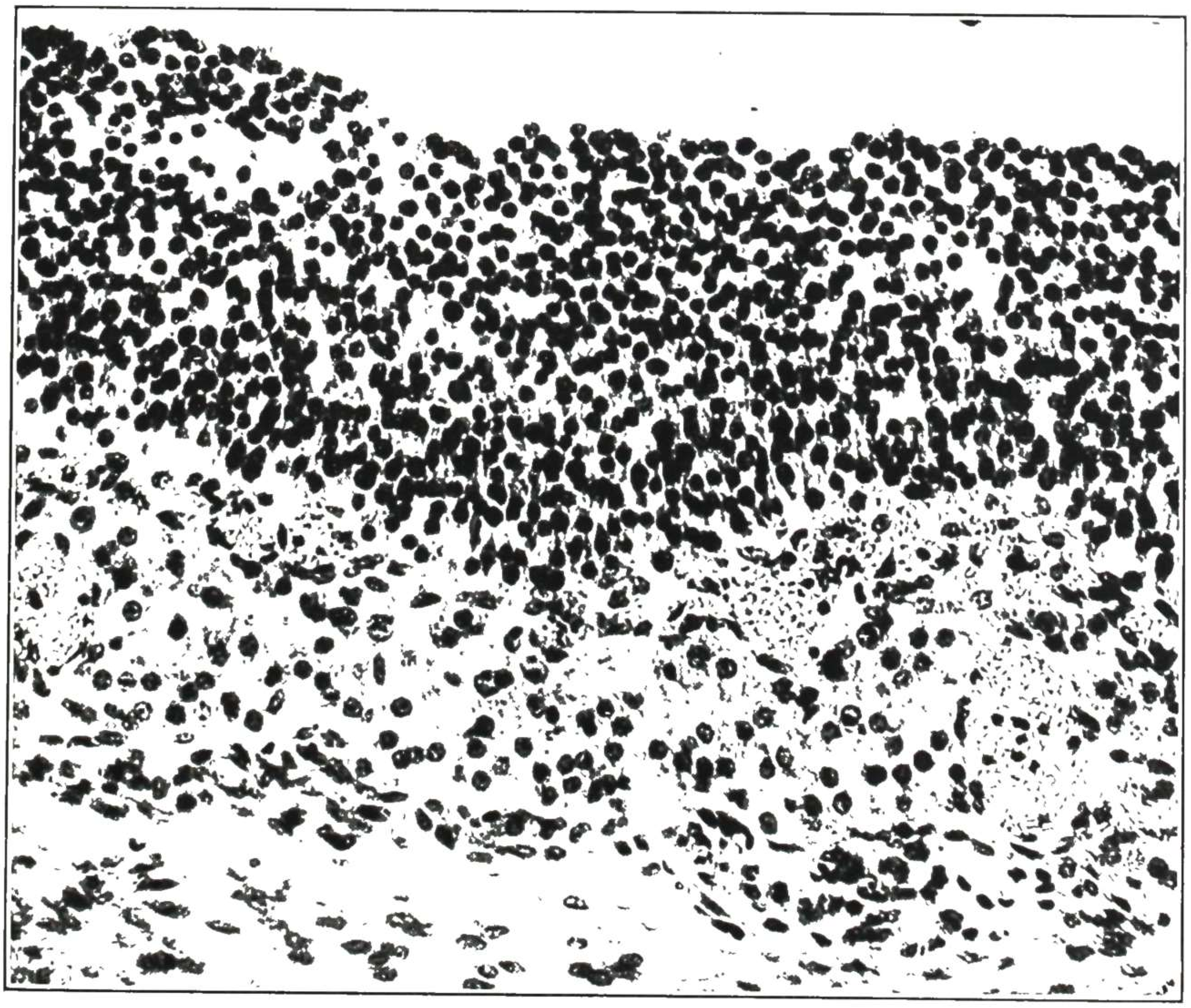


Fig. 33.—Photomicrograph, corpus luteum of proliferation. High power, showing the cellular characteristics of the three layers. Notice the large theca interna cells filled with light staining lipoid substance. The capillaries of the theca interna are widely dilated and filled with blood cells. The sharp line of demarcation between the theca interna and the granulosa cells is easily seen. *M.G.*, Membrana granulosa. *T.I.*, Theca interna. *T.E.*, Theca externa. Gyn. Lab.

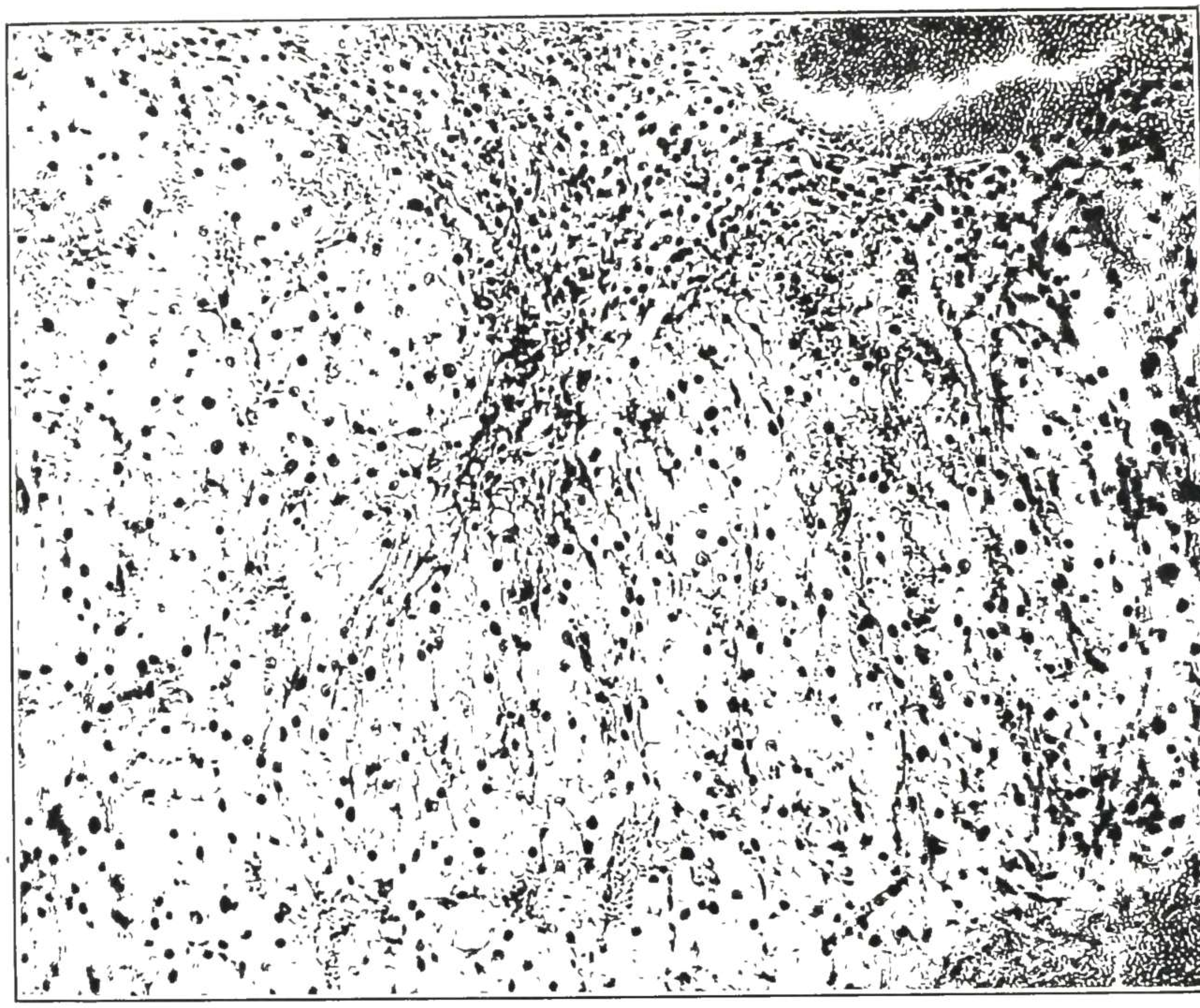


Fig. 34.—The theca interna cells have diminished in size due to a loss of their fat content. The capillaries of the theca interna are seen invading the granulosa layer, the cells of which have assumed a lutein character. In this luteinized layer the blood cells can be seen in capillaries and also lying free among the lutein cells. In the lower right corner of the figure a few endothelial cells can be seen invading the blood in the cavity. *T.I.*, Theca interna. *L.*, Lutein layer. *C.*, Cavity. Gyn. Lab.

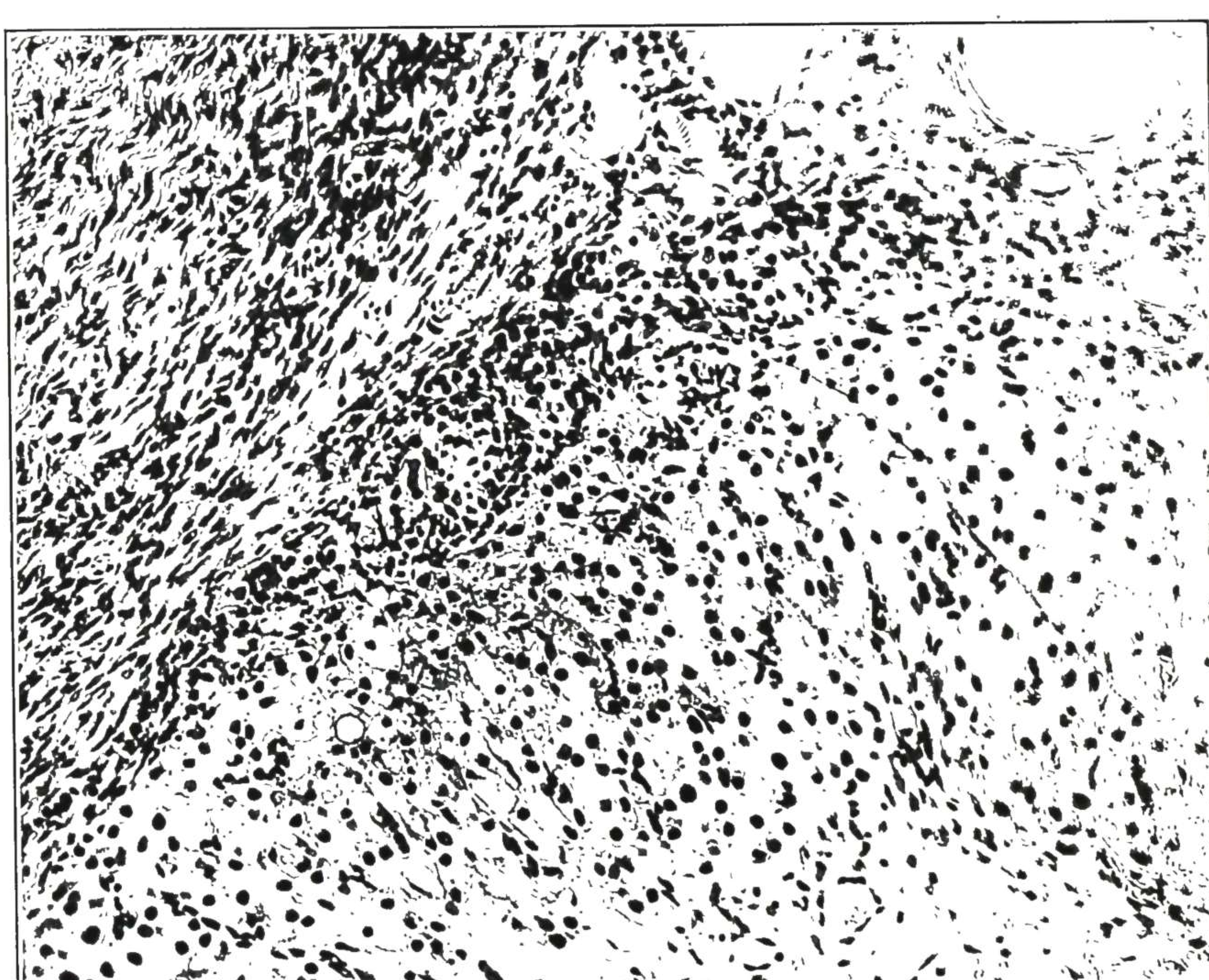
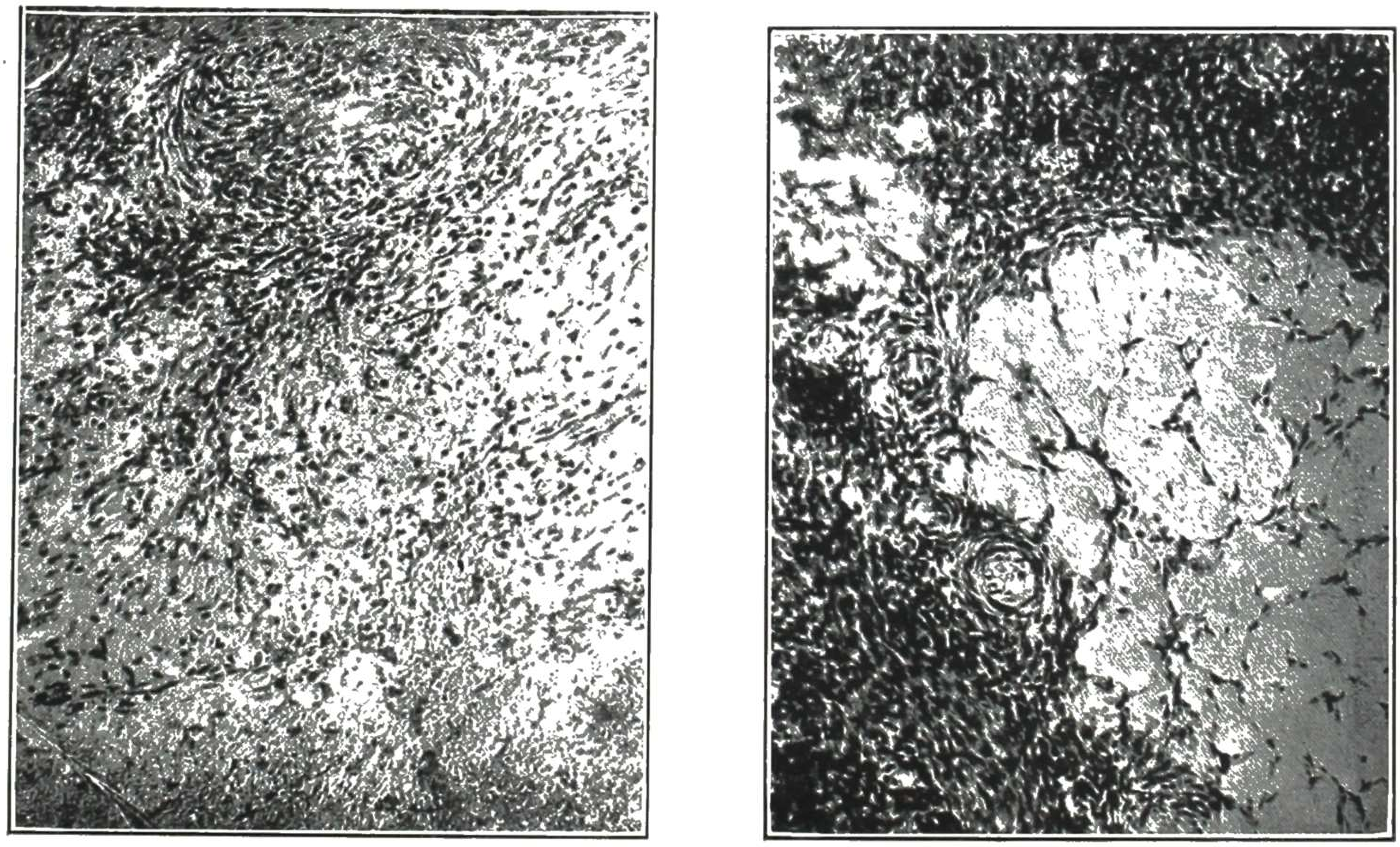


Fig. 35.—Corpus luteum of maturity, showing an area near the central cavity. A vascularization septum is shown at the left. The layer of connective tissue which separates the lutein layer from the cavity can also be seen.

3. The stage of Maturity (twenty-third to twenty-sixth day). When the dividing line of connective tissue between the lutein cells and the central cavity is complete, the stage of maturity has been reached. Fig. 35 shows the very large lutein cells of this stage. The lutein zone assumes a more marked undulating outline, owing to the rapid increase in these cells as compared to the surrounding tissue. The theca cells in the septa, at this stage, are large and take on an alveolar arrangement. In the gross section the corpus luteum in this stage is a conspicuous yellow body. The yellow substance in the corpus luteum is carotin and is identical with that found in carrots. On the surface of the ovary the corpus luteum appears as a dark red protuberance, which may be mistaken for a hemorrhagic cyst.



A. *B.*

Fig. 36.—*A*, Corpus luteum in the early stage of retrogression. Connective tissue fibrils can be seen invading the shrivelled lutein layer. Connective tissue fibers can also be seen invading the cavity at the lower border of the figure. The lutein cells still retain their nuclei. *B*, Corpus luteum in the late stage of retrogression. The lutein cells have lost their nuclei and the remaining hyaline-like mass is being invaded by connective tissue fibers. Gyn. Lab.

In view of the new facts brought out by Brewer's work, this stage should perhaps be designated as the stage of Early Regression; however, Robert Meyer in his discussion of Brewer's paper (1942) states: "The beginning of regression does not mean cessation of function of the whole corpus luteum, the outer layers of which may be well preserved for a much longer time."

4. The stage of Retrogression (twenty-sixth to the fourteenth day of the next cycle). This stage starts shortly before menstruation and is characterized by a shrivelling of the lutein layer as a result of a development of connective tissue fibrils between the lutein cells. The process of organization of the contents of the lumen proceeds very rapidly. The theca interna becomes less distinct and disappears. As the process gradually advances, the stroma outside and the organized central core encroach on the shrinking wall of lutein cells, which show marked hyaline change. Little by little the lutein

cells disintegrate, until finally there remains only the shrunken hyalinized outline of the wavy lutein layer, surrounding a central core of well-formed connective tissue. The structure is then white and hence is designated the "corpus albicans." It is called also the corpus fibrosum. Stages of this process are shown in Fig. 36, A and B. After many follicles have ruptured and passed through the various stages, the surface of the ovary presents many depressed scars, giving an irregular rough appearance.

Corner in an article on "The Fate of Corpora Lutea and the Nature of Corpora Aberrantia in the Rhesus Monkey" describes the two types of regression. With the standard type gradual shrinkage occurs, the cells are contracted and heavily laden with small lipid granules and acquire yellowish pigmentation. The theca externa, which is sharply defined in an active corpus luteum, gradually disappears and the outline of the corpus luteum itself is indistinct, though there is still a narrow cone of old corpus luteum cells extending to the surface of the ovary. Accessory corpora lutea, formed simultaneously from unruptured follicles, contain undischarged ova and they follow a course similar to the corpus luteum.

An alternative mode of regression results in a corpus aberrans. Certain corpus lutea after the period of bloom come under some atypical influence, probably pituitary, and instead of degenerating in the usual fashion pass into prolonged existence resembling that of a corpus luteum of pregnancy. Epitheloid cells somewhat smaller than the corpus luteum cells persist well preserved but without lipid infiltration. They are characterized by folding on the wall and clumps of theca interna cells about the border and at the base of the folds. These structures persist a long time, and as they age they regress like ordinary corpora lutea, except that they lose their connection with the surface of the ovary. There is usually a superficial crater or pit with connective tissue extending to the center of the corpus aberrans.

ENDOCRINE RELATIONS CONCERNED IN THE OVARIAN CYCLE

WILLARD ALLEN, M.D.

With the onset of puberty, a cycle of changes is initiated involving the anterior lobe of the pituitary, the ovary, and the adrenals. Just why this awakening of the ovaries occurs at the usual age is still obscure, but the cause must lie in the excretion of increased amounts of gonadotrophic hormones. In rare cases the anterior lobe seems to function in an adult manner during childhood, and when it does the ovary matures and precocious puberty results. Sexual maturity, however, is not achieved abruptly regardless of the age at which it begins. A considerable period of time, at least three or four years, is required for the reproductive organs to become mature. There can be no doubt regarding the significance of the internal secretion of the ovary in this process of growth and maturation which occurs in the uterus, fallopian tubes, vagina, external genitalia, and breasts. There may be some questions regarding the relationship of gonadal function and the appearance of the pubic and axillary hair, since there are women who never seem to have ovarian activity but who do have pubic and axillary hair. In any case, the hormonal alterations which are involved with puberty are intricate, but in the normal person the irregular and uncertain endocrine activity of the ovaries soon becomes stable and the reproductive organs settle down to the normal cycle pattern of adult life.

The first investigation pertaining to the endocrine function of the sex glands was made in 1849 by Berthold.[1] He found that transplantation of the testes of cockerels to another site prevented the development of capons. In 1900 both Knauer[2] and Halban[3] observed that transplantation of the ovaries in rabbits and guinea pigs prevented the atrophy of the reproductive organs which normally follows simple castration. A few years later, Born began to inquire more deeply into the further ramifications of endocrine activity of the ovary. He had observed that the corpus luteum seemed to reach maximum development during pregnancy. So he evolved the idea that perhaps the corpus luteum produced an internal secretion which helped to maintain pregnancy. This hypothesis of his was correct and, as will be seen later, his student Ludwig Fraenkel[4] in 1903 did the experiments which provided the key to the discovery of the hormone of the corpus luteum. These classical experiments of Halban, Knauer, and Fraenkel at the turn of the century, really served as the starting points of as brilliant a series of investigations as any in entire medical history. In the short span of fifty years the endocrine glands have changed from anatomical and cytological curiosities to miniature factories producing hormones which regulate much of our biochemical economy. The chemical compounds are now well known and the interrelations between the various endocrine glands are fairly well understood.

The first attempts to isolate the active principles of the gonads were undoubtedly made soon after the observations on transplantation of the gonads. No real progress was made, however, until 1912 when Iscovesco[5] discovered that organic solvents such as alcohol or ether would extract an active principle from ovaries and human placentae, and this extract produced hypertrophy of the uterus. His important observation was promptly followed by similar studies by Adler,[6] Fellner,[7] Seitz,[8] and Hermann,[9] and in this country in 1915 by Frank and Rosenbloom.[10] This pioneering work proved beyond doubt that the ovaries and placenta were endocrine glands. It is of passing interest also that the estrogenic hormone, the corpus luteum hormone, and the placental hormone (chorionic gonadotrophin) were all discovered between 1912 and 1914, although the discoverers did not fully appreciate the biological properties of the compounds which they were obtaining. The alcoholic ovarian and placental extracts undoubtedly produced uterine growth and hence contained estrogen; the alcoholic extracts of pig ovaries (Hermann), as shown in an illustration of the effect on the rabbit's uterus, most certainly contained progesterone; and an aqueous extract of human placenta (Adler) must have contained chorionic gonadotrophin since the extract produced growth of the ovaries with hemorrhagic cysts and progestational changes in the endometrium of immature rabbits. These different responses, which seem so easy of interpretation now, were not correctly evaluated by their discoverers because they were only interested in isolating a substance which produced growth of the uterus. Their work was not at fault, the biological test was not sufficiently accurate.

The first real step forward in the isolation of the estrogenic hormone was made in 1923 when Edgar Allen and Doisy[11] discovered that extracts of follicular fluid produced cystologic changes in the vaginal epithelium of the castrated mouse. This produced a rapid and inexpensive method of bioassay. Using this test the hormone was soon rediscovered in the ovaries of animals and in human placentae. Attempts to isolate the active principle from these sources were abruptly terminated by the discovery of Aschheim and Zondek[12] in 1928 that large amounts of the hormone were present in the urine of pregnant women. The active workers in the field immediately directed their efforts to this new source. The finding of the hormone in the urine proved to be a great discovery since in only two or three years the isolation of a pure crystalline compound was announced almost simultaneously by Doisy, Veler, and Thayer[13] and by Butenandt[14] (1929), and a little later by D'Amour and Gustavson[15] and Dingemanse, DeJongh, Kober, and Laqueur.[16] Soon other estrogenic compounds were isolated from various sources. Estriol was isolated in 1930 by Marrian[17] from human urine, and by Browne[18] in 1932 from human placenta, and in 1933 Girard[19] obtained equilin, hippulin, and equilenin from the urine of pregnant mares. However, it was not until 1935 that the active principle of follicular fluid, the source originally used, was isolated by MacCorquodale, Thayer, and Doisy.[20] The active principle proved to be estradiol, the most active of all of the natural estrogens.

The more strictly chemical studies which were made between 1925 and 1935 have been followed by a wealth of study of the biological effects of the estrogens. Much of the worth-while study has been directed toward unraveling some of the metabolic effects of estrogens, toward clinical uses of the hormone, and toward the search for more active, cheaper, and more readily administered compounds with estrogenic activity.

In the search for the estrogenic hormone, the observation originally made by Ludwig Fraenkel, namely, that the ovaries were essential to the continuation of pregnancy, was overlooked. It was only after a more detailed study of the estrogenic hormone had been made that it became obvious that this hormone did not have the biological properties necessary to maintain pregnancy in recently ovariectomized pregnant rabbits. However, the hormone presumably removed by castration during pregnancy should have the ability to maintain pregnancy after removal of the ovaries.

As a result of the review of the deficiencies of the biological properties of the estrogenic hormone, the second ovarian hormone, progesterone, was discovered. But the brief statement does not do justice to the event. This hormone, as we all now know, is produced by the corpus luteum. Long before the hormone was isolated, its supposed biological properties were well known, thanks to careful work showing the relationship between the corpus luteum and the changes which take place in the endometrium in the early days of pregnancy. This knowledge was all available in 1929 when the active search for the corpus luteum was begun, mostly because of the work done in the guinea pig by Leo Loeb[21] in 1907, in the rabbit by Bouin and Ancel[22] in 1910, in the domestic pig by Corner[23] in 1917, and to work in the rhesus monkey done by Corner[24] and by Hartman[25] in the twenties. It was George Corner who had sufficient vision to see that the hormone of the corpus luteum had not as yet been isolated, and it was he who knew enough of the cytology of the endometrium to devise the test animal which made possible the isolation of progesterone in the short span of about five years.

The test originally used by Corner and Willard Allen[26] for the assay of extracts of the corpus luteum was simple but tedious. Sexually mature rabbits were castrated eighteen hours after mating and then given daily injections for five days. On the sixth day the animals were sacrificed and the uteri examined for embryos and for progestational changes in the endometrium. When the extracts contained the active principle, the endometrium showed the characteristic alteration originally described by Bouin and Ancel[22] in 1910 and shown by them to occur only when the ovaries contained functioning corpora lutea. The active extracts also maintained pregnancy to term in animals castrated one day after mating,[27] thereby explaining why Fraenkel[4] had observed that castration of rabbits in early pregnancy always prevented continuation of the pregnancy. The extracts also produced progestational changes in the endometrium of monkeys[28] and in women.[29] Actually the test used was but an animal counterpart for what clinicians now use in producing a secretory endometrium in the human female. Actually, the changes in the rabbit endometrium induced by progesterone are quite similar to the changes in the human endometrium which were originally described by Hitschmann and Adler in 1907.[30]

During the development of the method for the isolation of progesterone it soon became obvious that the hormone differed chemically as well as biologically from the estrogens. The natural estrogens are without exceptions phenolic in nature. The active principle of the corpus luteum was soon found to be a chemically neutral compound. Procedures were worked out and in a few years[31] the isolation of the pure compound was announced virtually simultaneously in 1934 by Butenandt[32]; Slotta, Ruschig, and Fels[33]; Allen and Wintersteiner[34, 35]; and Hartmann and Wettstein.[36] The conversion of stigmasterol and pregnanediol to progesterone served to fully identify the compound.[37, 38]

There is still another hormone which historically has to be considered with the ovarian hormones even though it is now presumed to be a protein rather than a steroid. This hormone is called relaxin because it has the particular property of inducing relaxation of the pelvic ligaments of the guinea pig so that the innominate bones may be moved freely and independently of each other. In the guinea pig the young are born in a very mature state and are so large that delivery would be impossible were it not for the extraordinary separation of the pelvic bones which occurs during pregnancy. Thus far this hormone has found no place in clinical medicine although it seems probable that it may be responsible for the loosening of the pelvic ligaments and the separation of the symphysis pubis that is seen in some women near term.

During the course of the studies directed toward the isolation of the active principle of the corpus luteum various biological tests were used to determine the activity of the extracts. One such test was the induction of relaxation of the pelvic ligaments of the estrous guinea pig. Using this test Hisaw[39] in 1929 found that the blood of pregnant rabbits, pig's corpora lutea, and rabbit placentas contained a substance with this property. The extracts also contained the substance which produced progestational changes in the endometrium. It is not surprising, therefore, that for a time it was thought that relaxin and progesterone were the same.[40] Since relaxation of the symphysis can be achieved in several days by the injection of estradiol, there has been some doubt regarding the presence of a separate hormone. However, relaxin produces its effect in

FORMULAE OF THE STEROID HORMONES
AND SOME RELATED COMPOUNDS

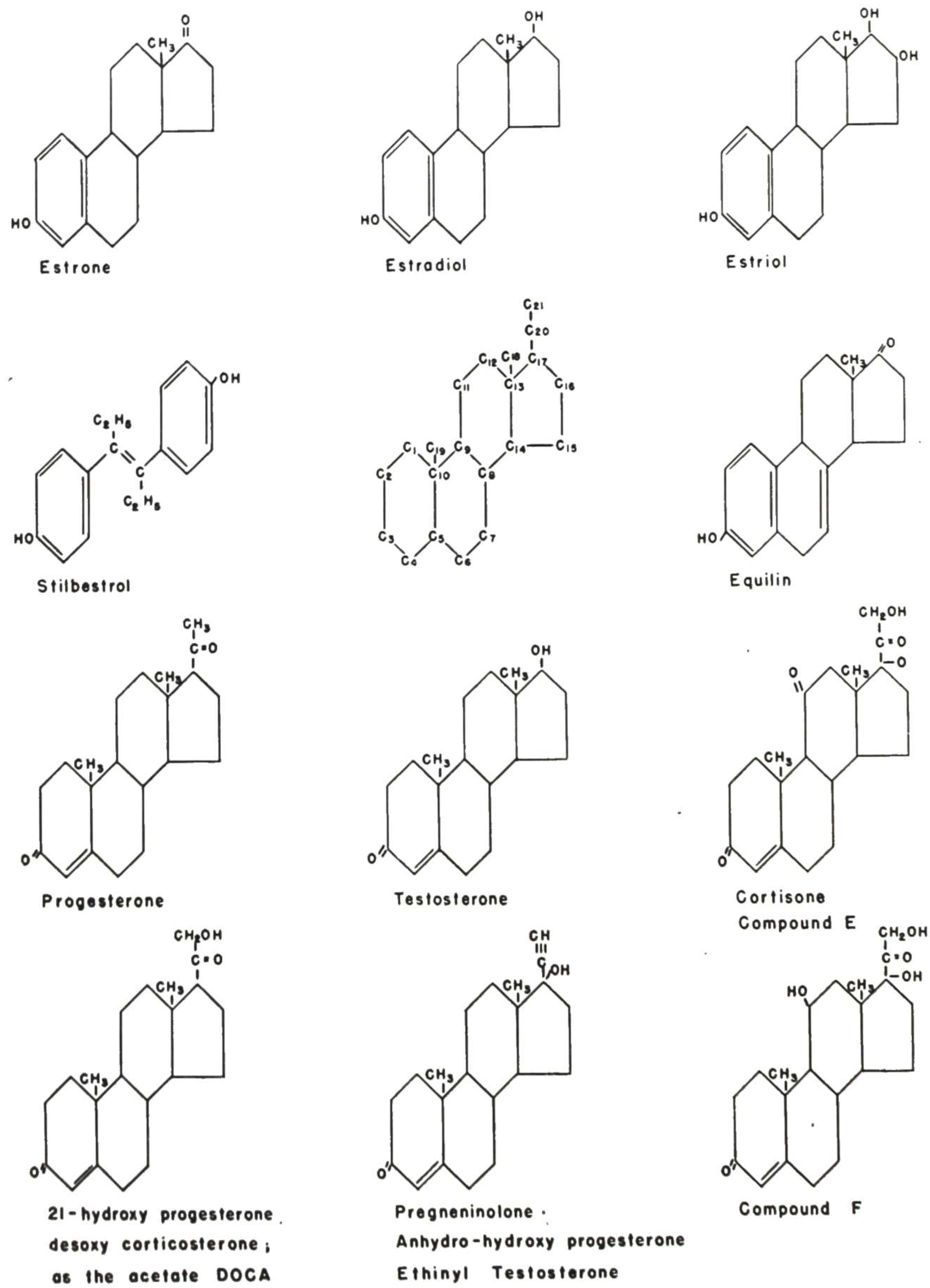


Fig. 37.—Structural formulae of the sex hormones and adrenocortical hormones showing the similarity in structure. The unlabeled formula is that of the steroid nucleus.

only a few hours. Because of this marked difference between the effects of relaxin and steroid hormones the subject has been restudied by Hisaw and his co-workers.[41] New methods have been developed which virtually eliminate any possibility of the preparations containing either estrogen or progesterone. These preparations are highly active and produce prompt relaxation.

There are certain differences in the effects of the highly purified relaxin and the relaxation produced by estrogens and progesterone. The effect of relaxin is manifest in six hours whereas estradiol has to be given for ten days. Progesterone likewise produces relaxation in about three days but only in case estrogen has been given previously. It is supposed that estrogen and progesterone cause the production of relaxin within the body, possibly in the uterus, and that in the end the relaxation is still due to the presence of relaxin.[42] The subject is still very confusing but the presence of relaxin as a specific hormone related to pregnancy but entirely different from progesterone seems fully established.

This short historical account of one of the fascinating developments in modern biology serves to remind us that when the sex hormones are used in treating patients the physician should give homage to the group of great scientists who through a combination of wisdom, skill, and good fortune have made such treatment possible. No physician today can call himself an educated man in affairs medical without having a speaking acquaintance with the steroids.

The sex hormones are now reasonably well identified and their chemical formulae are known (Fig. 37). While it may seem pointless to record more than the structural formulae of the sex steroids, it is of more than passing interest that the male sex hormones and the adrenocortical hormones are very closely related to the female sex hormones. Only minor structural changes in the important parts of the molecule bring about startling changes in biological activity. The similarity between progesterone and testosterone is obvious. However, their biological properties are different yet strangely similar despite the fact that one is the product of the testes and the other, progesterone, is produced by the corpus luteum. In fact, testosterone will produce progestational changes in the endometrium virtually identical with those produced by progesterone, provided a much larger dose is given. Also progesterone is the hormone which induces sexual receptivity in estrogen-primed castrated guinea pigs, whereas testosterone markedly enhances sexual desire in women as well as in men. The similarity between progesterone and cortisone is seemingly even closer, and in certain animals progesterone may actually prevent death from adrenalectomy but only if large doses are given. Also progesterone has been isolated in pure form from adrenal glands. Then to make matters even more confusing, the urine of the bull contains large amounts of estrogen, even more than the urine of the pregnant cow. The practical application of these bizarre facts, however, is comparatively simple as long as the endocrine glands in a given sex are functioning normally.

The estrogens likewise appear to be closely related to the other sex and the adrenal steroids. However, more careful examination of their structure reveals that they are actually quite dissimilar. Testosterone, progesterone, and cortisone and their sister compounds are all neutral steroids. The compounds in this group which have high activity are all alpha-beta ketones, i.e., ring A contains a ketone grouping at C_3 and a double bond between C_4 and C_5. The variations in structure at the other end of the molecule (at C_{17} especially), and at C_{10} in the case of the adrenal steroids, determine what the biological properties will be. The estrogens, on the other hand, are all phenolic in nature. Even the synthetic estrogens which may appear to differ greatly from the natural estrogens are phenols of one type or another. These compounds are weak organic acids. Actually the estrogens may be considered unique in the steroid field since they are quite dissimilar from the other known steroids. Their biological properties are also unique in that they do not produce any of the biological properties which reside in the neutral steroids and conversely none of the neutral steroids produce estrogenic effects.

With this introduction it is now possible to unravel the female reproductive cycle and explain those aspects which are understood. The cycle in the human female is divided into two parts. The first part is called the follicular phase. If the cycle is four weeks in duration, this phase lasts two weeks and is primarily under the influence of the estrogenic hormone. At the mid-point of the cycle, ovulation occurs as a result of stimulation of the ovary by anterior lobe hormones. The follicle then ruptures and the egg is discharged. Certain changes take place in cells lining the graafian follicle, and the corpus luteum is formed, which produces progesterone.

If the egg is not fertilized the corpus luteum regresses in about two weeks, the endometrium is shed, and a new cycle begins. If the egg happens to be fertilized the corpus luteum continues to produce progesterone for at least two or three months in the woman; but, unlike the common laboratory animals in which the ovaries are necessary throughout pregnancy, the ovary then becomes unimportant in so far as the continuation of pregnancy is concerned. In the woman, Nature has improved upon the situation found in many animals. She has provided an extragonadal source for the sex hormones in the placenta. Pregnancy in the woman becomes a self-propagating mechanism, hormonally speaking, after the second or third month. In fact, the urine of pregnant women who have been castrated after pregnancy has become well established continues to contain normal amounts of estrogen and pregnanediol (Jones and Weil[44]; Young[45]; and Willard Allen[46]).

The cycle just outlined is ovulatory in nature, and during it the endometrium is put through the normal sequence from the resting to the progestational type by stimulation first with estrogen and in the second half by estrogen and progesterone acting simultaneously. Then, pregnancy having failed to occur, the corpus luteum stops functioning and the menstrual period occurs because of progesterone deficiency.

All cycles, however, are not ovulatory in nature. Cyclic bleeding, similar in every overt way with that produced by involution of the corpus luteum, can occur in the complete absence of a corpus luteum. The bleeding which occurs in this type of cycle occurs from an interval type of endometrium. It is an incomplete cycle, one in which progesterone has not been acting.

The anovulatory cycle is hormonally quite different from the ovulatory cycle and much needless bickering has been caused thereby (Fig. 38). Some insist that the bleeding of the anovulatory cycle is not menstruation. If not, what is it? The facts are simple. Cyclic bleeding can be produced with ease in ovariectomized women simply by the administration of estrogen for three weeks. Estrogen withdrawal bleeding occurs one week later from an endometrium histologically identical with that found in the anovulatory cycle (Fig. 39). Similarly a "synthetic ovulatory cycle" can be produced by giving estrogen and progesterone, bleeding being produced by withdrawal of progesterone. The vascular changes which are related to the two types of bleeding are identical. Hence, there seems no sound reason for not considering both types of bleeding as menstrual bleeding.

The actual alterations which take place in the uterus during the cycle are best explained by describing the effects of the female sex hormones on the endometrium. The cyclic changes include growth, secretion and retrogression. This succession of events in the endometrium is characteristic of all mammals from the lowest to the highest but only in higher primates, i.e., old-world monkeys, anthropoid apes and man, is the retrogression of the endometrium accompanied by frank bleeding. Lower forms do have cycles which are just as characteristic as the menstrual cycle but there is one very important difference. In man, menstrual bleeding occurs at the end of the cycle when, and because of failure to conceive, much of the endometrium is cast off in the preparation for another cycle. In the nonmenstruating mammals, the external manifestation of the cycle is estrus. This occurs just prior to and at the time of ovulation and is the time when the female will accept the male. There is no definite period in man when the female may be said to be in heat. However, it is obvious that estrus in the lower forms is equivalent to the short period approximately midway between the menstrual periods when ovulation occurs. But despite these great differences between the lower forms and man the same hormones are operating in much the same manner and for the same reason.

The changes in the endometrium which occur during the ovulatory cycle can be reproduced in the ovariectomized or postmenopausal woman by the use of estrogen and progesterone in the following manner: First, the endometrium has to be under the influence of estrogen. In the recently castrated individual, 1.0 mg. estradiol benzoate is given two or three times weekly. Then, after about two weeks, the same dose of estrogen being continued, 10 mg. of progesterone are given daily for about 12 days. Under these stimuli the endometrium goes through the normal course of growth and secretion and reaches full progestational development. At the end of 12 days treatment with progesterone that hormone is discontinued and within 36 to 48 hours a typical menstrual period begins (Fig. 40). This simple experiment seemingly provides the final proof regarding the hormonal control of the menstrual cycle. The natural conclusion from this experiment is a simple one; menstrual bleeding occurs because of withdrawal of progesterone. This interpretation is, of course, in complete agreement with the ideas put forward many years ago that menstruation occurs because of the involution of the corpus luteum and loss of the corpus luteum hormone.

There are some additional aspects of experimentally induced progesterone withdrawal bleeding which have been discovered through intensive study of the effects of this hormone in women.[47] What, for example, is the effect of progesterone when it is administered for less than optimum time for the production of full progestational changes? In the study of this simple question some very unexpected results have been obtained. As would be expected the endometrium

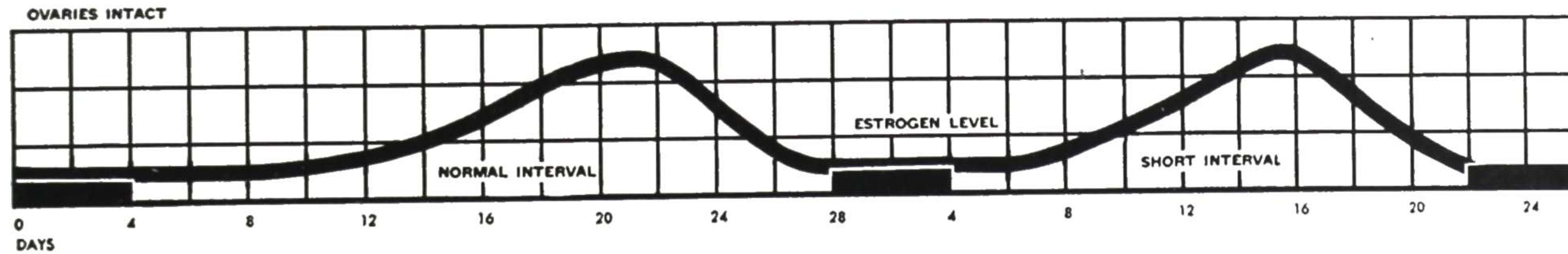


Fig. 38.—Curve of estrogen level in anovulatory bleeding with ovaries intact.

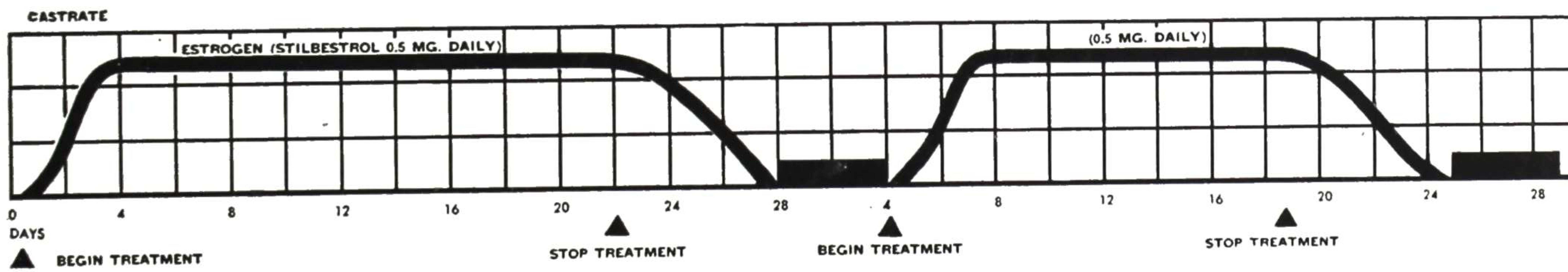


Fig. 39.—Induction of bleeding by estrogen withdrawal in a castrate.

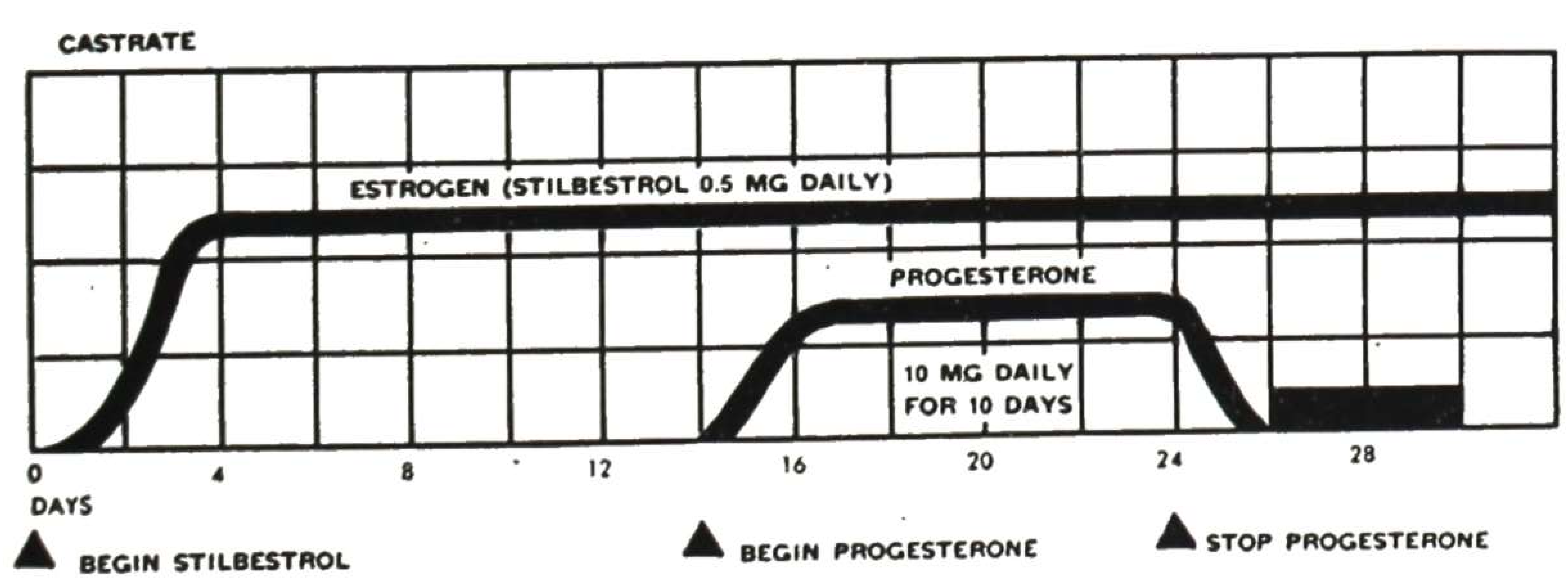


Fig. 40.

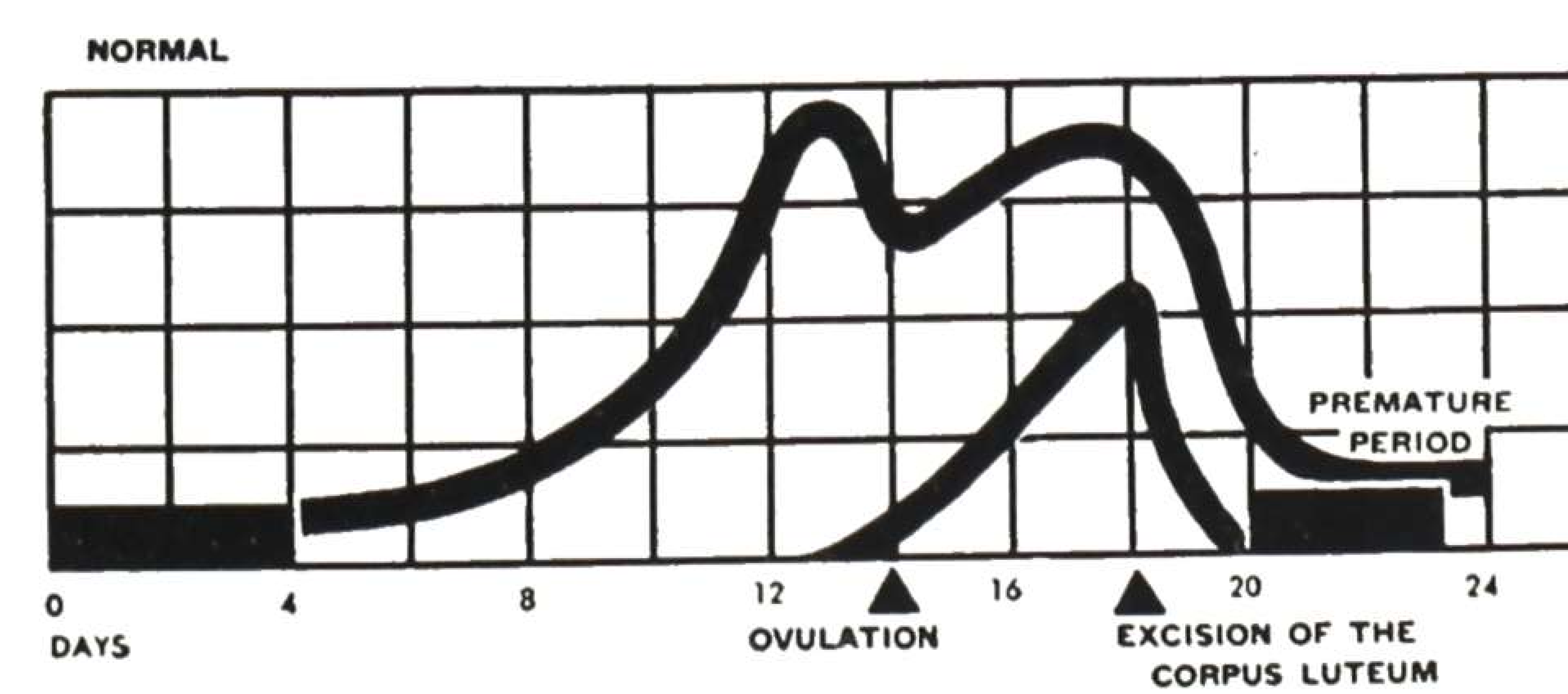


Fig. 41.

Fig. 40.—Induction of bleeding by progesterone withdrawal in castrate.
Fig. 41.—Induction of bleeding by excision of the corpus luteum with resulting progesterone withdrawal.
(Figs. 38-41 courtesy Seminar, Sharp & Dohme, Inc.)

does not become late progestational in type when progesterone is given for only five or six days. The cytological picture is identical, however, with that observed five or six days after ovulation. It takes time, therefore, for the endometrium to change from the interval to the late progestational type. Again, when progesterone is discontinued after a few days' treatment, withdrawal bleeding takes place, but in this instance the endometrium is not in the late progestational phase. With this observation in hand, the question arises as to what will happen if only a single injection of progesterone is given when the endometrium is already well stimulated by estrogen. This experiment likewise results in withdrawal bleeding but from an endometrium which shows virtually no demonstrable effect from the progesterone. This series of experiments then brings forth one very important fact. An estrogen-stimulated endometrium must inevitably break down after it has been subjected to progesterone regardless of whether the progesterone has been acting for two weeks, one week, or one day. The histological picture at the time of breakdown depends on the duration of the action of progesterone but bleeding is seemingly independent of the duration of treatment. In a sense, this result is not too unexpected because it has been known for many years that excision of a corpus luteum, even one only a few days old, is followed in a few days by a menstrual period (Fig. 41).

One additional question of even greater importance has been answered by study of the effects of estrogen and progesterone on the endometrium. The question is, why does the corpus luteum involute at the end of two weeks assuming pregnancy has not taken place? Since the discovery of human chorionic gonadotrophin, it has been assumed that this hormone, which is produced by the placenta, prevents retrogression of the corpus luteum. If this be the case, administration of this hormone to normally ovulating women should prevent regression of the corpus luteum and hence should delay the expectant onset of the menses. This has now been shown to be the case.[48] The supposed explanation for the delay of the menses is that the chorionic gonadotrophin causes the corpus luteum to continue to secrete progesterone and the progesterone prevents the endometrium from breaking down and bleeding. However, that seemingly is not the correct interpretation of the result, because the administration of progesterone beginning a few days before the expected onset of the flow does not prevent menstruation. In other words, menstruation will occur, presumably as a result of involution of the corpus luteum, even though progesterone is given to replace the progesterone which the corpus luteum can no longer produce. The next simple experiment would be that of giving estrogen. However, estrogen likewise does not prevent the appearance of bleeding at the expected time either. The paradoxical facts are simple; chorionic gonadotrophin prolongs the functional life of the corpus luteum and prevents menstruation, yet neither estrogen nor progesterone will prevent bleeding associated with the involution of the corpus luteum. The explanation of these bizarre facts, however, has been achieved by a study of the administration of both estrogen and progesterone to normally ovulating women. When 25 mg. of progesterone in an aqueous suspension and 1.0 mg. of stilbestrol are given daily beginning a few days before the expected onset of the flow, the menstrual period may be delayed for as long as three weeks even though the woman's own corpus luteum undoubtedly involutes and stops producing progesterone.[49] This experiment, of course, suggests that chorionic gonadotrophin causes the ovary to produce both estrogen and progesterone in amounts which prevent breakdown of the endometrium and which also actually produce the glandular pattern and decidual changes that are characteristic of early pregnancy.

The facts pertaining to the ovulatory cycle then are now reasonably clear. In the first half of the cycle, the ovary produces estrogen. This brings the endometrium into a state which enables it to respond to progesterone. Then progesterone is added to the hormonal picture. The two hormones acting together produce progestational changes which make growth and implantation possible. The young trophoblast produces chorionic gonadotrophin, which in turn causes the ovary to continue to produce both estrogen and progesterone, thus maintaining the endometrium. In the absence of fertilization of the ovum there is no trophoblast, hence no chorionic gonadotrophin, and consequently the corpus luteum becomes nonfunctional after a life span of twelve to fourteen days and menstruation occurs. If, by chance, the corpus luteum fails to function for the usual twelve to fourteen days a menstrual period will occur prematurely and the endometrium will be incompletely developed.

There still remain two aspects of the hormonal control of the cycle which are not understood (excluding from consideration for the moment the role of the pituitary gonadotrophins). The reason for the involution of the corpus luteum is still an enigma. Why does it die in two weeks when, with proper stimulation, it is capable of functioning much longer? It has been suggested that it brings about its own execution. In order for progesterone to have any effect on the end organs, the end organs must have been exposed to estrogen, and for progesterone to maintain an endometrium longer than it does in the infertile cycle, estrogen has to act concurrently with progesterone. Likewise, in certain experiments in rabbits where one ovary is removed and the other partially removed, the ovarian fragment will not function properly, i.e., a functional corpus is not possible unless estrogen be given to the animal. It would seem, therefore, that a certain base-level of estrogen is needed before the corpus luteum will continue to produce progesterone. Also in the rabbit, the administration of estrogen will prevent involution of the corpus luteum. It may be then that the production of progesterone, which by itself is anti-estrogenic and which also leads to involution of the more mature graafian follicles, produces a state of estrogen deficiency which in about two weeks' time causes the pituitary to secrete too little luteotrophin to maintain the corpus. The implication of this theory is simple. May not chorionic gonadotrophin cause the ovary to produce estrogen and this in turn cause the corpus to continue to produce progesterone?

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STRUCTURES IN THE BROAD LIGAMENT

The parovarium is the remains of a fetal organ, the wolffian or mesonephric body. Many of the generative organs are derived from this fetal structure. It consists of a triangular group of tubules (mesonephric tubules) situated in the portion of the broad ligament lying between the ovary and the fallopian tube (oviduct). The apex of the triangle lies near the hilum of the ovary and from this area the tubules extend in a fan-shaped formation upward, entering a longitudinal tube called the wolffian or mesonephric duct. This duct terminates in a small cul-de-sac near the fimbriated end of the tube (Figs. 42 and 43). Very often this little cul-de-sac becomes distended with fluid and forms a miniature cyst on the surface of the broad ligament. But the little cyst thus formed is apparently distinct from another miniature cyst usually found in the same vicinity and called the "hydatid of Morgagni." The hydatid of Morgagni is the dilated end of another fetal structure—the duct of Müller, which forms the fallopian tube.

Another smaller group of these tubules, remnants from the lower end of the mesonephric body, lie mesial to the ovarian vessels in the mesovarium. These tubules which lie near the uterus are also mesonephric tubules and this group is called the "paroophoron" (Figs. 42 and 43). The mesonephric struc-

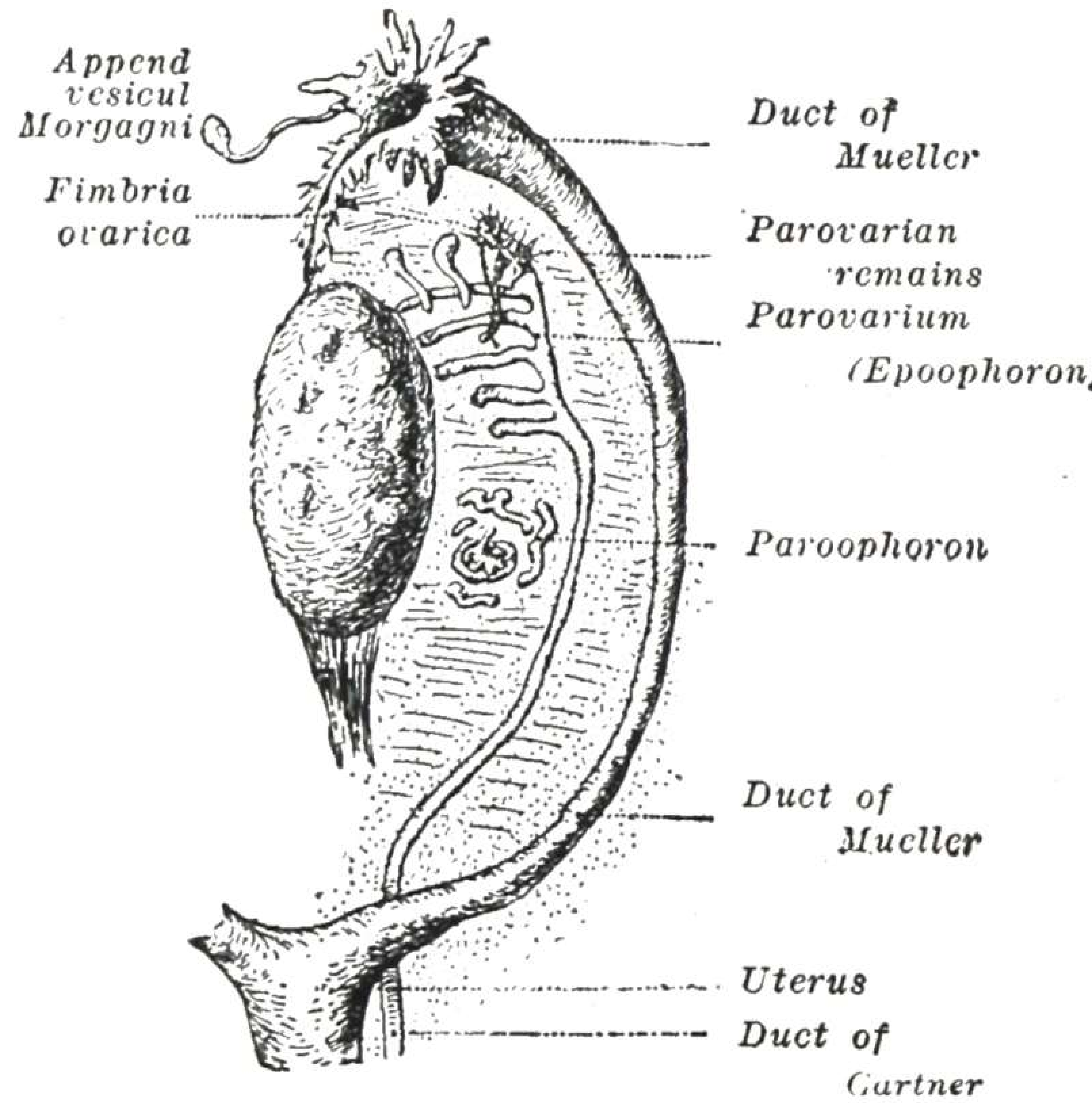


Fig. 42.—Embryonic genital organs, showing the parovarium and paroophoron, and their relation to the tube and ovary and duct of Gärtner. (Abel, after Kollman: Gynecological Pathology, William Wood & Co.) (See new terminology under Fig. 43.)

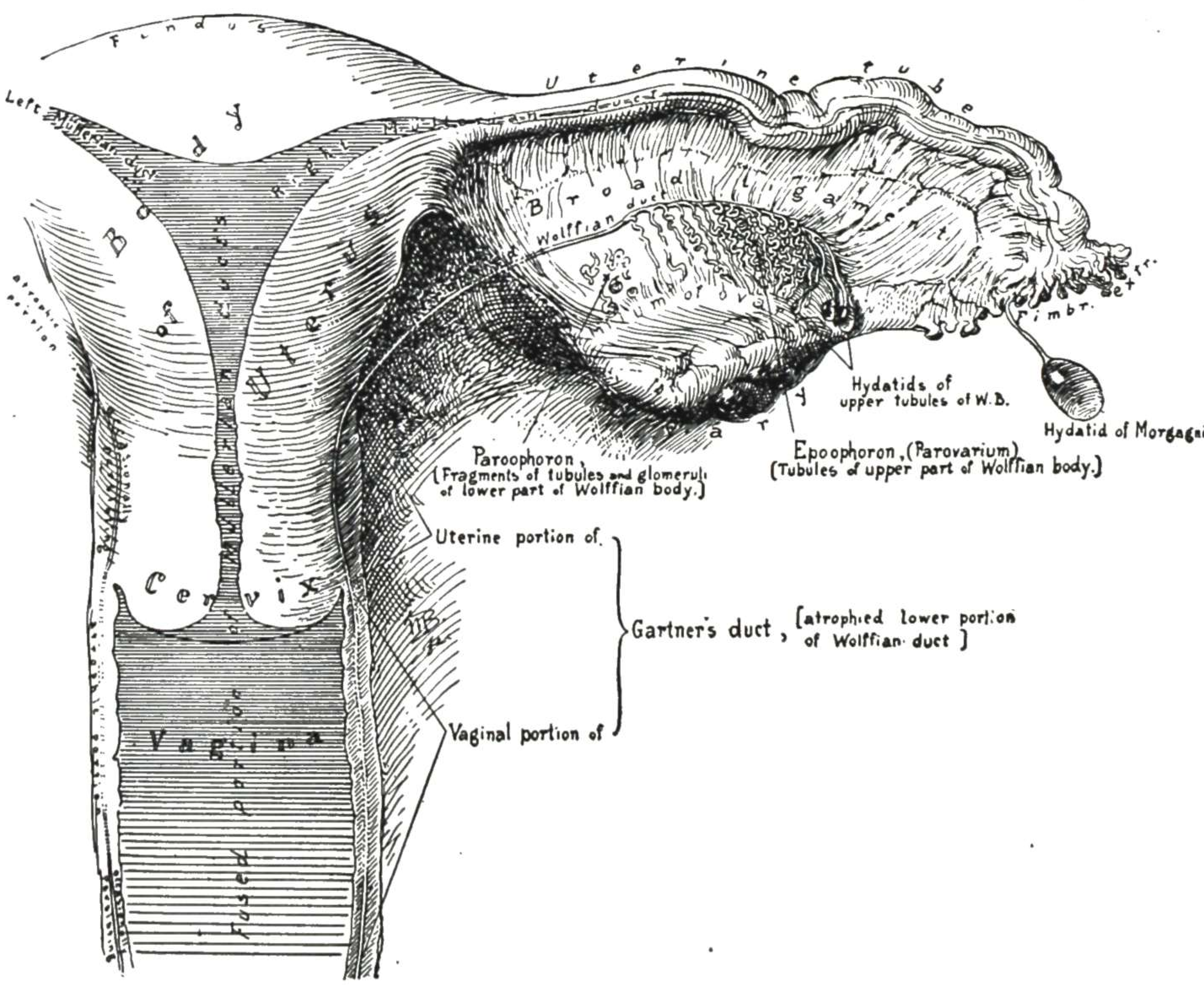


Fig. 43.—Adult genital organs showing parovarium, Gärtner's duct and various other structures. (Kelly, after Cullen: Operative Gynecology, D. Appleton-Century Co.) The new terminology proposed by Gardner, Greene, and Peckham is shown below.

Proposed Terminology	*Commonly Used Terminology*
Mesonephric body	Wolffian body, organ of Rosenmüller, epoophoron, parovarium, Kobelt's tubules, parovarial tubules
Mesonephric duct	Wolffian duct, longitudinal tubule of epoophoron
Mesonephric tubules	Wolffian tubules, Kobelt's tubules, epoophoral tubules, transverse tubules of epoophoron
Paramesonephric duct	Müllerian duct
Oviduct Uterine tube	Fallopian tube
Accessory oviducts	Accessory fallopian tubes

tures are embedded in the delicate connective tissue between the layers of the broad ligament and have no connections with any of the surrounding organs.

The müllerian duct, the forerunner of the tubes and the uterus, is derived from the paramesonephros.

Gardner, Greene, and Peckham in a recent article reviewed the question as to the origin of the various normal and cystic structures found in the broad ligament. They found that a differential point in determining the derivation of broad ligament cysts is the fact that the epithelium of those of paramesonephric origin shows the same cyclic variations in response to the sex hormones as does the tubal epithelium. Cysts of mesonephric origin showed no such cyclic epithelial changes. These workers proposed a new terminology based on the embryological derivation, and they felt that this method of designating the various structures would be simpler than using various proper names such as Fallopian, Müllerian, Wolffian, and others. Their table of equivalents is shown in the legend of Fig. 43, and in addition they list accessory oviducts. They feel that the hydatids of Morgagni are hydropic accessory oviducts.

UTERUS

The uterus is the organ which receives the fertilized ovum, provides for its embedding and nourishment, sustains and protects it through the various stages of growth, and expels the developed child at term. While secondary to the ovaries in the general scheme of reproduction, it is in its own right a remarkable organ. It is unique in its capacity for enormous enlargement to meet the needs of the growing fetus. Hardly less remarkable is its prompt return to nearly its former small size. Remarkable also is its strange lining mucosa, the endometrium, which disintegrates and is renewed at approximately monthly intervals over a period of thirty years.

Almost as striking as the phenomena themselves is the fact that though recurring the world over, for thousands of years, it is only within the last few decades that there has been any rational explanation of how the controlling factors worked, or even what those factors were. The wonderful revelations in this respect serve as indications of the new worlds of knowledge opened by the splendid clinical and laboratory investigations of modern medicine.

ANATOMY

The surroundings and general relations of the uterus are shown in Figs. 2 to 6. It is **situated** about the center of the pelvic cavity, between the bladder and the rectum, and projects upward into the lower part of the peritoneal cavity, and its convex surface, except the lower portion, is enveloped by peritoneum. The upper end of the uterus is directed forward. The lower end is directed backward and downward and projects into the upper end of the vagina. The uterus is freely movable, especially the upper portion, and may be pushed backward by a full bladder or forward by a full rectum.

The uterus is **shaped** somewhat like an inverted pear (Fig. 44). Its lower constricted portion is called the cervix uteri (neck of the uterus) and to this the vagina is attached. The remainder of the organ is called the corpus uteri (body of the uterus). It is from the upper portion of the uterus, the widest portion, that the fallopian tubes arise. That portion of the uterus lying above the fallopian tubes is known as the fundus uteri (Fig. 45).

The uterus has a small central **cavity** (Figs. 44 and 45) which is lined with mucous membrane and which communicates through the vagina with the outside world and through the fallopian tubes with the peritoneal cavity. This is the only continuous opening from the outside of the body into the peritoneal sac, and it is because of this direct opening into the peritoneal cavity that peritonitis is so much more frequent in women than in men.

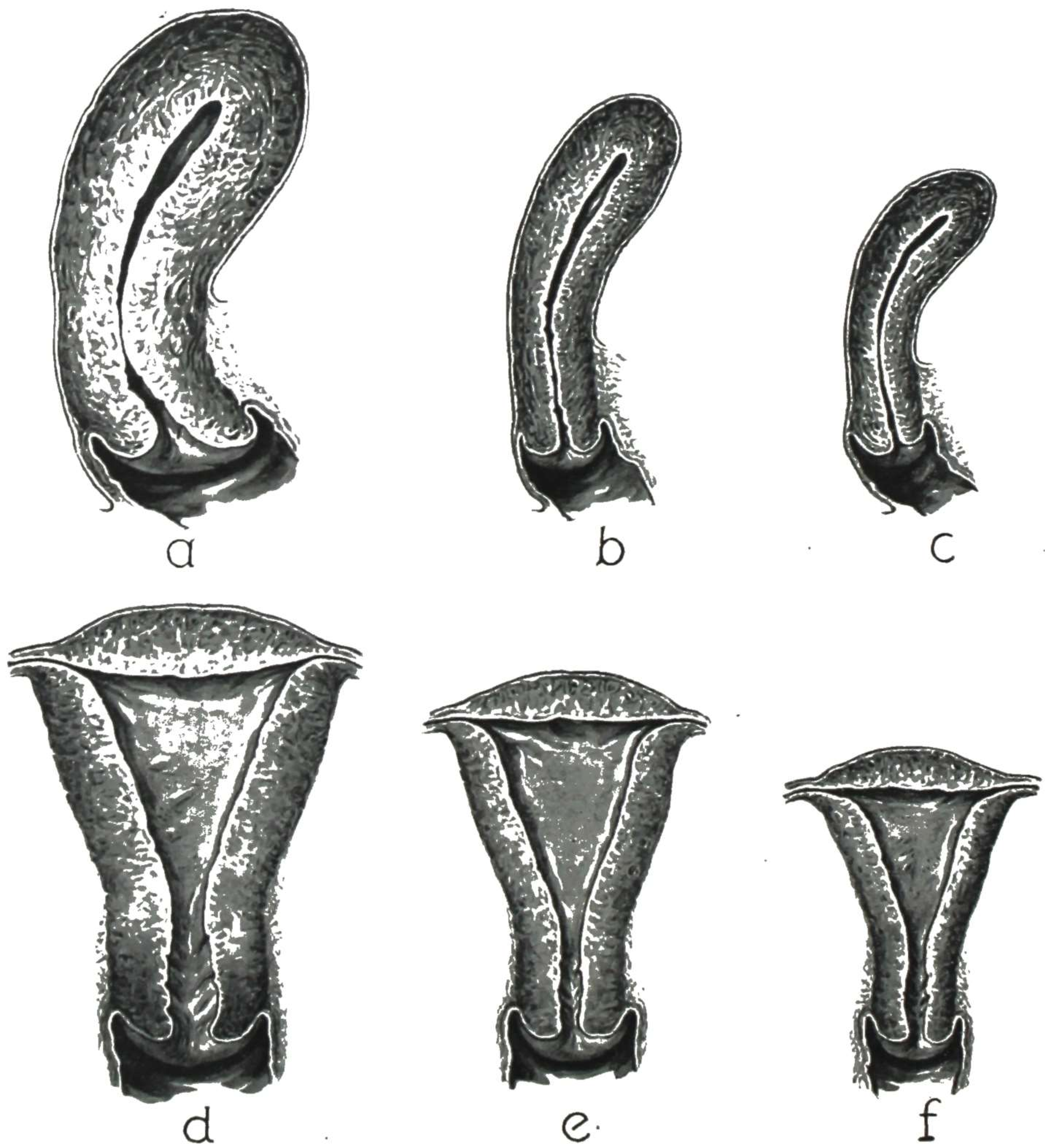
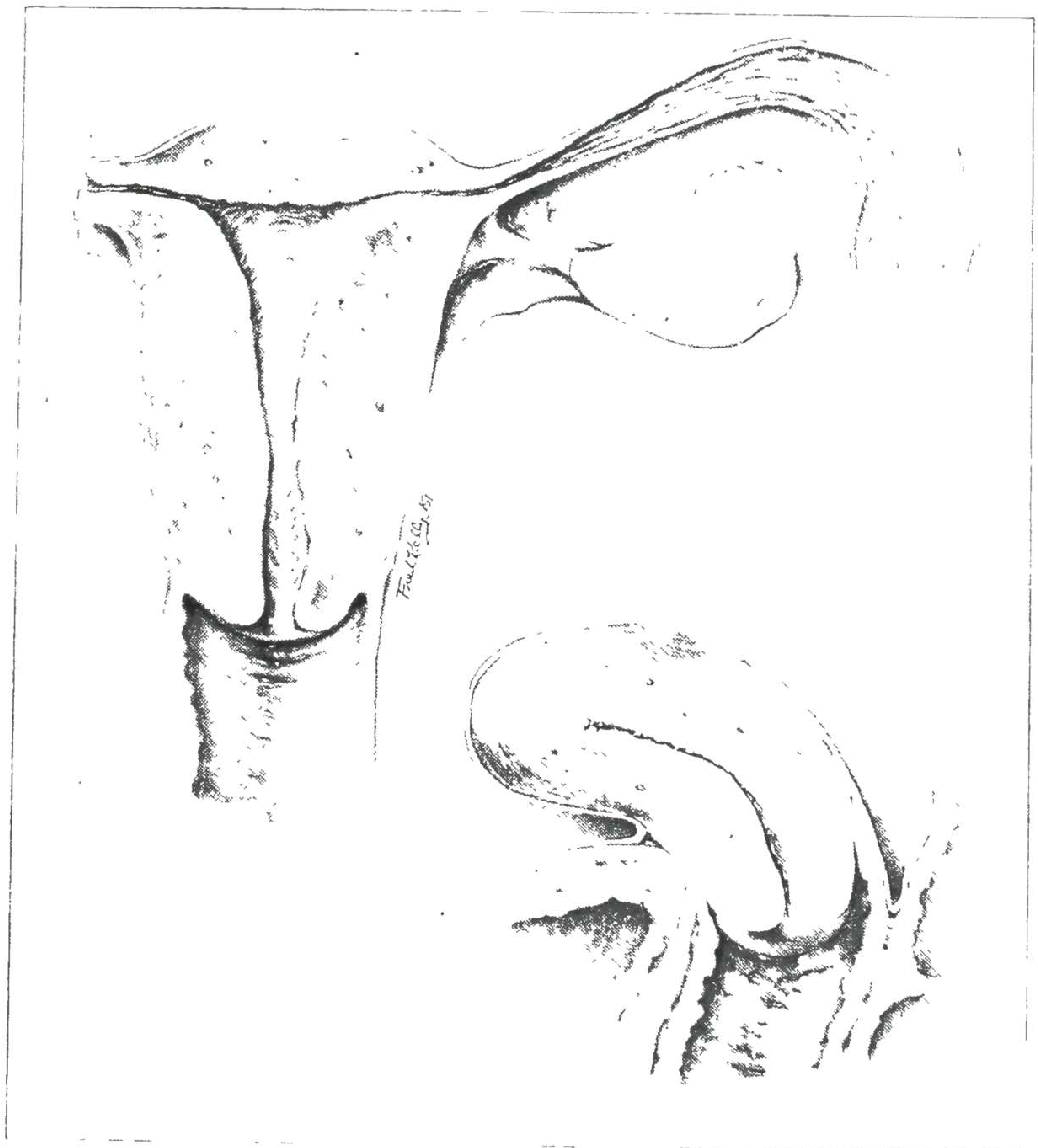


Fig. 44.—Drawings made directly from autopsy specimens. *a*, Anteroposterior section of uterus from an individual, aged twenty-three years; *b*, aged fifty years; *c*, aged seventy years; *d*, *e*, *f*, transverse sections of the same uteri; *d*, aged twenty-three years; *e*, aged fifty years; *f*, aged seventy years.

The **size** of the uterus is, of course, different in the different periods of life (Figs. 44 and 46). **At birth** it is a trifle over one inch long and the cervix comprises two-thirds of the organ (Fig. 46). It is important to keep in mind



A. B.

Fig. 45.—*A*, Uterus and right fallopian tube sectioned at a point just posterior to the insertion of the right uteroovarian ligament. The triangular shape of the uterine cavity in this plane is evident. As can be seen, there is a continuous channel from the vagina through the cervix and uterus and fallopian tube to the peritoneal cavity. *B*, Sagittal section showing the anterior peritoneal pouch in front and the posterior pouch or cul-de-sac of Douglas behind.

Fig. 46.—Comparative sizes of uterus and adnexa in (*A*) a stillborn infant at term (cervix hooked dorsad), (*B*) mature adult. The importance of actual sizes of organs in relation to both diagnosis and pathology is indicated. (From Schauffler: Surg., Gynec. & Obst., September, 1940.)

the peculiarities of the infantile uterus, for occasionally an adult presents a uterus somewhat infantile and accompanied with troublesome symptoms due to lack of development. In the fetus, the uterus lies very high and the cervix is very long. At first the axis of the cervix lies almost in the axis of the vagina. Normally, as development progresses, the corpus uteri gradually comes forward, and the cervix becomes directed somewhat backward, across the vaginal axis. In the cases of imperfect development already referred to, the corpus uteri comes forward normally but the cervix fails to assume its backward direction, remaining in practically the fetal position (directed along the axis of the vagina) and causing a sharp "anteflexion of the cervix."

The significance of this condition, when found on examination, is that it indicates the uterus is underdeveloped due to imperfect endocrine balance.

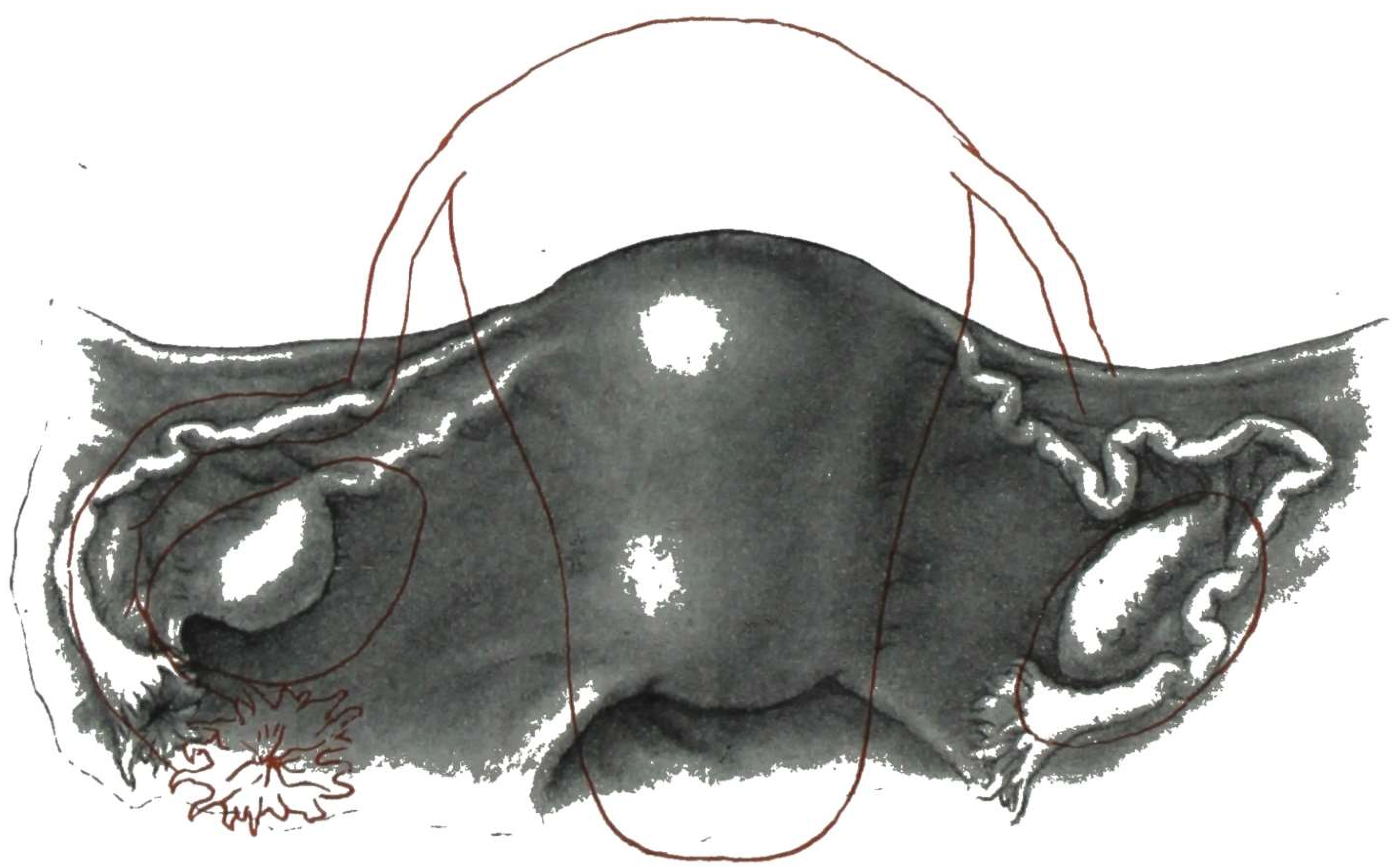


Fig. 47.—Drawing directly from an autopsy specimen of the ovaries, tubes, and uterus at seventy years of age. The shrinkage from age is very marked, but is so uniform that the relative size of the organs is maintained. The tubes have diminished more in thickness than in length. The marked senile shrinkage is indicated by the superimposed twenty-three-year-old organs, in red outline.

As to the approximate measurements, the adult virgin uterus is 7.5 cm. (3 inches) long, and the cervix forms one-third of the organ. The transverse measurement at the widest part is 3.5 to 5.0 cm. (1½ to 2 inches) and averages about 2.5 cm. (1 inch) in thickness. The cavity of the uterus including the cervix is 6.5 cm. (2½ inches), and it weighs 50 to 60 grams. In parous women the uterus is always a little larger than the virgin uterus. The cavity of the parous uterus measures from 7.0 to 7.5 cm. or 2¾ to 3 inches. After the **menopause** there is marked atrophy of all the genital organs, including the uterus (Fig. 47). The extent of the atrophy of the uterus is variable. In the very aged it may be reduced to a nodule the size of the end of the thumb, and the cervix then no longer projects into the vaginal cavity but is felt simply as an indurated area, with a small central opening, situated in the upper part of the anterior vaginal wall.

In structure the uterus is a hollow muscle. The central cavity is lined with mucous membrane while the external surface of the muscle is covered with peritoneum. The wall of the uterus is, therefore, composed of three layers—peritoneal, muscular, and mucous (Fig. 44).

1. Peritoneal Layer.—This forms a delicate serous covering to the uterus. It does not differ materially from peritoneum elsewhere. There are certain portions of the uterus which are not covered by peritoneum, namely, the lateral portions of the body and the front and sides of the cervix.

2. Musculature.—The muscle wall of the uterus is 11 to 15 mm. thick. The arrangement of the muscle fibers has been extensively studied, and as early as 1885 Bayer described the three layers now recognized to be present. It is very difficult to recognize these layers in the nonpregnant uterus but in the uterus at full term they are more easily identified.

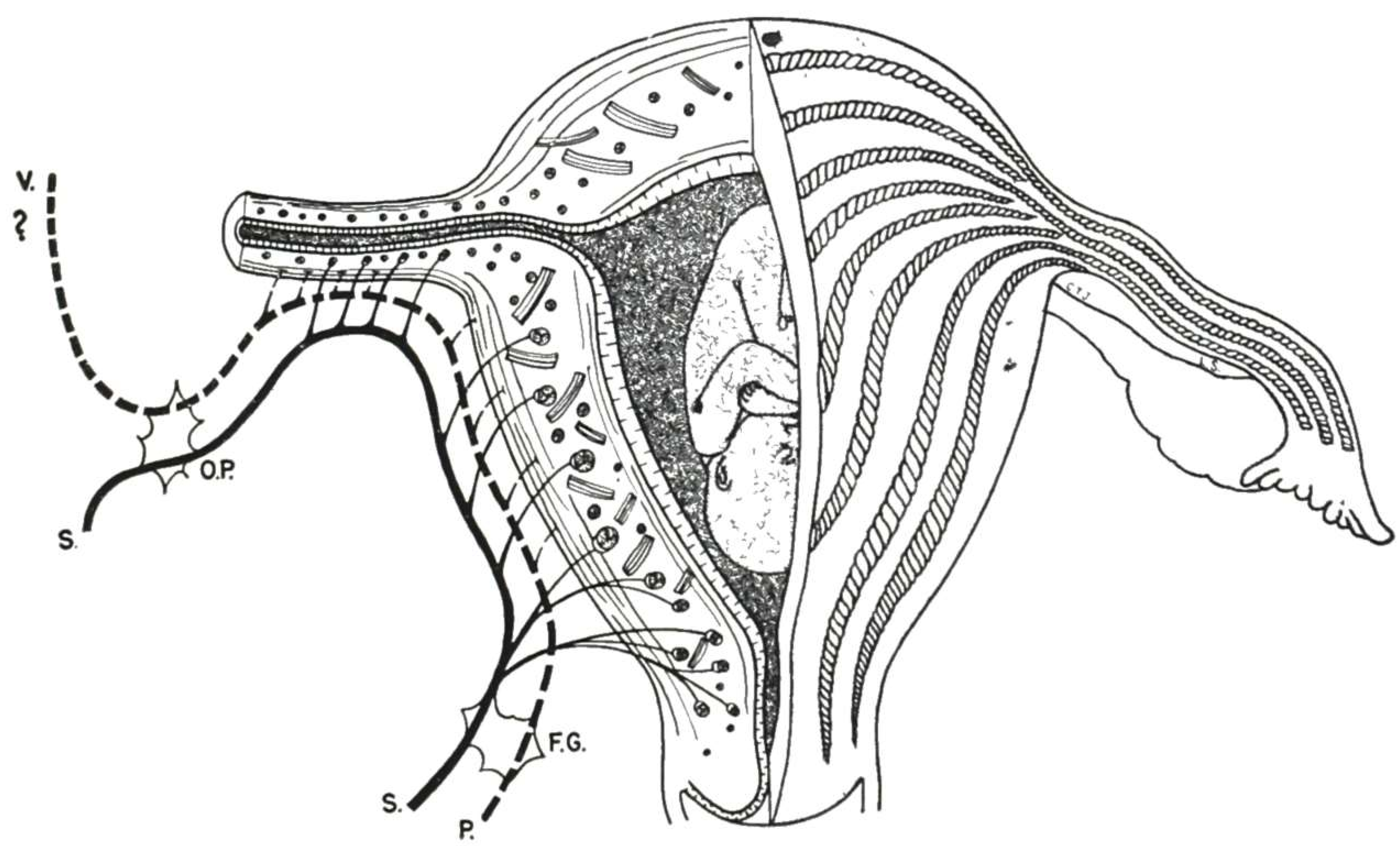


Fig. 48.—Diagram of the longitudinal and circular (and spiral) muscle fibers of the uterus and cervix, together with their probable innervation, which is bilateral although only one side is shown. O.P., Ovarian plexus; F.G., Frankenhäuser ganglion; S., sympathetic; P., parasympathetic. (From Javert and Hardy: Am. J. Obst. & Gynec., September, 1950.)

The outer layer is thin and the fibers run longitudinally, interlacing in the midline of the uterus with some of the fibers crossing from the opposite side. The middle layer is very thick, the fibers in this layer running in a circular and oblique direction. This layer contains the main vessels of the uterus. The inner layer is thin and the fibers run in an ascending counterclockwise spiral (Fig. 48).

The various layers of the uterine musculature are intimately integrated with those of the tubes and supporting ligaments. When one considers the development of the genital apparatus, the logic of this arrangement is evident. The importance of this function of the müllerian tubes in the physiology of the uterus is discussed later under physiology.

The **connective tissue** of the muscular layer comprises most of the connective tissue of the uterus. It is not distributed in the form of distinct strata but appears as irregular masses surrounding and supporting the important elements. There is a very intimate connection between the mucous membrane lining the uterus and the connective tissue of the muscular layer.

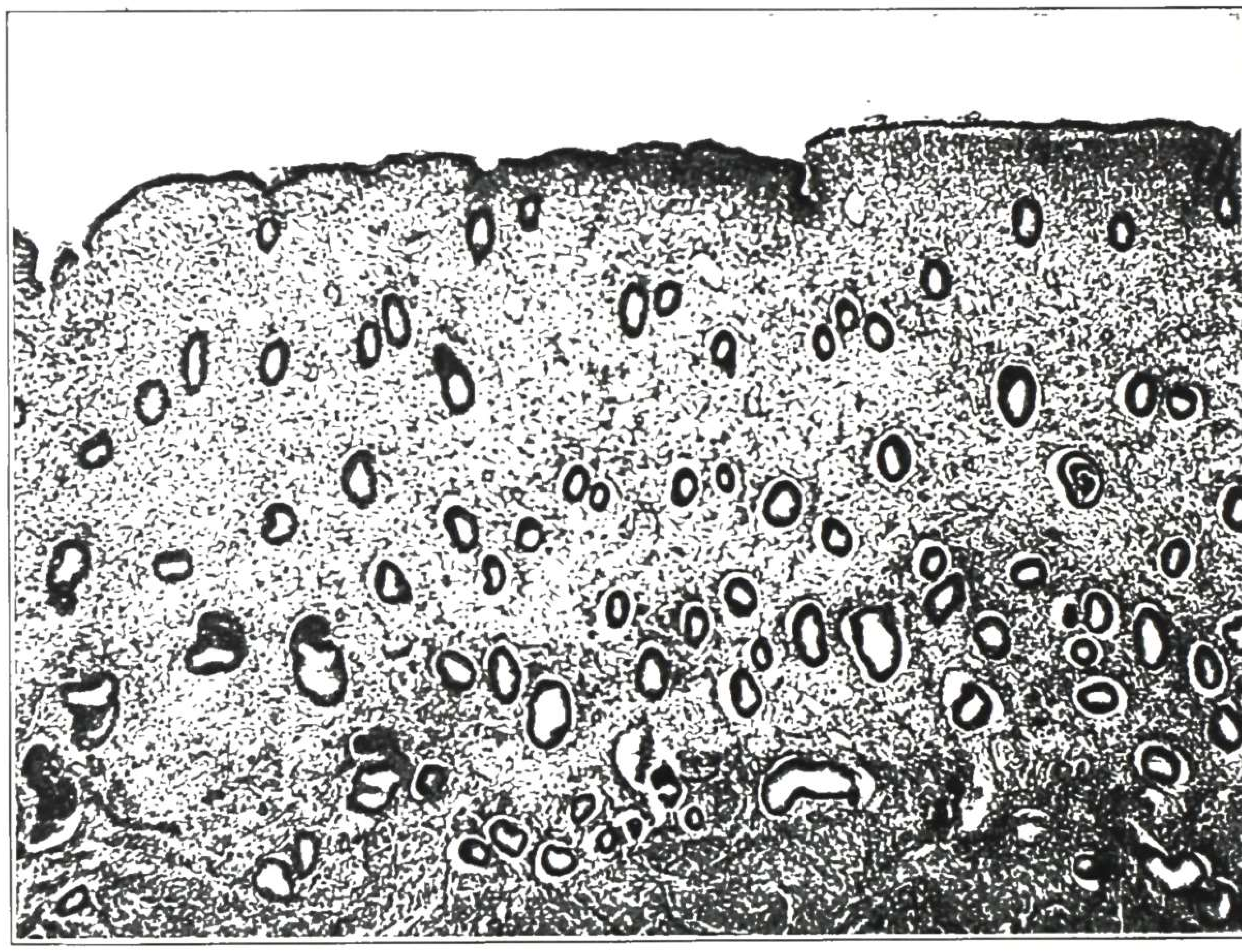


Fig. 49.—Normal endometrium, midgrowth stage. The stroma is quite compact and the glands are seen as simple tubular glands. They are not so simple, however, as appears on one cross section. Modeling of the glands from serial sections demonstrates their frequent branching. Gyn. Lab.

Fig. 50.—A microscopic section of the endometrium, showing the stroma cells and also a cross section of a gland. The structures are magnified 420 times. (From Williams: Obstetrics.)

The **blood vessels** of the muscular wall include most of the blood vessels of the uterus, and they are particularly large and numerous in the middle layer.

The arteries are distinguished in a microscopic section by their thick walls and folded intima. The outer vessels run in a longitudinal direction, while the inner vessels run perpendicular to the mucous surface. There is a dense capillary network close to the mucous membrane.

The veins are very large and have thin walls.

The **lymphatics** of all the coats of the uterus (peritoneal, muscular, and mucous) empty into large lymphatic vessels in the external muscular stratum. These in turn empty into efferent trunks at the sides of the uterus.

The **nerves** of the muscular layer are derived from the autonomic system. The filaments ramify among the muscular bundles and terminate in the nuclei of the muscle cells.

3. Mucous Layer.—The mucous membrane of the uterus lies directly on the internal muscular stratum, the usual submucous layer of loose connective tisue being absent (Fig. 49). Scattered muscular filaments extend into the mucosa, so the connection between the two is firm. The mucous membrane of the body of the uterus is known as the "endometrium," that lining the cervix is known as the "cervical mucosa."

The **endometrium** is from 2 to 6 mm. thick in the childbearing period and is disposed over the interior of the uterus as a smooth layer. It is soft and velvety to the touch and when perfectly fresh has a pink color. There is a great difference in the thickness and general appearance of the endometrium in the different periods of life and also in the different stages of the menstrual cycle. The cyclic changes of the endometrium associated with menstruation are discussed and illustrated in detail under Physiology of the Uterus.

The interglandular supporting tissue of the endometrium is composed almost exclusively of oval cells, somewhat larger than a leukocyte and having a round or oval nucleus that stains lightly (Fig. 50). The nucleus is so large that it occupies most of the cell. When stained it is reticular, i.e., it shows the chromatin bands and does not stain a solid dark color as does the nucleus of a lymphocyte. These oval cells with the large reticular nuclei are known as **stroma cells** (Fig. 50). They are packed closely together, with nothing separating them except a few cell processes and a small amount of serous or mucoid intercellular substance. This stroma is developed in response to the downgrowth of the columnar epithelium of the fused müllerian ducts. It is called cytogenic tissue and is a specific type of stroma found only in the endometrium. When a specimen of it is stained, the microscopic field seems to be almost entirely occupied by rounded or oval reticular nuclei (Fig. 50). The cell protoplasm stains so lightly and is so small in amount that it is scarcely noticeable. Under certain conditions, however, the cells become swollen and stain more lightly. This occurs in the premenstrual stage and, especially, during pregnancy. In the latter case, they greatly enlarge and become the decidua cells. Under these conditions, also, the intercellular serous or mucoid material becomes noticeable, thus giving the whole an edematous appearance.

The stroma is rich in capillaries which become much increased in size and number in the premenstrual stage. They arise in the basal layer and course upward, forming right-angled loops near the surface.

Embedded in the stroma are the **uterine glands** (Figs. 49 and 50). These are lined by a single layer of epithelial cells, the nucleus of each cell being placed near its center. In the stage of secretion, they crowd each other, forming a very irregular line, unlike the regular arrangement of the nuclei in the cervical glands. The glands extend from the depth of the endometrium and open upon the surface. They vary considerably in different parts of their course, especially in the premenstrual stage.

These cyclic changes of the endometrium are discussed under Physiology of the Uterus.

Cervix Uteri

The structure of the cervix differs from that of the body of the uterus in several particulars, as follows:

1. The greater part of the cervix has no peritoneal covering (Fig. 51).

2. The cervix is composed chiefly of fibrous tissue. Danforth by means of differential staining estimated that the smooth muscle comprises only about 15 per cent of the tissue and that a good deal of this is found around the blood vessels. He was not able to discover any muscle cell arrangement indicating a sphincter. There was a rather sharp transition from fibrous to muscular tissue in the area just above the cervix.

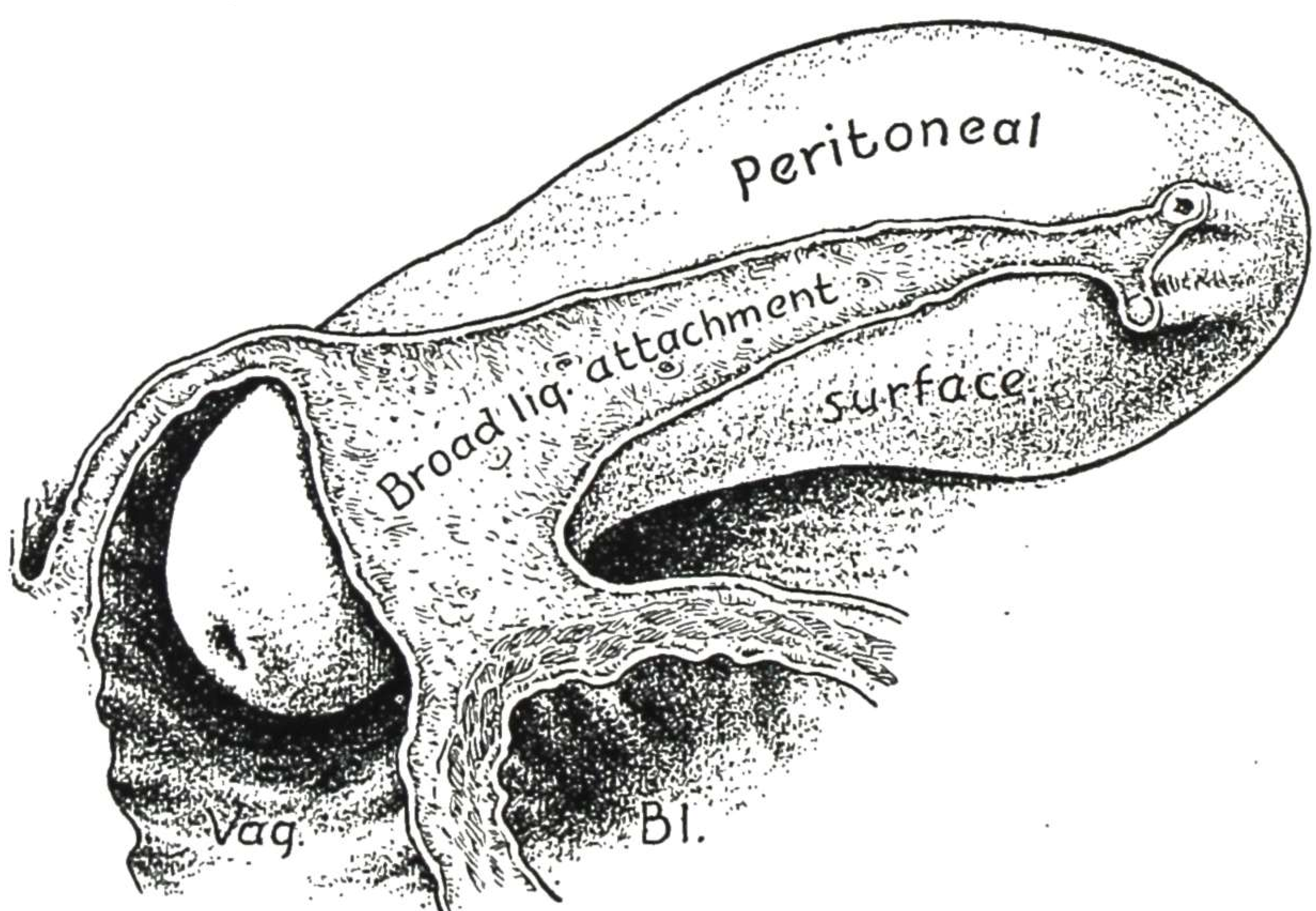


Fig. 51.—This diagrammatic anteroposterior section to the right of the median line shows the broad-ligament attachment to the uterus, and also the relations of the peritoneum anterior and posterior to the uterus. (Modified from Dickinson: American Textbook of Obstetrics.)

3. There are no large venous sinuses in the cervix and the blood vessels have thicker walls and smaller lumina than those in the uterus.

4. The mucous membrane lining the cervical canal starts at the junction of the squamous epithelium of the portio below and ends above at the internal os. The membrane is disposed in prominent folds which extend more or less obliquely outward from two ridges, one situated near the posterior lip and the other near the center of the anterior lip. The cells of the epithelium are tall columnar, with basal nuclei and cytoplasm rich in mucin. The racemose glands, formed by the infolding of this lining membrane, are surrounded

by a very thin layer of stromal tissue composed chiefly of spindle cells. The thick mucus secreted by these glands forms a cervical plug which helps to prevent infection of the uterine cavity (Figs. 52 and 53).

The mucosa undergoes changes during the menstrual cycle, during pregnancy, and at the menopause which are described here instead of later under Physiology of the Uterus.

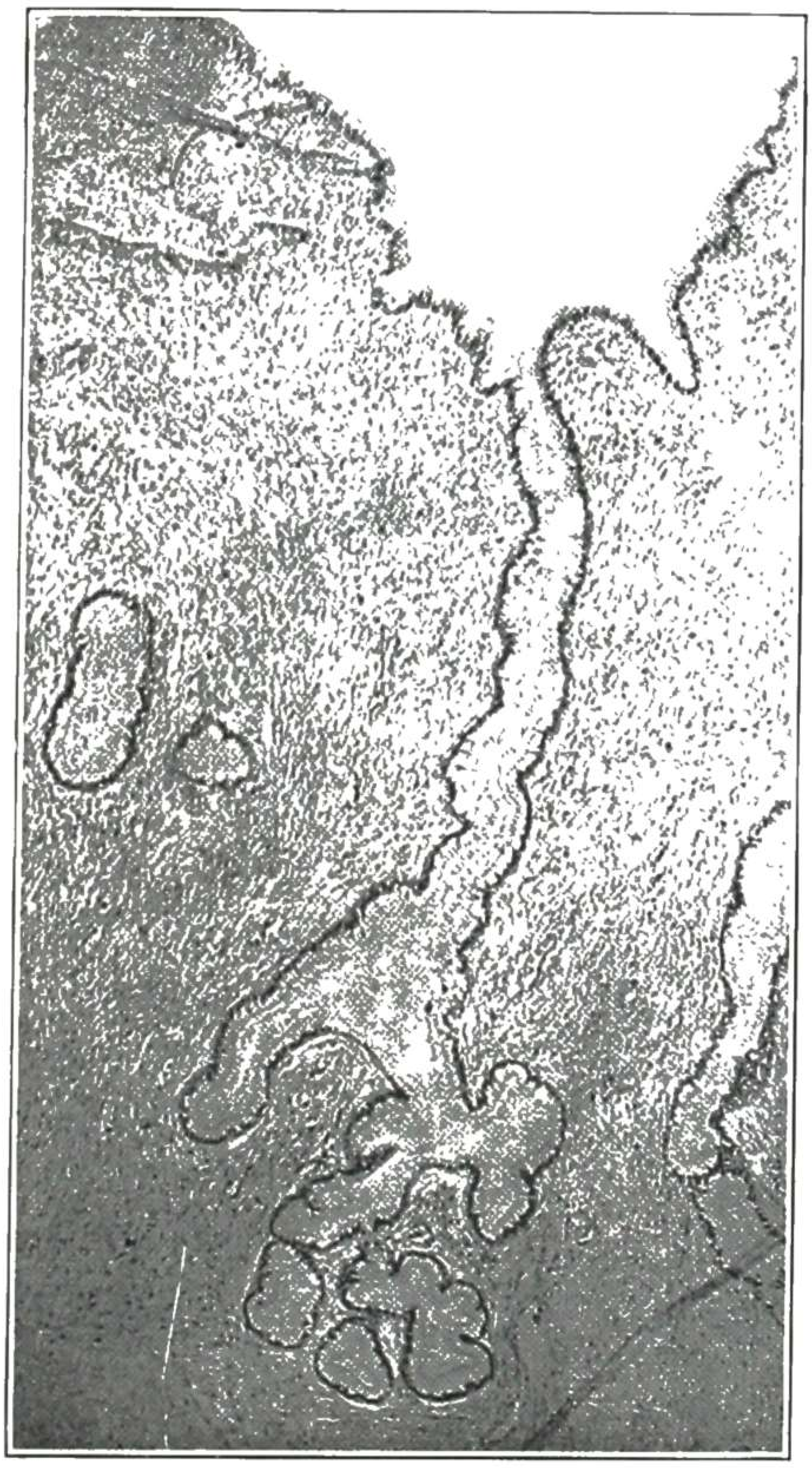


Fig. 52.

Fig. 53.

Fig. 52.—A typical cervical gland is seen in center of picture, with its long neck connecting it with the cervical canal. Gyn. Lab.

Fig. 53.—Cross section through a practically normal cervical gland. The branched character of the glands is well shown in this and the preceding photomicrograph, also the high cell with the nucleus placed definitely at the base. Gyn. Lab.

The vaginal portion of the cervix is covered with squamous epithelium continuous with that of the vagina. Three layers are present: the basal layer, consisting of cuboidal or low columnar cells which take a dark stain, the intra-epithelial horny layer with its large polygonal cell, and the superficial layer made up of flat pavement cells (Fig. 54).

In regard to cyclic changes in the cervix, Wollner feels that the epithelium lining the cervix goes through cyclic changes which are influenced by the hormones. The two most evident stages are shown in Figs. 55 and 56, the legends of which explain the characteristics. This subject was recently reviewed by Bradburn and Webb.

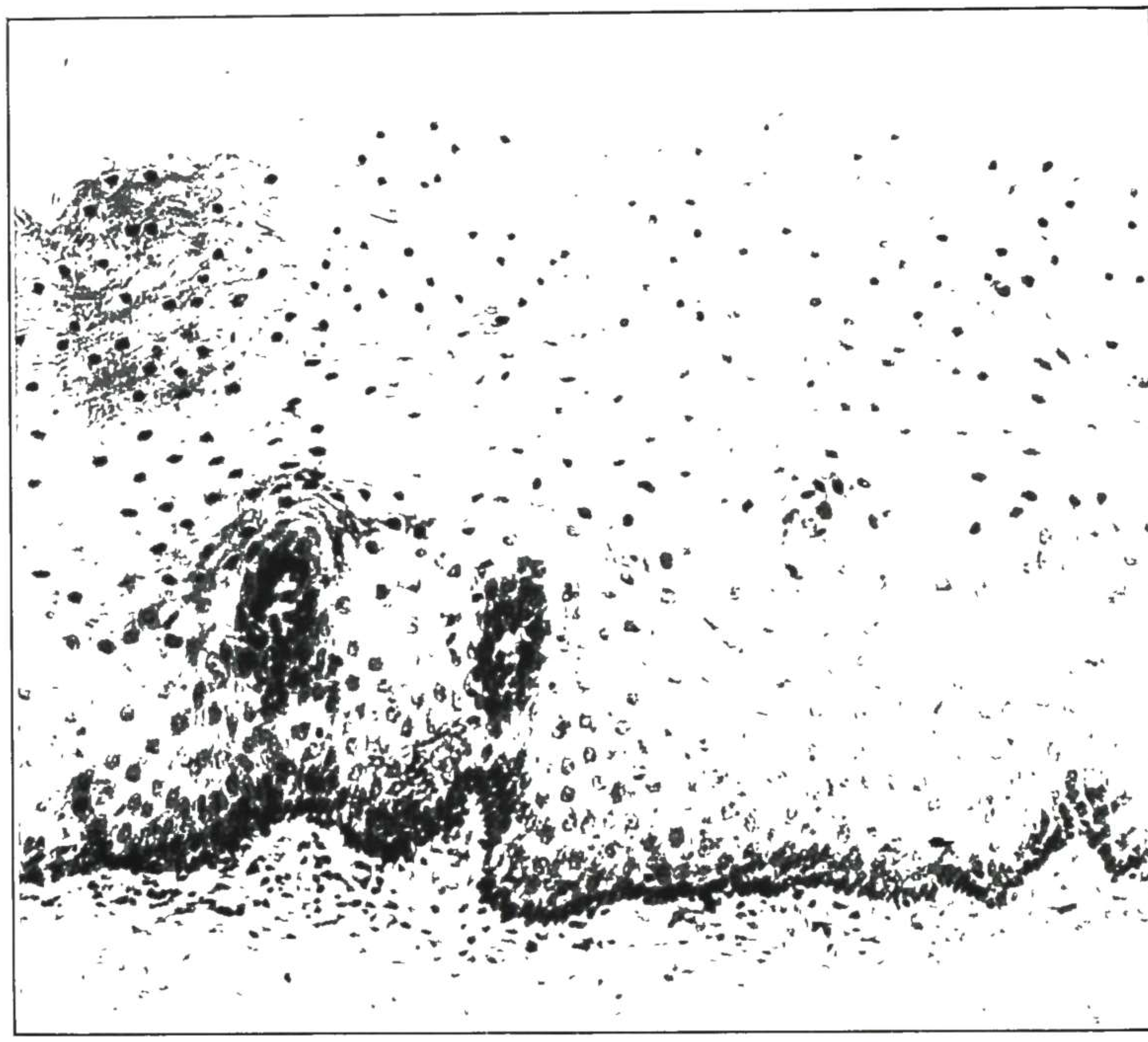


Fig. 54.—Epithelial covering of cervix uteri. Note the three layers: the superficial layer of flat epithelial cells with small nuclei and indistinct cell margins, the middle layer of cuboidal cells, with larger nuclei and fairly distinct cell outline, and the basal layer of high cuboidal cells with basal nuclei. This latter layer takes a much darker stain than do the other two. Gyn. Lab.

Fig. 55.

Fig. 56.

Fig. 55.—High-power photomicrograph of a specimen obtained seven days after the onset of menstruation. The surface epithelium forms a regular line of moderately high columnar cells with oval-shaped nuclei near the basal membrane. The cells have a sharp outline. The stroma is dense, the cells are widely scattered and reveal little cytoplasm. (From Wollner: Surg., Gynec. & Obst.)

Fig. 56.—High-power photomicrograph of a specimen taken from the same patient twenty-three days after the beginning of her last menstruation. The regularity of the arrangement, size, and shape of the epithelial cells is lost. The cells are higher and broader than in the previous specimen and they have now an irregular outline. Some of them reveal the discharge of their secretion. The nuclei are larger, spindle shaped, and situated near the center of the cell. The stroma is markedly cellular and the cells have more cytoplasm. (From Wollner: Surg., Gynec. & Obst.)

The portion of the uterus just above the cervix is called the "isthmus." It is an indefinitely outlined area extending from the internal os, as determined histologically, to the constriction in the uterine lumen at the lower border of the corpus, called the anatomic internal os. Danforth, in the comprehensive study previously mentioned, concluded that the isthmus was not a distinct entity, and that this concept should be eliminated because the muscular and epithelial elements of this region are essentially the same as those of the corpus and hence, like the fundus, should be considered a part of the corpus.

Ligaments of the Uterus

The uterus is held in its position by the pelvic floor and by certain ligaments (Fig. 57). They are the broad ligaments, the round ligaments, the sacrouterine ligaments and the vesicouterine ligament. Muscle elements of these ligaments interlace with the various layers of the uterine musculature.

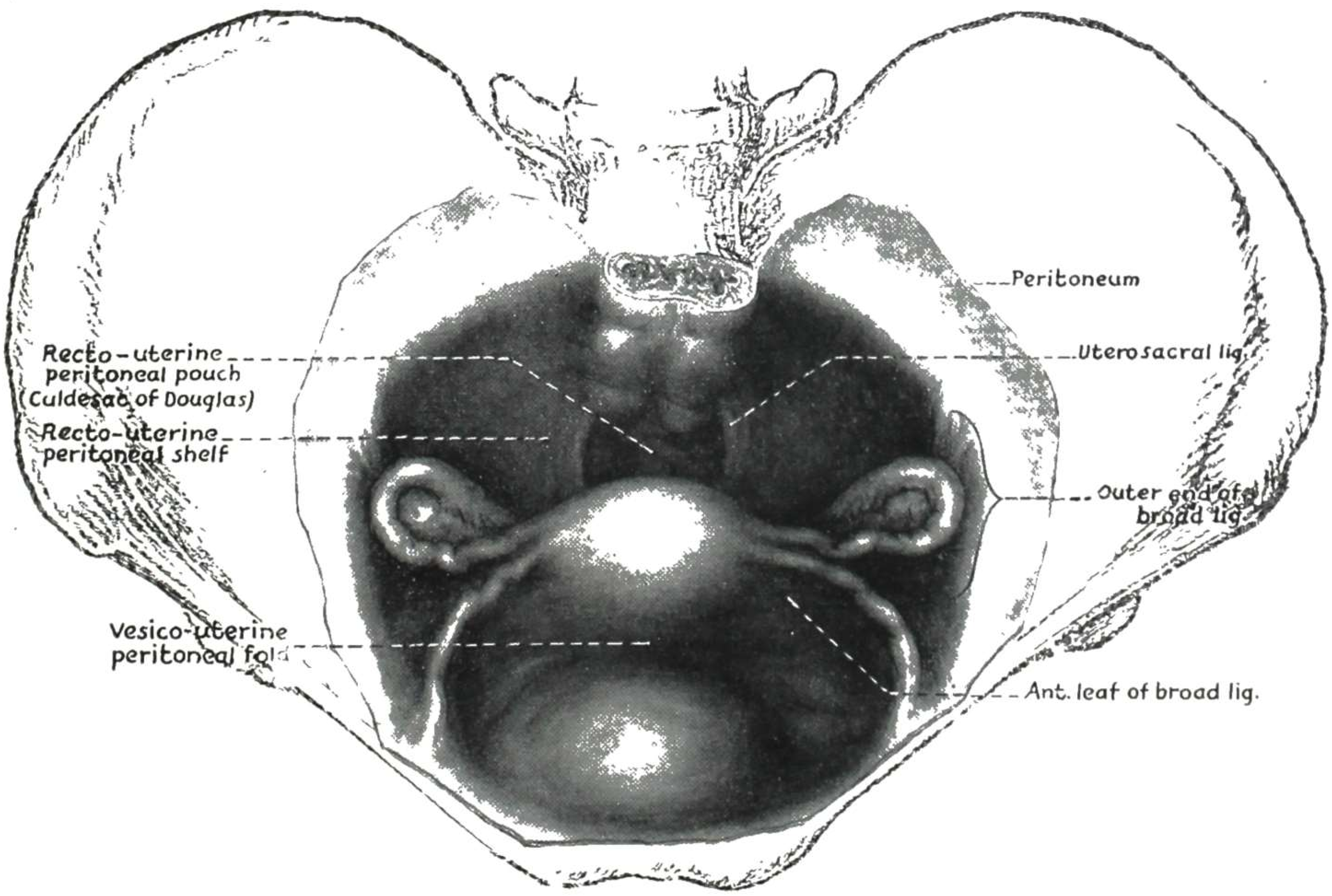


Fig. 57.—Showing the distribution of the peritoneum within the pelvis, and the various ligaments and pouches thus formed. It is as though a thin cloth were laid over the pelvis and then tucked in around all the organs and their wall connections.

The **vesicouterine ligament** is simply a fold of peritoneum extending from the uterus to the bladder.

The **sacrouterine ligaments** are peritoneum-covered bands of tissue extending from the posterolateral aspect of the cervix in the region of the internal os, around the superior boundary of the cul-de-sac of Douglas, to the presacral fascia at the lower portion of the sacroiliac articulation. The tissue elements present in the ligaments are connective tissue, muscle, blood vessels, lymphatics, and sympathetic and parasympathetic nerves with some fat. In a detailed study of the ligaments, Campbell found that the amount of muscle tissue decreased from the anterior to the posterior portion. The weakest part was that portion attached to the sacrum. He feels that if the ligament is well developed it may be used as supplementary support in prolapse or retrodisplacement of the uterus. The principal action of the ligaments is holding the cervix upward and backward (Figs. 5 and 57).

The **round ligament** of each side is a fibromuscular cord which arises from the top of the uterus just in front of the fallopian tube and extends outward and forward in the upper part of the broad ligament to the internal inguinal ring (Fig. 57). It then passes through the inguinal canal, and at the external ring divides into fibrous filaments which are lost in the tissues covering the pubic joint. The round ligaments are four or five inches in length and tend to prevent marked backward displacement of the uterus. Ordinarily they are lax, but when the uterus is displaced backward by a full bladder or other condition, they are made tense and help to bring the uterus back to its accustomed position. It is the round ligaments that are shortened in certain operations for the cure of backward displacement of the uterus. They also serve as "guy wires" which help to stabilize the enlarging pregnant uterus.

The **broad ligaments** extend from each side of the uterus laterally to the pelvic wall (Fig. 57). The attachment to the uterus extends all along the side of the organ from the cervix to the fundus, and there is a wide attachment to the pelvic wall laterally. This broad band of fibromuscular tissue is covered on both sides by peritoneum which is continuous with that covering the anterior and posterior surfaces of the uterus. The connective tissue is concentrated at the lower portion of the broad ligament, forming a strong band known as Mackenrodt's ligament. These bands of tissue on each side of the uterus are the principal factors responsible for holding it in its normal position in the pelvis. The tissue adjacent to the uterus is known as the "parametrium," and inflammation in this tissue is designated as "parametritis." Between the layers of the broad ligament are the following structures: round ligament, fallopian tube, ovarian and uterine vessels (Fig. 58), the ureter, and the vestigial structures previously described in the mesovarian and mesosalpinx. The ureter, in its course to the bladder, lies in the lower part of the broad ligament near the cervix where it passes under the uterine artery, as shown in Fig. 58.

Blood Vessels

The blood supply of the uterus comes from the uterine and ovarian arteries. The **uterine artery** of each side arises from the anterior trunk of the internal iliac (Fig. 59) and passes inward and downward between the layers of the broad ligament to just above the lateral vaginal fornix. It then turns upward and runs in a very tortuous course along the side of the uterus. Near the top of the uterus it joins the descending branch of the ovarian artery, as shown in Fig. 58.

As it runs along the side of the uterus, the uterine artery gives off many branches which run horizontally about the organ and supply various segments. These anastomose with corresponding branches of the opposite artery. These branches are very tortuous, the tortuous and spiral arrangement being so

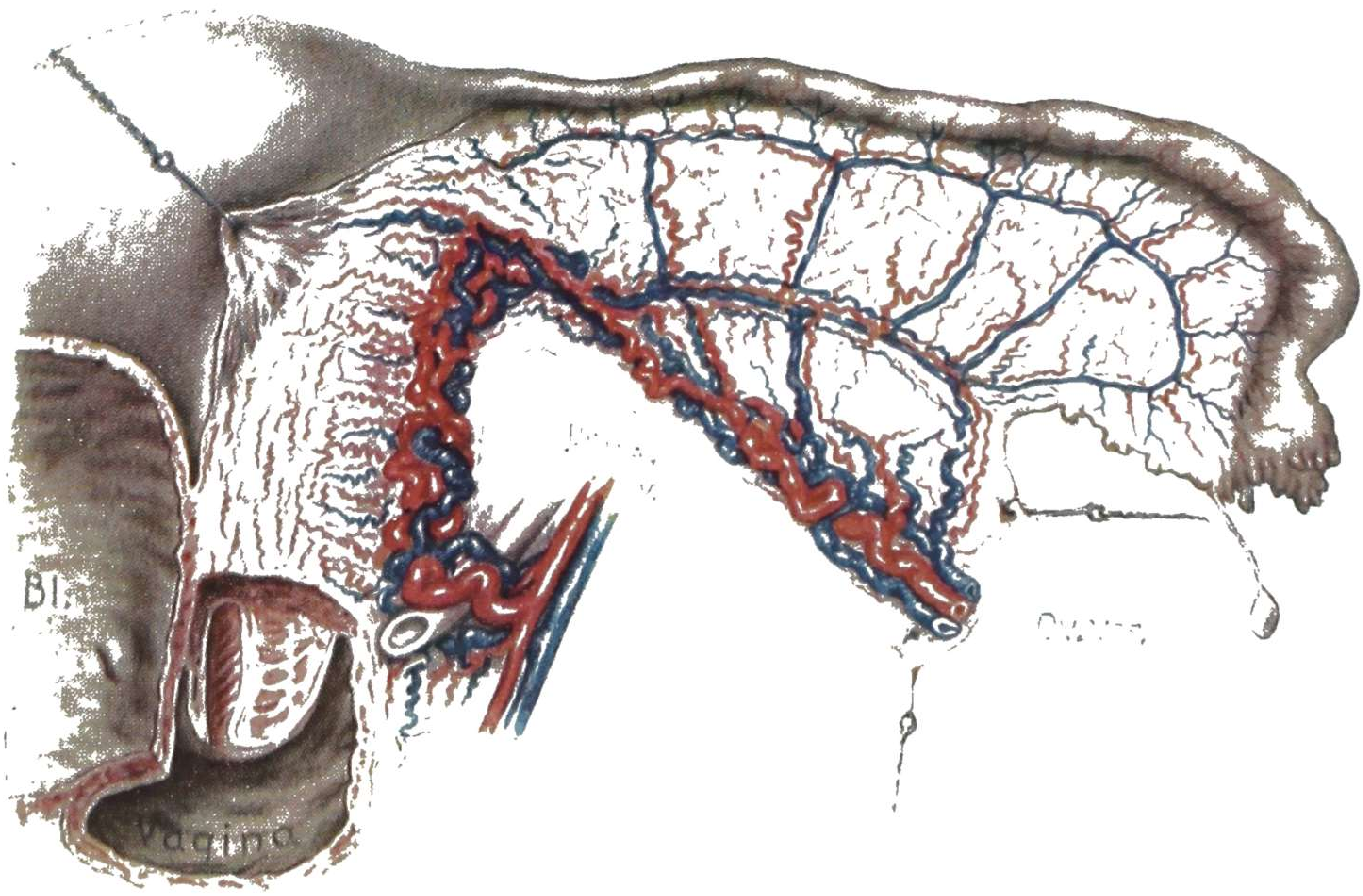


Fig. 58.—The blood supply of the uterus, tube, and ovary. View from the front, with left half of bladder removed, showing the relation of the ureter to the uterine vessels. (After Kelly: Operative Gynecology, D. Appleton-Century Company.)

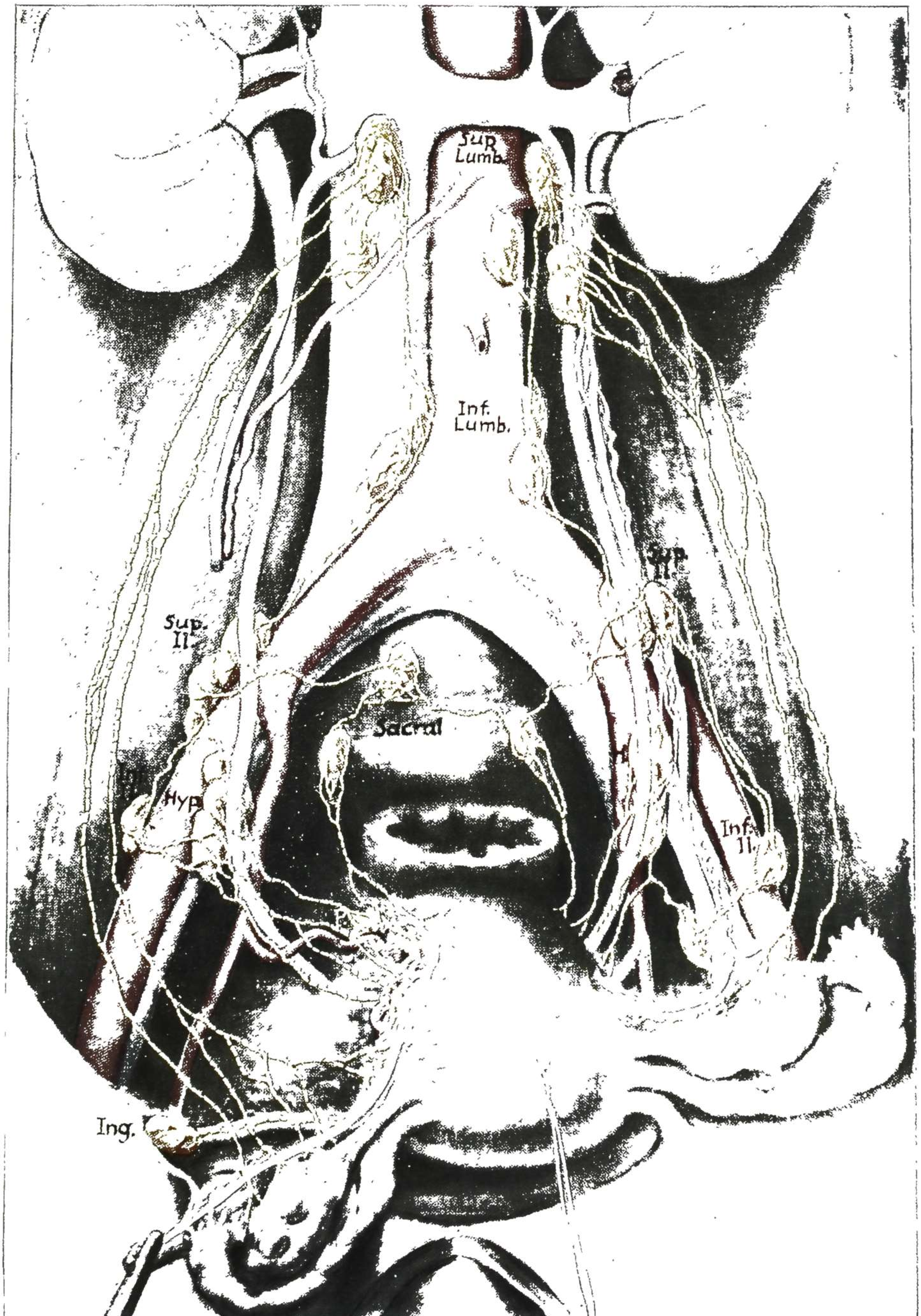


Fig. 59.—The distribution of the lymphatics of the uterus to the various groups of glands. (After Doederlein and Kroenig: Operative Gynaekologie.)

marked that they have been called the "curling arteries" of the uterus. A horizontal branch of considerable size at the level of the internal os is known as the "circular artery."

The **ovarian artery** of each side supplies the tube and ovary and upper part of the uterus, as shown in Fig. 58. These arteries correspond to the spermatic arteries in the male and arise directly from the aorta. The artery of each side passes downward and enters the broad ligament. After giving off the branches that supply the ovary, the artery passes on to the upper part of the uterus where it divides into two branches. The upper branch supplies the fundus uteri and anastomoses with the corresponding branch of the opposite artery. The lower and larger branch descends along the side of the uterus and anastomoses with the uterine artery. Some authorities describe the uterine artery as supplying all the side of the uterus and a part of the tube, and anastomosing with the ovarian artery some distance out along the tube. Possibly the distribution differs considerably in different individuals.

The **veins** of the uterus are exceedingly numerous. The organ is surrounded by a vast network of these vessels, which receive the blood from the veins and sinuses within its walls. There is free communication of this plexus with the vaginal and vesical plexus below and with the ovarian (pampiniform) plexus above, the blood ultimately emptying into the internal iliac vein.

Lymphatics

The distribution of the uterine lymphatics to the various gland groups is shown in Fig. 59. The lymphatics constitute the drainage system of the pelvis, by which are carried away those waste products of tissue activity and maintenance which the blood stream cannot handle. The blood-vascular system for carrying needed supplies to the tissues and waste products from them and the nervous system for carrying coordinating messages back and forth have largely monopolized attention as far as carrier service is concerned, but the lymphatic system has a necessary and very important function. The fact that we hear so little about disturbances in this extensive plumbing system is evidence of its efficient working in spite of the wear and tear of daily functional stresses and accidents. It is interesting to study the pelvic drainage system from this viewpoint—to consider the various kinds of substances to be removed and the facilities for accomplishing that removal satisfactorily in spite of difficulties due to the smallness of the working parts in the human machine and to the physical and chemical and electrical reactions which must continue undisturbed.

The fine radicles of the lymphatic drainage system start as intercellular spaces among the functioning cells of the uterine muscle and connective tissue. The waste-laden fluid, giving up its carbon dioxide and certain other constituents to the venous capillaries on the way out, passes into small thin-lined lymphatics. These combine to form larger vessels which pass through the uterine wall, joining with others on the way to form vessels of increasing size. These join with neighboring vessels to form larger ones and these with others until finally there is formed the main lymphatic trunk, the thoracic duct. A peculiar characteristic of this drainage system is that the collected material is not cast out of the economy directly but is emptied into the blood stream (through the left subclavian vein) to be worked over again before being cast out through the various excretory organs. Thus intake is economized by repeated extraction of elements that can be utilized in the body mechanism.

In certain places along the lymphatic vessels there are nodes or glands which serve as catch-stations to stop the progress of particles, such as bacteria and cancer cells, where phagocytes may destroy them. The phagocytes, however, are not always able to destroy these invaders, which then infiltrate the glands of that group and also pass on to the next group. Hence, the lymphatic glands draining an area of cancer must receive careful consideration in treatment of that cancer.

The lymphatic vessels of the uterus fall naturally into two groups—those of the cervix and those of the corpus. Those of the cervix uteri join with those of the upper part of the vagina and empty into the sacral and hypogastric and superior iliac glands. The lymphatics from the corpus uteri join with those of the tube and ovary and empty into the lumbar glands. A few lymphatics from the uterine cornua pass along the round ligaments and empty into the inguinal glands. No definite lymphatic vessels have been found in the endometrium.

Nerves

The nerves of the pelvic organs, like those of other internal organs, are derived from the autonomic nervous system. Fig. 60 shows the large autonomic trunk ganglia (vertebral ganglia) which lie along each side of the spine back of the abdominal viscera. Fig. 61 shows the complex reflex arc of the autonomic system (yellow and red) compared with the simple reflex arc of the spinal system (black).

The autonomic system is for the transmission of motor impulses of various kinds to the functioning structures, and it utilizes the sensory spinal nerves to complete its reflex arc. For example, in the reflex arc shown in Fig. 61 the sensory impulse comes in over a spinal nerve (yellow), and passes to the autonomic nerve (red) at the synapsis in the cord. The outgoing motor impulse to the viscera passes along the autonomic nerve (red) in the posterior root and in the white ramus to the thoracic autonomic ganglion (vertebral ganglion) and on to the prevertebral ganglion, where there is synapsis with an autonomic nerve fiber going directly to the viscus. If the autonomic motor impulse is destined for the skin structures, it passes through a synapsis in the vertebral ganglion, then back through an autonomic fiber in the gray ramus to the spinal bundle and on to its peripheral distribution. In the abdomen and thorax there are large collections of nerve fibers and within these are masses of synapsizing cells, each such mass of cells being called a ganglion, as in Fig. 61. Such a collection of nerve fibers and cells is also referred to as a plexus. The great collections in the abdominal cavity are indicated in Fig. 62, along with the fields they control; the pelvic plexuses are shown in Fig. 63.

The above detailed reflexes apply to the autonomic nerves issuing from the thoracic and lumbar segments of the cord. Those from other segments (sacral, cervical, mesencephalic) have a somewhat different reflex arc in that the motor impulse is carried by a continuous autonomic fiber from the cord to

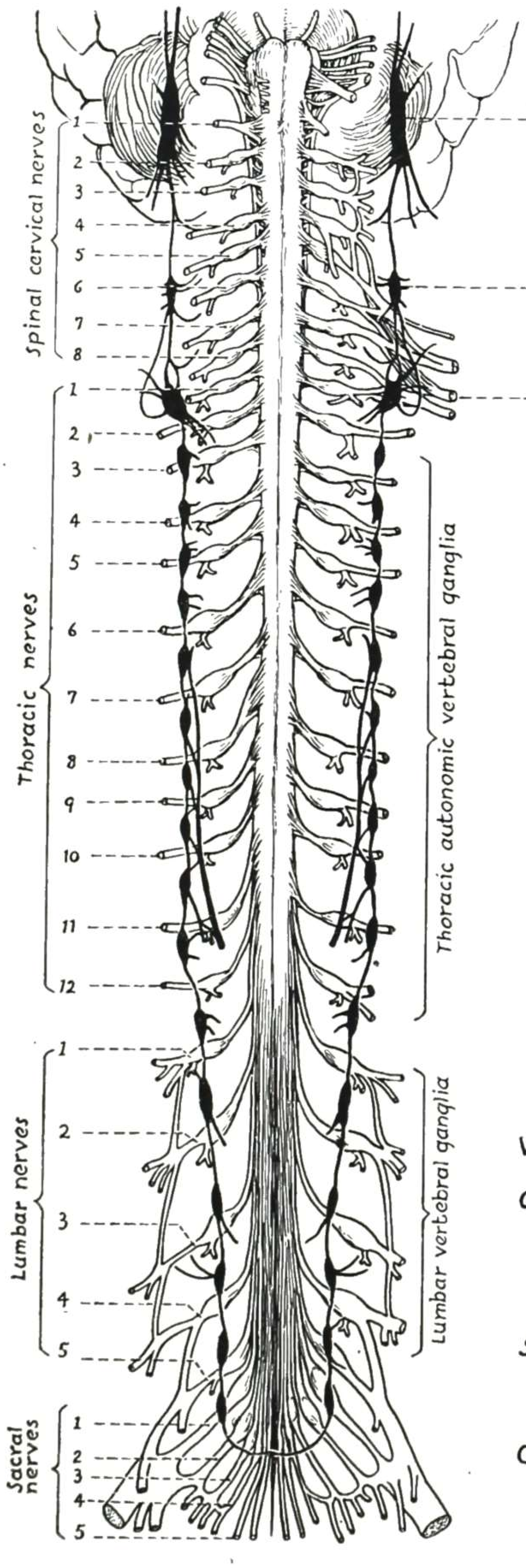


Fig. 60.

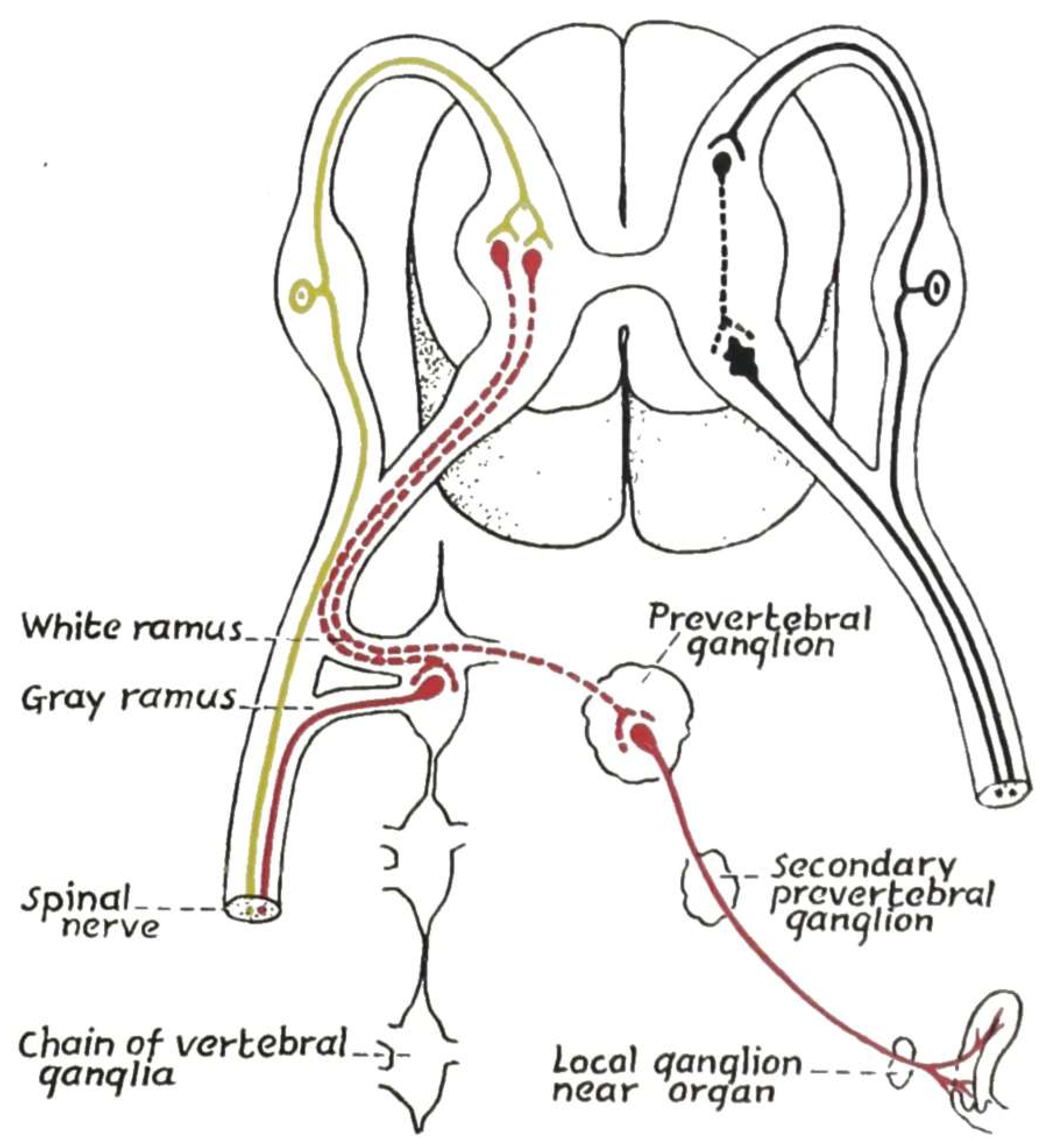


Fig. 61.

Fig. 60.—The nerve supply of the pelvic organs. The vertebral ganglia of the autonomic nervous system. (Modified from Jackson-Morris: Human Anatomy.)

Fig. 61.—Contrasting the autonomic reflex arc (in yellow and red) with the ordinary spinal nerve reflex arc (in black). (Modified from Best and Taylor: Physiological Basis of Medical Practice, Williams & Wilkins Company.)

a local ganglion near the viscus, where there is a synapsis with the viscus fiber. In each type of reflex arc the autonomic fiber extending from the cord to the synapsis ganglion is called "preganglionic," and the fiber extending from the synapsis to the organ is called "postganglionic."

It is seen then that in the thoracic portion the synapsis between the preganglionic and the postganglonic fibers takes place in a main autonomic ganglion (vertebral or prevertebral) while in the cervicosacral portions the synapsis takes place in a local ganglion near the organ innervated. The autonomic nervous system is thus divided into two parts, the thoracic portion being designated the "sympathetic" and the mesencephalic-cervical-sacral

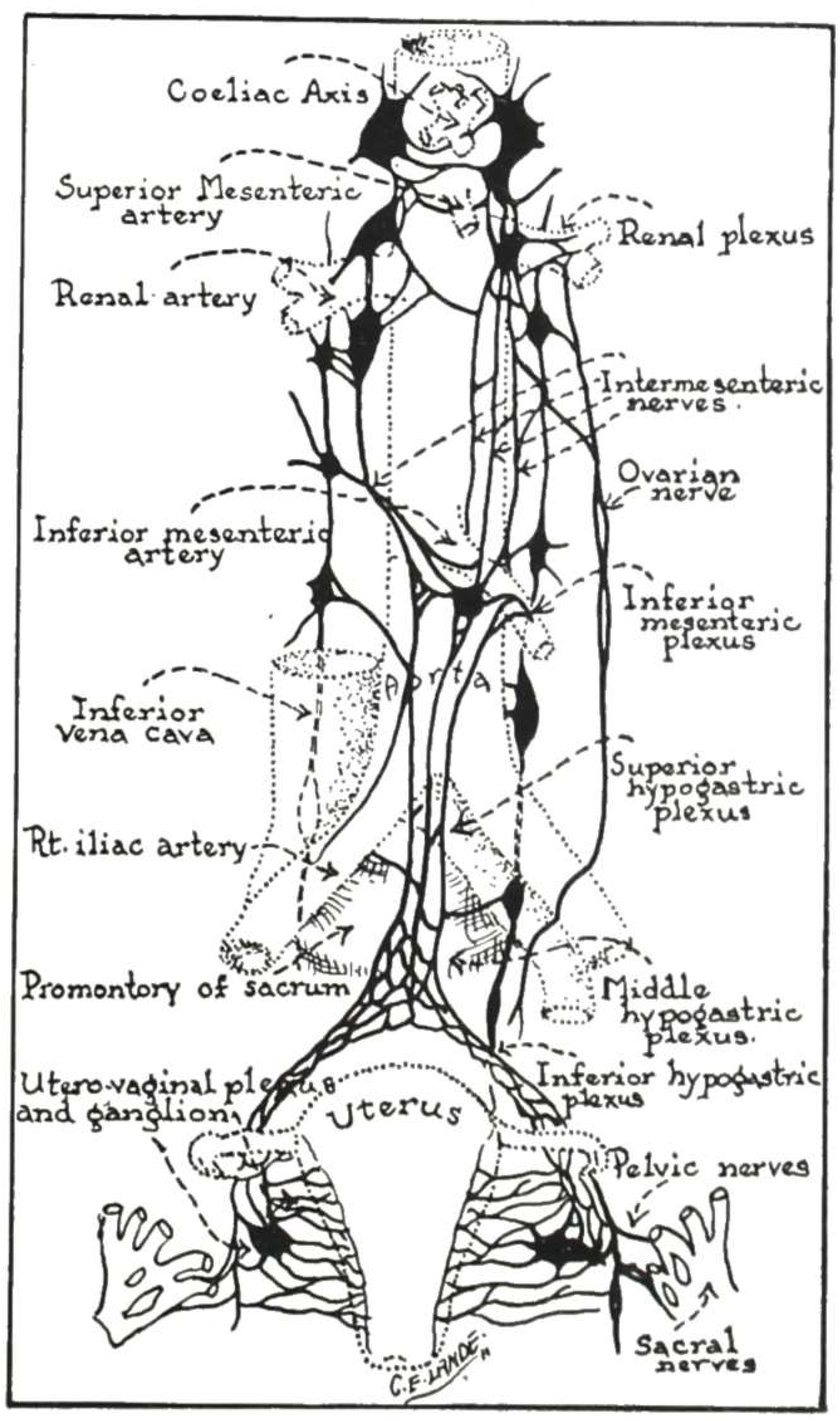
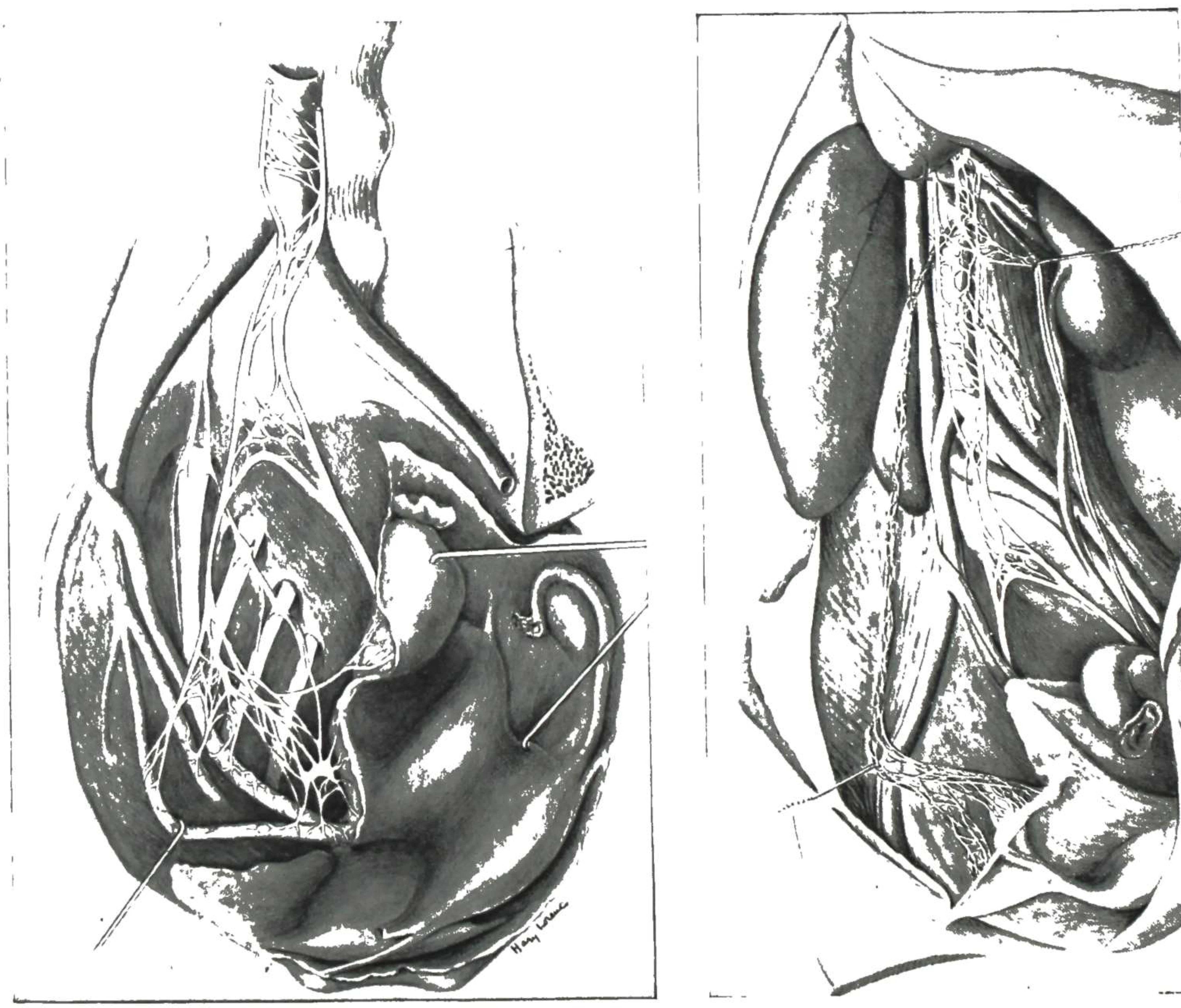


Fig. 62.—Diagrammatic illustration showing the preaortic plexuses and the extrinsic nerve supply of the uterus. (After Dhal, modified.) (From Cohen, Brown, and Gowan: Am. J. Obst. & Gynec., May, 1942.)

portion the "parasympathetic." In addition to the difference in location of the synapses, there is also a difference in function. In fact, the two parts of the system are largely antagonistic, such antagonism being necessary to adequate functioning of the organs. For example, in the pupil of the eye stimulation of the sympathetic fibers causes dilatation, and stimulation of the parasympathetic fibers causes constriction.

This same contribution to complete functioning extends throughout the body wherever two active antagonistic actions are necessary. In some situations simple action (muscular contraction or cellular functioning) and relaxation will suffice, as in skin structures. Practically all internal organs, however, are supplied with both sympathetic and parasympathetic control, the fibers extending in various directions and to various distances to reach them. For each, the preganglionic fibers are indicated by broken line and the postganglionic fibers by solid line (Fig. 64). The antagonistic actions of the two parts of the autonomic system are utilized in modern therapeutics, pharmacological experimentation having demonstrated that certain drugs stimulate the sympathetic nerves and others stimulate the parasympathetic (Fig. 65).

The nerves of the uterus are derived from the following: the aortic plexus and its branches, the superior and inferior hypogastric plexus and its branches, and branches of the sacral nerves.



A. *B.*

Fig. 63.—The nerve supply of the pelvic organs. *A*, Showing the superior hypogastric plexus and the right inferior hypogastric plexus. Showing also the extensions from the latter to the uterus and rectum. *B*, Showing the right ovarian plexus of autonomic nerves, extending along the ovarian vessels and supplying the ovary and tube. (From Labate: Surg., Gynec. & Obst.)

The motor fibers from the sympathetic system pass downward from the solar and renal plexuses into the aortic plexus. The latter forms a dense network over the aorta. At the level of the sacral promontory the fibers continue downward on each side, forming the superior hypogastric plexus which is known also as the hyogastric or presacral nerve. As the nerve fibers continue downward and laterally they form the inferior hypogastric plexus, and these in turn merge with the fibers of the pelvic plexus. The pelvic plexuses on each side terminate in the uterovaginal plexus, commonly called

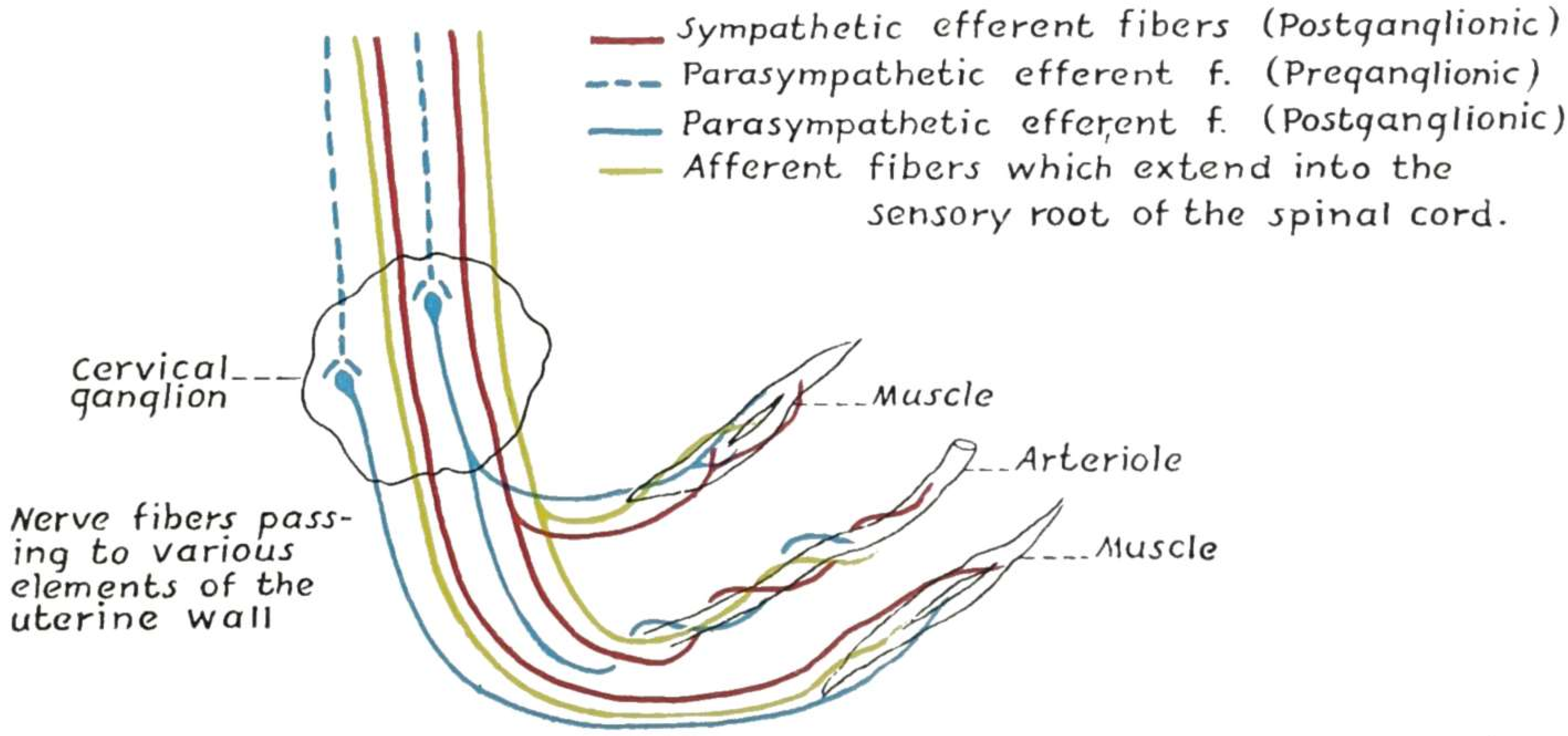


Fig. 64.—The nerve supply of the pelvic organs. Diagrammatic representation of the extensions of the autonomic and spinal nerves into the functioning areas of the uterus.

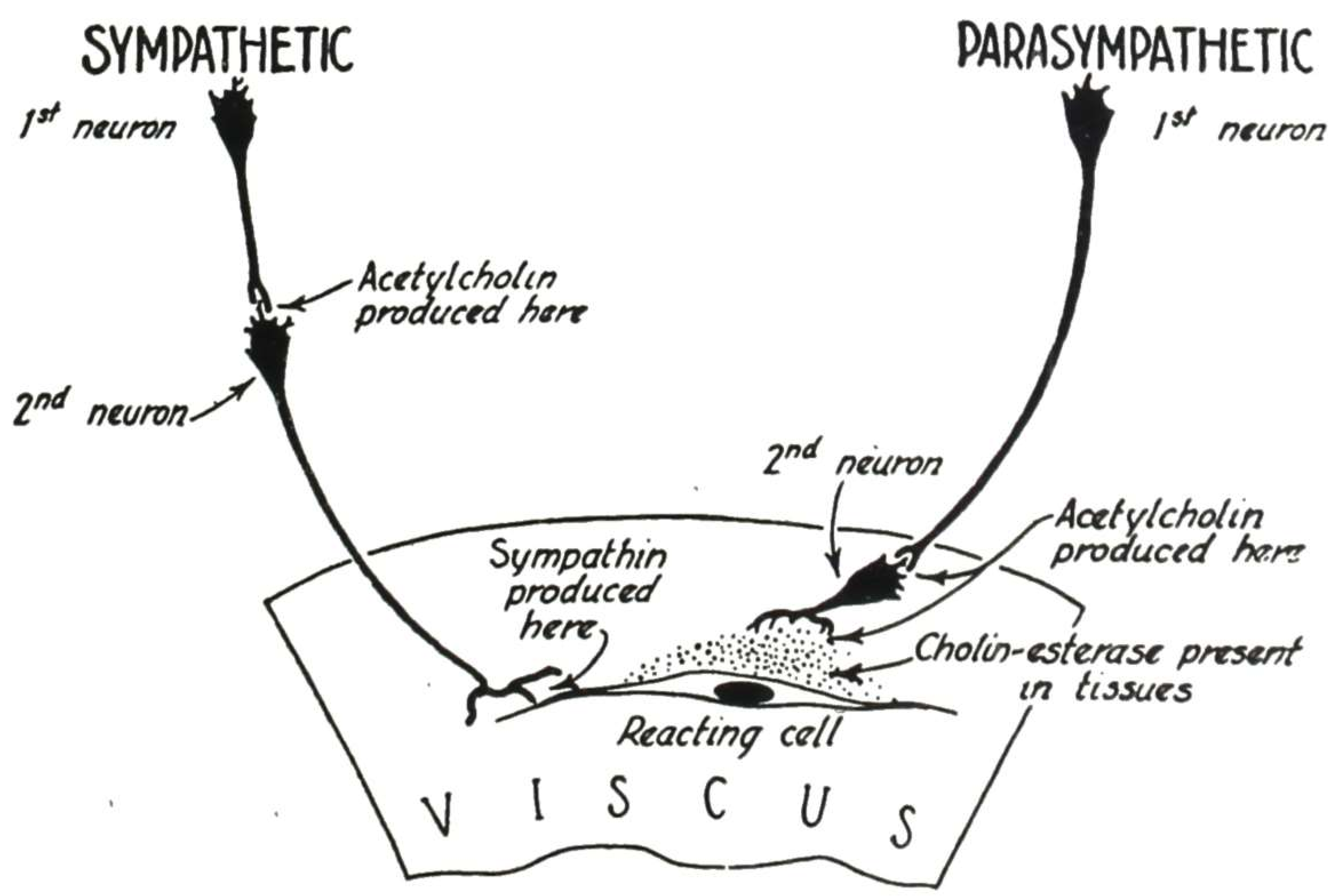


Fig. 65.—The nerve supply of the pelvic organs. The balánce between sympathetic and parasympathetic nerves and esterase. (From Myerson: J. A. M. A.)

the ganglion of Frankenhäuser, and these ganglia contain both sensory and motor fibers. These sets of plexuses comprise the chief nerve supply to the uterus, bladder, and rectum. The ovarian nerve supply comes from the aortic plexus in the region of the ovarian artery and follows the artery through the ovarian pedicle into the ovarian ganglion.

Parasympathetic fibers and additional sympathetic fibers from the pelvic plexuses also receive fibers from the anterior roots of the second, third, and fourth sacral nerves.

In spite of the detailed studies of the pelvic autonomic nervous system, its importance in pelvic function is still not well understood. We know that section of the presacral nerve will relieve pain in certain pelvic disorders, but the intricate relationship of the nerves to the mechanism of menstruation, uterine and tubal contractions, and the mechanism of childbearing is far from clear. The findings of Markee that transplanted endometrium goes through the usual menstrual changes though completely severed from its nerve supply may indicate that nervous control is indirectly mediated through the action of the autonomic system on the endocrine glands.

The importance of the minute extension of the nerves into the areas of cellular function, where nerve impulses meet endocrine or other factors which condition response, is indicated in Fig. 65. The current concepts are shown in Fig. 48.

In recent years a great deal of investigative work has been done on the mechanism of transmission of nerve impulses. There is some evidence that the nerve impulse, instead of being transmitted directly to the effector cell, releases a substance (neurohormone) which reacts on the cell, causing it to produce its characteristic effect. In an excellent review of the subject, Tainter and Luduena conclude that the sympathetic ganglionic nerve cells produce *l*-epinephrine and *l*-Arterenol; and that these neurohormones pass through the nerve trunks via neurotubules to the nerve endings. Nerve stimulation causes a release of the neurohormones to the effector cell.

PHYSIOLOGY OF THE UTERUS

The uterus has two functions: namely, menstruation and childbearing. The first is a preparation for the second. Menstruation with its various phases and associated endometrial changes will be considered here. Pregnancy and parturition belong to obstetrics.

In the years preceding puberty the endometrium develops slowly, the glands being formed by ingrowths from the surface epithelium, as shown in Fig. 66. As puberty is approached, more rapid development takes place in preparation for the change from a quiescent, fairly fixed structure to an actively functioning membrane, undergoing partial destruction and renewal every few weeks.

MENSTRUATION

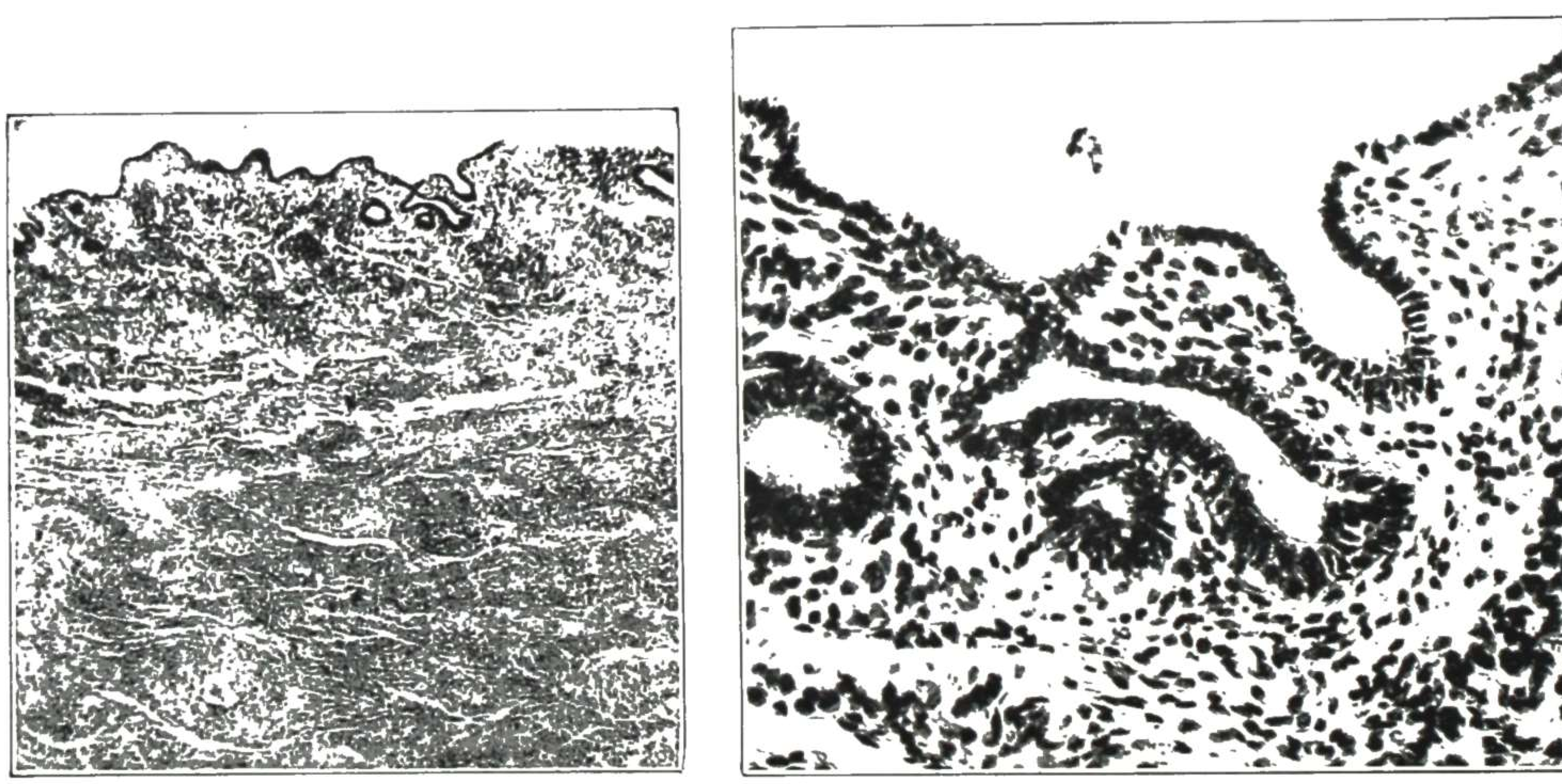
Definition

The term "menstruation" has been used in recent years by different writers to express quite different concepts. The dictionary defines it as "A periodic discharge of a sanguineous fluid from the uterus, occurring during the period of a woman's sexual activity, from puberty to the menopause." As knowledge of the mechanism of menstruation unfolded, normal menstruation came to be defined as "the bloody flow resulting from the breakdown of an endometrium normally prepared for pregnancy."

Meyer states:

"For the gynecologist, the essential feature of the whole problem revolves about fertility. This is not only important to the woman concerned, as an individual physiologic process, but is a point of great biologic significance in the broad biology of perpetuated life.

"It is in this broad field that the gynecologist acts as custodian. He must count on the relation of a true menstrual cycle and potential fertility. Only under these circumstances is there hope that the function of reproduction will be completed. This should be the thought of every gynecologist and should explain his objection to the use of the term menstruation for other processes. The term menstruation is not a meaningless word or a matter of opinion. It represents a function that carries the significance of a long historic background and has a scientifically determined, sharply circumscribed meaning, the goal of which is life.



A. B.

Fig. 66.—*A*, Microscopic section of uterine wall of child, aged eight years. *B*, Higher power of the upper central portion of *A*. Gyn. Lab.

"The whole question, then, is not a simple academic argument, but represents the clashing of two thought processes. The biologist thinks in terms of etiology and the gynecologist in terms of ultimate ends.

"The fact that experimental biology and gynecology consider the problem from entirely different angles gives rise to their opposing positions. Because the gynecologist thinks in terms of ultimate ends, he will not allow the term menstruation to stand for anything except that which has been traditional. It is the symbol of sexual maturity and potential fertility. Without corpus luteum there can be no pregravid phase, without which there is no true menstruation."

After the investigations of Corner and of Hartman, it became clear that in the normal monkey during the summer months a monthly bloody discharge occurs which is not preceded by ovulation. This type of flow also occurs in the human in early menstrual life, before the ovulatory mechanism has been established, and during the climacteric when regular ovulatory periods are ceasing. It may occur sporadically during the childbearing period.

From the above discussion it can be seen that the term menstruation is capable of several interpretations, and, unless the writer defines his meaning of the term, this leads to ambiguity and confusion. It is indeed unfortunate, for a definition should be fixed, so that the term, whenever used, would embody a clear-cut, definite idea; until such a definition is agreed upon, we will continue to use the term to denote the regular monthly flow which is preceded by ovulation and progestational endometrial changes. As stated in his portion of this chapter, Willard Allen feels that any periodic uterine bleeding, whether ovulatory or anovulatory, should be designated as menstruation.

In dealing with the subject of menstruation there must be taken into consideration the following three phenomena:

Puberty and beginning of menstruation (menarche).
Menstruation when fully established.
The menopause or cessation of menstruation.

Puberty

Puberty is the period at which the girl becomes capable of childbearing. It was formerly believed that the onset of the first flow or the *menarche* was the clinical sign of the onset of this period. The changes frequently described as puberty changes actually precede the menarche by many years.

Normally there is very little difference in the development of the general body configuration between the sexes until the child is seven or eight years of age. From then on until eighteen to twenty years of age, marked changes occur not only in growth of bone, muscle and fat distribution, but also in glands and organs of the body and in emotional and psychological reactions.

At approximately nine years of age, according to Simmons, girls begin to gain in height at an accelerating rate up to twelve or thirteen years, during which year the rate of growth is at its maximum. After this time the rate of growth decelerates rapidly and growth ceases about three years later.

During this period not only is growth evident but there is also a change in the general configuration of the body. The hips become rounded, due partly to deposition of fat and partly to a broadening of the bony pelvis. Concurrent with this the breast goes through a series of changes. At about ten years of age the areola becomes elevated, and the nipple, still undeveloped, seems to be imbedded. Over the next two years fat is deposited under the areola and it appears as a small elevated cone. During the next three or four years fat is deposited under the entire breast, and the breast itself grows, incorporating the areola so that the nipple alone protrudes above the surface.

The pubic hair begins to appear some time after the changes mentioned above, around ten to twelve years of age, and the axillary hair appears a year or two later. The pubic hair appears first above the labia and gradually spreads centrally to the pubis. In the early stages the hairs are short, sparse, and soft; during the next four years they grow larger and become wiry and more dense, so that by fourteen years of age the typical triangular female escutcheon is usually well developed.

Changes in the Pelvic Structure and Psyche.—The vulva becomes more prominent, chiefly due to deposits of fat in the labia majora, which up to this period have been perfectly flat. Fat is also increased over the pubes, resulting in the mons veneris. The tissue about the hymen becomes hypertrophic.

The vagina, which in childhood is lined by a three or four cell layer of epithelium, enlarges, and the epithelial lining gradually is converted into a multilayered epithelium, the cells of which contain glycogen. The contents of the vagina, which are alkaline (pH 7.5) in early childhood, become slightly acid (pH 4.5), and later the normal vagina flora becomes established.

The uterus doubles in length from the tenth to the eighteenth years, most of the increase being in the fundus. The relative size of the cervix also is altered. Instead of being two-thirds of the entire uterus, as in the infant, the relative size is gradually reversed so that in the adult it is one-third to one-fourth of the organ. The endometrium begins its cyclic changes, as summarized later.

There is little enlargement of the ovary, according to Scammon, up to the eighth year, when moderately steady growth occurs, until the seventeenth year, when it has attained 30 per cent of its ultimate weight. Between seventeen and twenty years of age it adds the remaining 70 per cent through extremely rapid growth.

Profound psychological changes occur during this period. Interest in the opposite sex increases, as evidenced by attention to general appearance and modesty, blushing, coquettishness, and emotional upheavals. The proper understanding and handling of these changes is most important for the future psychological development of the individual, and modern educational methods recognize the need for courses in sex education at this time of life, both for the child and her parents. This is further discussed under management of the adolescent period.

Physiologic Changes in the Endocrine Glands.—The endocrine glands responsible for growth and maturation are the thyroid, the pituitary, the adrenals, and the gonads; their interrelationships are shown in Fig. 67. The thyroid frequently shows some hypertrophy during adolescence. It is, of course, very important in epiphyseal growth and union with the diaphysis. Its general regulation of metabolism is important in its relation to the general endocrine system.

According to Nathanson, Towne, and Aub, small amounts of estrogen are secreted from three to seven years of age, probably from the adrenal cortex. At about the age of eight, through some as yet unknown stimulus, the anterior lobe of the pituitary gland begins to increase its output of the adrenotrophic and gonadotrophic hormones. During this early period of secretion the chief component of the gonadotrophic hormone is the follicle-stimulating hormone (FSH). From the eighth to the tenth year there is a steady increase in the amount of estrogen in the blood. This estrogen causes the development of the various bodily changes known as the secondary sex characteristics. The estrogen produced up to this age is chiefly from the adrenal gland, as the ovarian follicles have not yet begun to secrete estrogen. In the average girl, sometime between the tenth and eleventh year the ovaries have matured sufficiently to respond to the pituitary FSH and the ovarian spiral arterioles have developed, and this causes the onset of follicular development and function. Up until this time there has been a constant and steady increase of the adrenal estrogen, but with the production of the ovarian estrogen the blood levels show cyclic changes with wide differences between the maximum and minimum amounts present. The additional ovarian estrogen stimulates growth and development of the uterus until it reaches the stage when it begins to react cyclically to the estrogenic stimulation. When the peak of the blood estrogen is high enough so that its withdrawal results in endometrial breakdown and bleeding, the first period, or menarche, occurs. The average age at which this first bleeding appears is between twelve and one-half and thirteen and one-half years, but this varies somewhat with climate, race, and socioeconomic conditions. In some otherwise normal girls it occasionally starts as early as six or as late as eighteen.

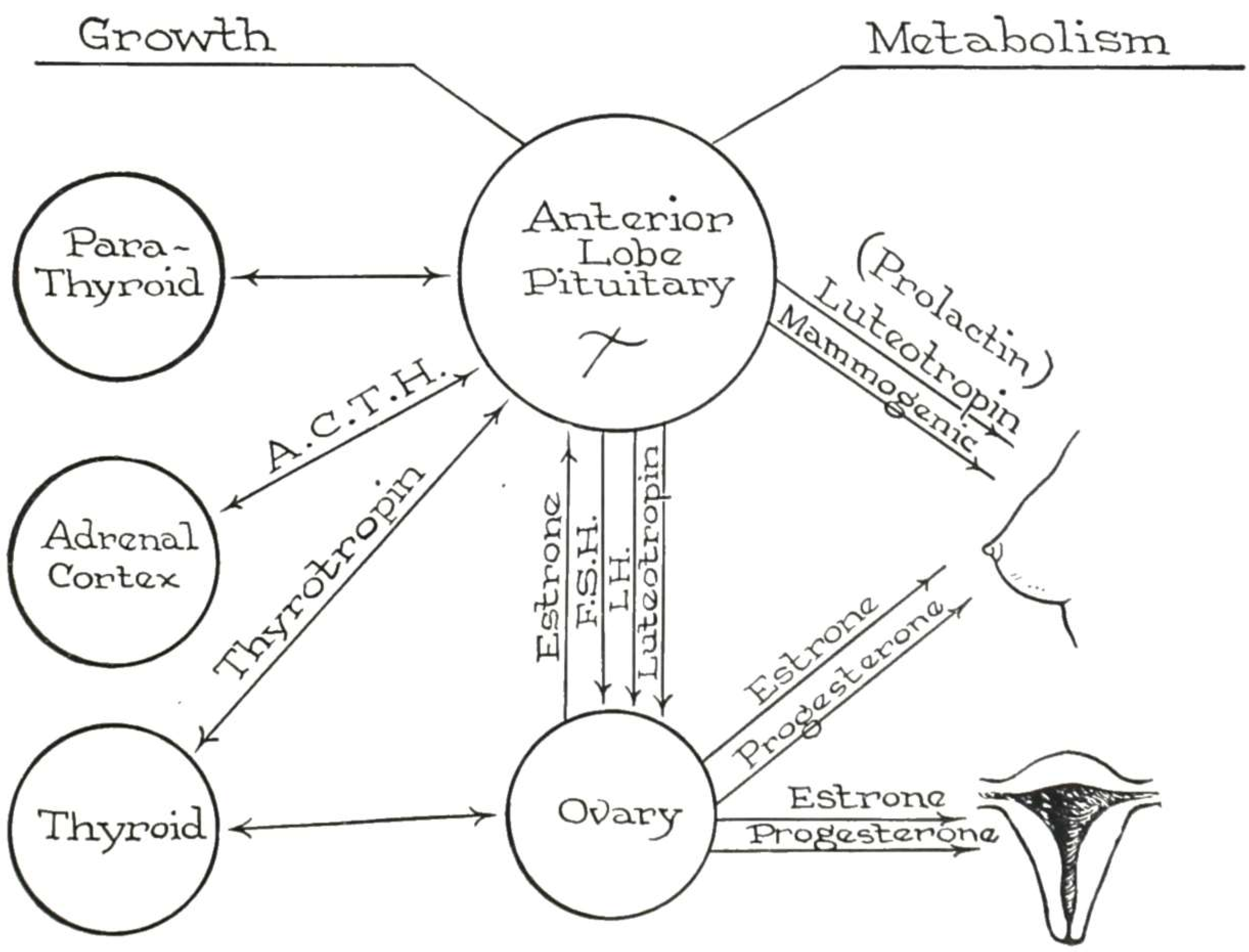


Fig. 67.—Chart showing some of the anterior pituitary hormones with their actions and interrelationships. All of these are either directly or indirectly concerned with pelvic function.

The early cycles are of the anovulatory type and these continue until the ovulatory mechanism begins to function. The evidence derived from a study made by Mills and Ogle on groups in which sexual promiscuity is frequent indicated that the lag between the menarche and pregnancy (hence ovulation) was several years. They found that pregnancy was extremely unlikely during the first year after the menarche and that, although pregnancy may occur earlier, it seldom does before the age of sixteen regardless of the age at which the first period occurred. Hence it is clear that the true ovulatory menstruation, with its desquamation of a previously prepared progestational endometrium, occurs only after the ovary has matured sufficiently to respond to both factors of the gonadotrophic hormone, namely FHS and LH (luteinizing hormone).

From this summary it is evident that there is a need to revise our ideas of the term puberty. Stuart suggested dropping the term entirely because of its indefinite connotation. In its place he suggests that the changes covered by the term adolescence (process of growing from childhood to womanhood) be divided into the prepubescent, pubescent, and postpubescent periods.

In the prepubescent period, from three to eight years of age, there is little difference between the sexes in build or development. The pubescent period extends from eight to sixteen years, and during this time the secondary sex characteristics develop and the sexual organs mature and begin to function. Menarche is merely one of the many outward signs of sexual development. The postpubescent period of adolescence extends from approximately sixteen to twenty years, during which the girl becomes a fully matured woman physically and psychologically. The upper limit of this period varies but is usually about twenty years.

The menarche may occur in normal girls as early as six years or as late as eighteen years of age, but the average in the United States is twelve and one-half to thirteen and one-half years of age. The time of occurrence of this first period is affected by the heredity, constitution, and environment of the individual. Those whose mothers have had a late or early onset of the menses tend to follow the same pattern. The **constitution** of the individual, as affected by diet, economic status, and disease, is probably the most important factor. Previous poor health and disease affect not only the physical development but also the endocrine development and function. During wars when large areas of the population live on subsustenance diets, not only is the menarche delayed, but women in the childbearing period have long periods of amenorrhea. Experimentally Allen and Stevens found that in guinea pigs kept on diets adequate in all essential elements but deficient in caloric value, definite changes occurred in the pituitary-ovarian mechanism. The changes which occurred in the ovary were reversible.

The general endocrine balance and the estrogen-androgen balance, in particular, play an important role in the menarche. Bayer found that girls with a normal feminine build menstruate earlier than those with a hyper- or hypofeminine build.

Environmental effects are evidenced by the fact that city dwellers usually menstruate earlier than girls raised in rural areas. Climate, though not as important as formerly supposed, has been found by Mills to exert some effect. In children reared in regions of depressing, moist heat, both growth and the menarche were delayed when compared with children raised in temperate climates. An interesting seasonal variation in the menarche was noted by Engle and Shelesnyak; they found that 82 per cent of the menarches occurred in the period from September to June.

The importance of **race** was investigated by Michelson. In a study of white and Negro girls he concluded that socioeconomic circumstances were much more important than race in the differences found. Similar conclusions were reached by Schaeffer in a study of Gentiles and Jewesses; hence, race is probably not a significant factor in the variations in the onset of the menarche.

Management of the Adolescent Period.—General hygienic measures at this period of life include plenty of rest, exercise, balanced diet, and protection from emotional strain whenever possible. In some cases a heavy school schedule, in addition to the psychological and emotional changes incident to this period, is sufficient to cause a so-called nervous breakdown. The significance of menstruation should be explained to the child before she experiences her first period so that she will know what to expect. Clow emphasizes the importance of avoiding such terms as "the curse," "unwell," and others denoting that the period is a "sick time," for these place the wrong psychological interpretation on a normal process. Clow also demonstrated the value of moderate exercise, warm baths, and proper mental attitude in the management of dysmenorrhea.

The question concerning the use of menstrual tampon is frequently asked by mothers of young girls. Since its introduction some twenty years ago its use for menstrual protection has become generally accepted in older women. Numerous studies have shown it to be effective and harmless in women in whom there is no pathologic condition such as chronic cervicitis which would contraindicate its use. In young girls the external pad is certainly preferable and it has been our practice to advise this method at least until the child reaches college age. Another question frequently asked concerns swimming. This, like many other taboos connected with menstruation, has been found by Thwing to be harmless except in rare incidences. In the majority of her cases she found no change in the interval, amount of flow, or length of flow, nor did it increase the incidence of dysmenorrhea. We feel that it is better to avoid very cold water and also to avoid swimming while the flow is heavy.

Menstruation

The menstrual discharge is about one-half to three-fourths blood, mixed with epithelium from the uterus and vagina. It is dark and rather viscid or stringy, probably due to the admixture with the cervical mucus. The odor usually present is due to the decomposition occurring in the vagina; menstrual blood taken from the uterine cavity is odorless.

Though no anticlotting enzyme has been isolated, normal menstrual blood does not clot. In an investigation of this peculiarity of menstrual blood, Glueck and Mirsky found that menstrual blood does not contain detectable amounts of fibrinogen, prothrombin, thrombin, or anticoagulants. They suggest that the blood leaving the endometrium clots, and then by some unknown lytic agent the clot undergoes digestion. With excessive flow the rate of lysis is not sufficient to prevent the expulsion of undigested clots. Such fibrinolytic activity has been demonstrated by Huggins and Davis and by Page and his associates.

Certain chemical substances have been recovered from menstrual blood. Calcium approximates the amount found in normal blood; the arsenic content is higher than that found in the circulating blood as is the nonprotein and amino nitrogen; estrogen is five times the concentration of that found in venous blood.

Macht, twenty-five years ago, described a menotoxin which he found in the menstrual discharge, blood, milk, and sweat of women at the menstrual period. He demonstrated its effect, by phytopharmacological methods, on the growth of *Lupinus albus* seedlings. In a recent paper he reports that he confirmed his original finding, namely that the substance is closely related pharmacologically and chemically to cholesterol and oxycholesterol and to female sex hormones. George Van S. and Olive Smith have isolated a tissue destroying euglobin in the menstrual discharge which even in minute doses is lethal to experimental animals. In addition to the euglobin they also isolated a fibrinolysin and a protective pseudoglobin. The pseudoglobin was different in chemical structure from both the toxin and the fibrinolysin. The Smiths feel that this menotoxin is identical with necrosin, a substance isolated by Menkin from inflammatory exudates in dogs. Both produce edema and capillary damage. The importance of this menotoxin in the mechanism of menstruation is discussed later.

With the many enzymes, hormones, vitamins, and other substances such as proteins, fats, and carbohydrates known to be present in the endometrium, it is evident that though not specifically isolated many of these must be present in the menstrual discharge.

The *amount* of blood lost at each menstruation varies greatly in different individuals. Barer and his associates found the blood loss in 100 women by extracting blood from pads and analyzing iron content. They concluded that the average loss is 23 to 68 c.c., and the extremes 7 to 179 c.c. The rate of flow (i.e., whether or not the flow is too free) is estimated usually by the frequency with which the napkins have to be changed. The usual flow requires a change about three times daily during the height of the menstruation. If more frequent changing is necessary, the flow is too free.

There is considerable variation in the duration of the menstrual flow, the average being three to four days. Some perfectly healthy women, however, menstruate only one or two days and others six or seven days. The scanty menstruation or the profuse menstruation, as the case may be, seems to be normal for that particular individual. The duration of the flow in the same individual is about the same at the different periods.

Statistics on the periodicity have shown it to be irregular even in the same person. The average time is reckoned as about twenty-eight days. The cycle is counted as beginning with the first day of flow. Arey made a study of 20,000 calendar records from 1,500 individuals of many races and varied ages. He found that an average woman must expect one-third of her menstrual cycles to depart more than two days from her mean cycle length. The mean cycle length, based on individual averages, was 33.6 days for girls and 29.5 for women. In no instance did perfect menstrual regularity appear over any significant period of time, though many women had previously believed themselves the acme of regularity.

Rock analyzed 600 cycles in young fertile women and found only 16.5 per cent beyond the range of twenty-four to thirty-two days. He considered menstruation to be abnormal if it occurred habitually beyond these limits. Haman's statistics based on 2,450 cycles in normal women agree closely with Rock's figures, as do those of Hamblen which were based on a very careful study of 109 normally ovulating women. Hamblen feels that the statement made by Fraenkel that "the only regular feature of menstruation is its irregularity," is unjustified, and that true ovulatory menstruation is not an erratic phenomenon.

Menstruation ceases during pregnancy and lactation. Exceptions to this rule are frequent. A few women menstruate for one or two periods after conception, and very often the menses return while a woman is still nursing her child.

The principal physiologic significance of menstruation is that it is a preparation of the uterus for the reception of a fertilized ovum. Why the phenomena, breakdown and casting off of the endometrium with bleeding, occur only in the human being and certain primates is still not known. It is probable, as mentioned by Stowe, that the phenomenon of menstruation occurs only in those animals which do not have channels in the endometrium through which the tissue catabolites can be carried away rapidly enough to prevent further destruction of the endometrium. The lack of demonstrable lymphatics in the human endometrium fits in with this explanation.

Endometrial Changes

The relations of the cyclic endometrial changes to follicle-maturing and ovulation and corpus luteum formation are shown in Figs. 68 and 69. The microscopic details characterizing the different stages of the menstrual cycle are shown by actual photomicrographs with explanatory drawings in Figs. 70 to 80.

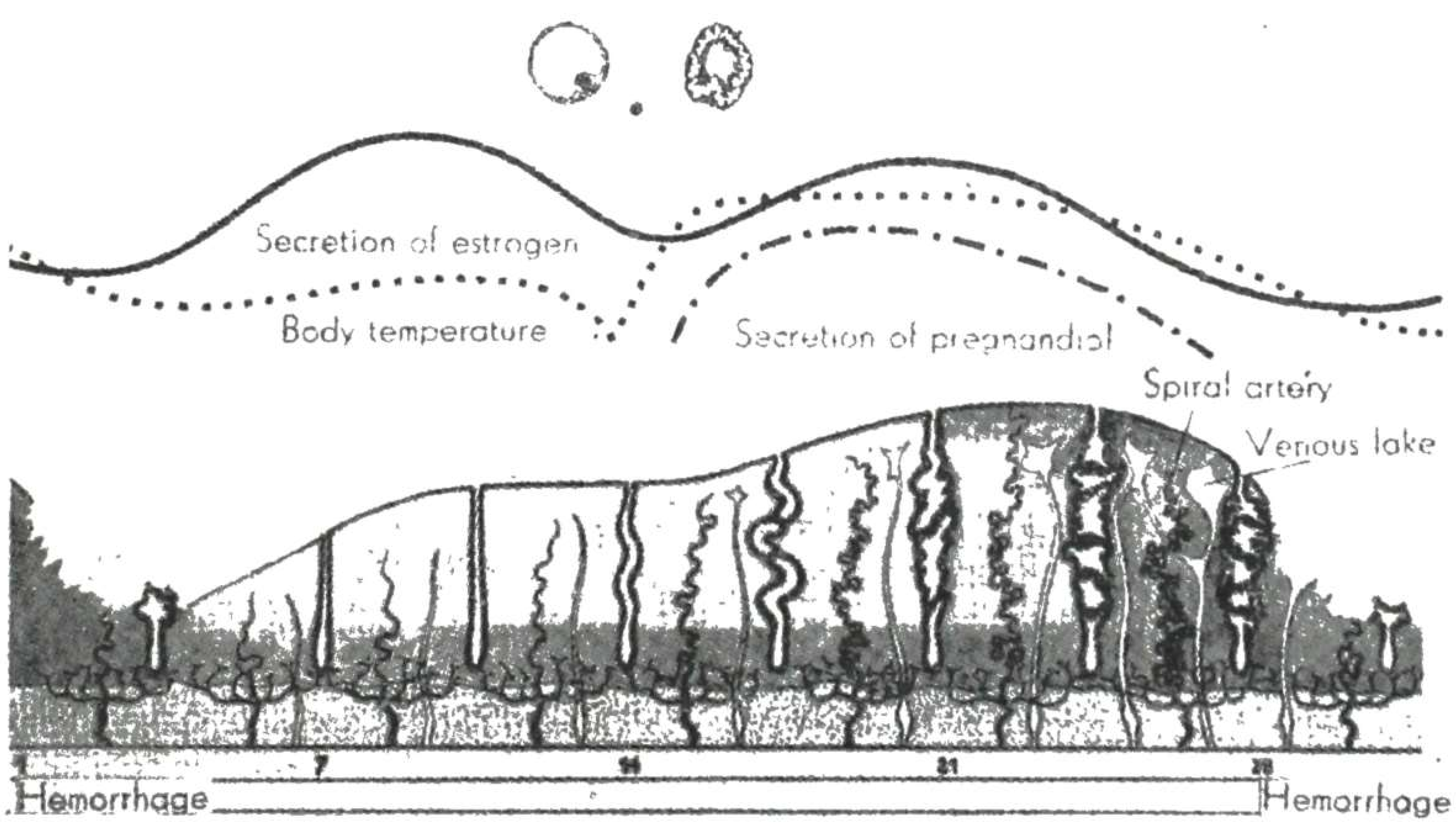


Fig. 68.—Diagram of the cyclic changes of the endometrium. The glands are bordered in black, the venous system is white, and the arteries are black. (From Ober: Geburtsh. & Frauenh., 1949.)

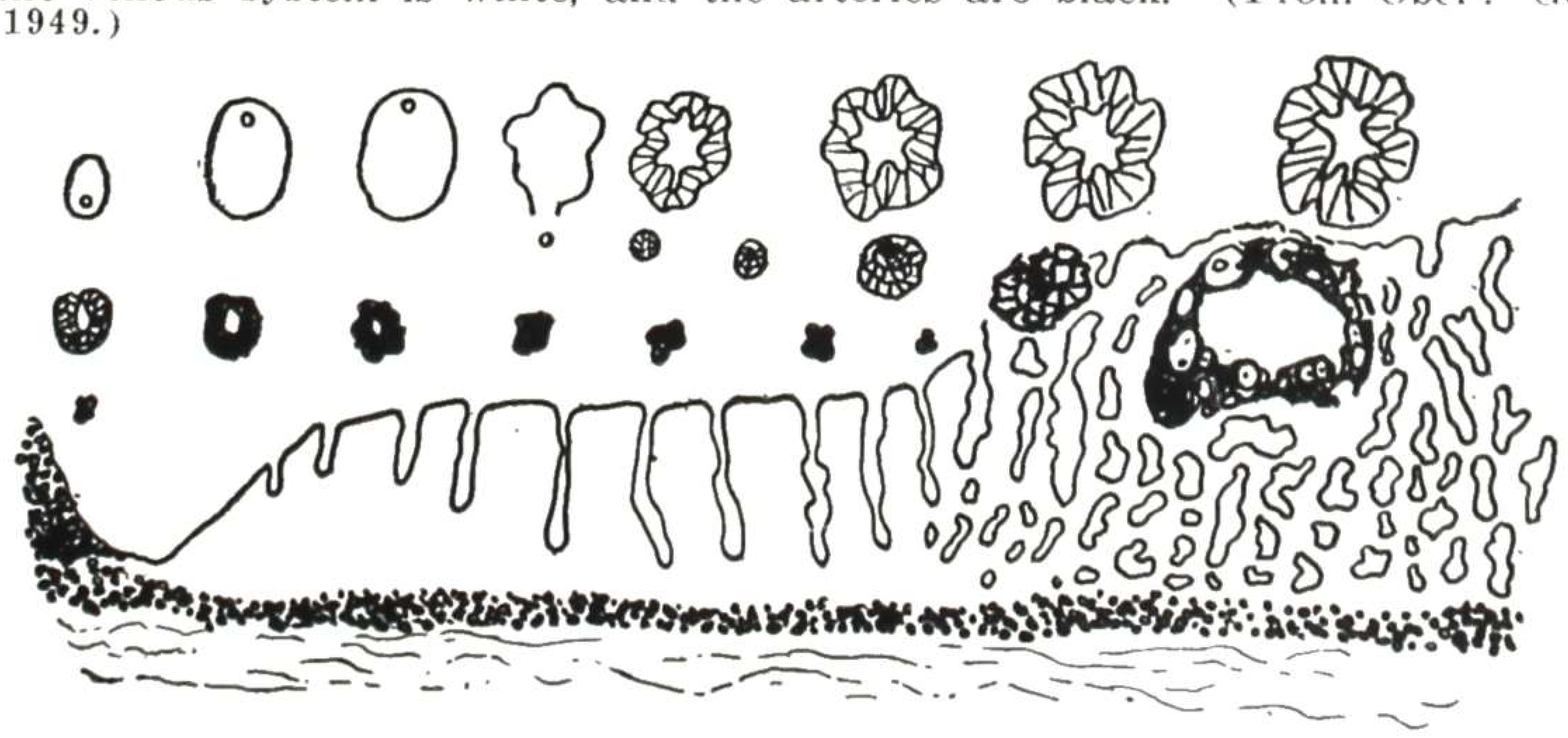


Fig. 69.—This represents the events occurring when pregnancy ensues. Ovum embedded, decidua formed, and corpus luteum enlarged and active. (After Schröder.)

The changes occurring in the endometrium during the menstrual cycle are so complex that for the sake of clarity it seems wise to discuss them under three main headings: Cyclic Glandular and Stromal Changes; Cyclic Arteriole and Venous Changes; and Cyclic Histochemical Changes. There will necessarily be some overlapping in the various descriptions.

In regard to designations for the stages of the cycle, understanding of the terms will be aided by keeping in mind that they refer primarily to changes in the endometrium. Ovarian changes and influences which accompany the endometrial "stages" are mentioned as "phases" in order to avoid the confusion which has resulted from the mixture and haphazard use of two sets of terms, one based on the endometrium and the other on the ovary. It must be kept in mind also that the time limits of the "phases" and "stages" are different, and hence that the imposing of one on the other is practicable in only a general way. For example, the luteal phase of ovarian influence on the endometrium is manifest in both the late growth stage and the premenstrual stage, but the endometrial picture in the latter is so different from the former that it constitutes a separate stage.

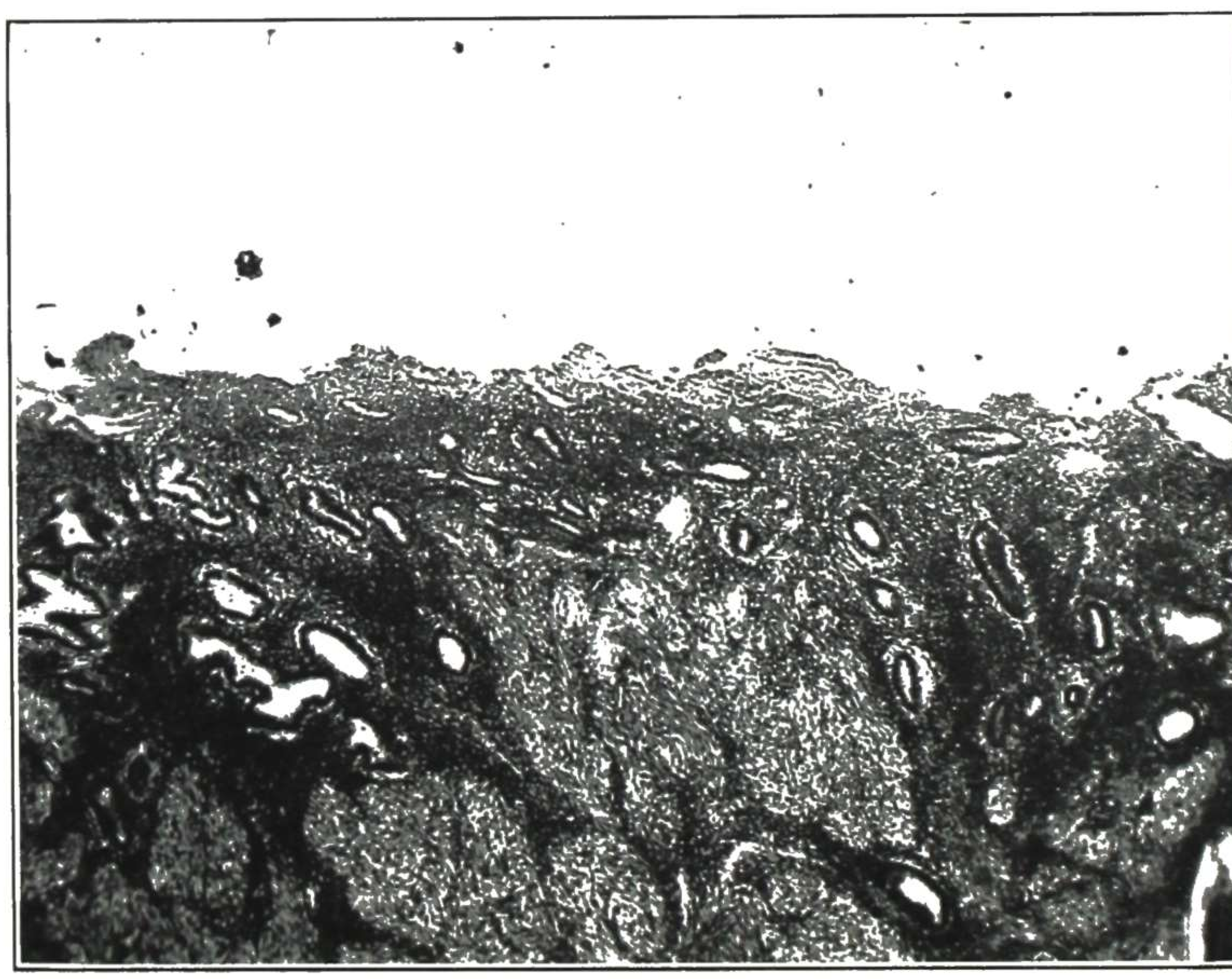


Fig. 70.—Endometrium at early growth stage. The breaking down of the endometrium is completed and the menstrual flow is well established. Probably the second or third day of menstruation. Gyn Lab.

Another item is that the stages have only one point of coincidence with the menstrual flow, and that is that the beginning of the flow marks the breakdown which ends the premenstrual stage and inaugurates the next cycle of growth. Hence the "menstrual stage" has no relation to the length of flow but only to its beginning. The end of the flow determines no particular change in the endometrium; hence there is no occasion for the term "postmenstrual stage." The term "interval stage" also has been outgrown, for we know now that there is continuous growth from one breakdown to the next and consequently no resting or "interval" stage as formerly supposed.

The terms used in describing the stages of endometrial change are as follows: early growth stage (follicular phase), late growth stage (luteal phase), premenstrual stage, menstrual stage (breakdown). The breakdown is a piecemeal affair, still continuing in some parts of the endometrium while growth is advancing in other parts. However, as the classification is based on growth, and as regeneration starts with the breakdown (first day of flow), the early growth is counted as beginning at that time, though some days are required for the development of typical features.

Cyclic Glandular and Stromal Changes.—

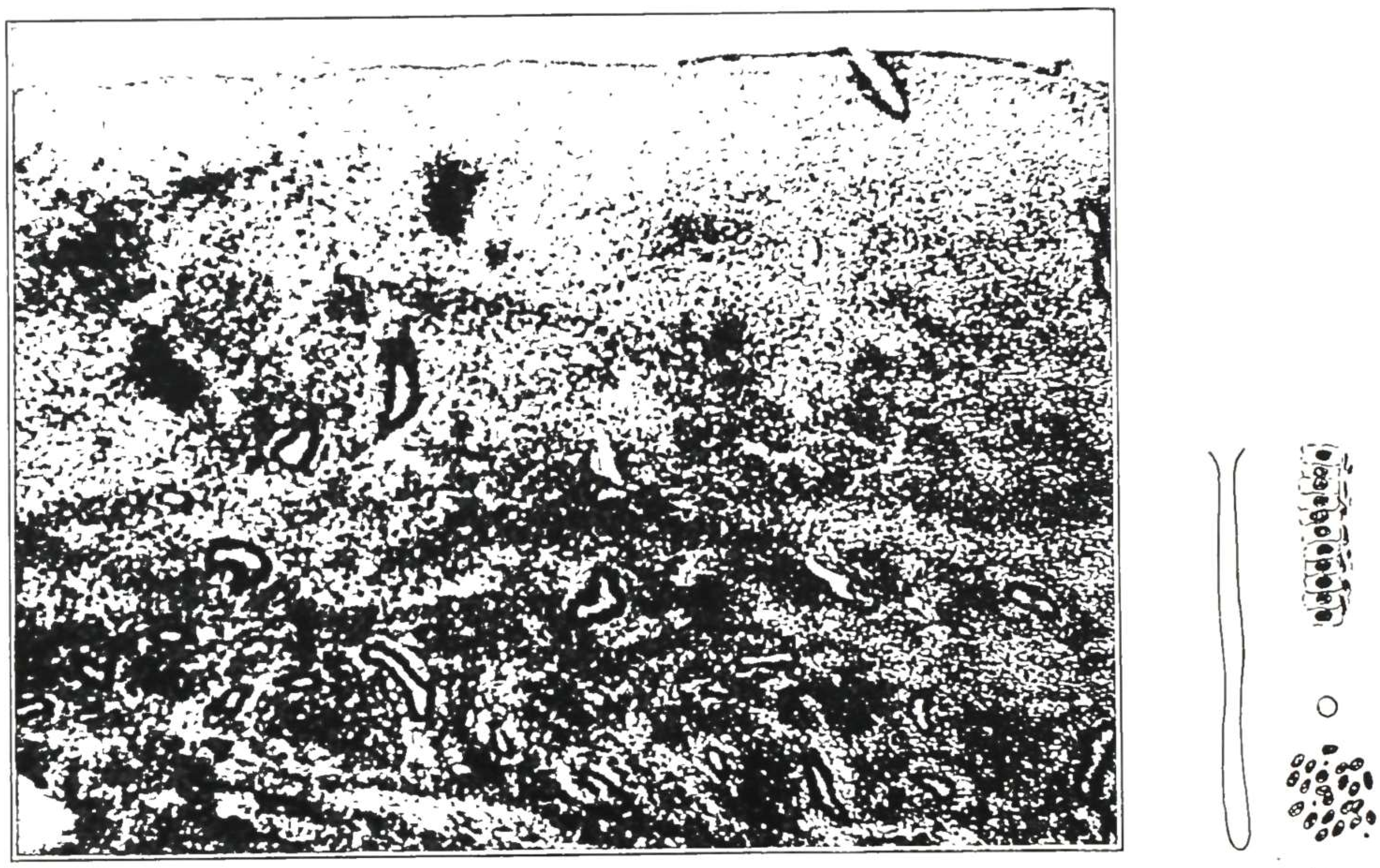
EARLY GROWTH STAGE ("FOLLICULAR PHASE").—The microscopic characteristics of this stage are shown in Figs. 71 and 72. Campbell, Lendrum, and Sevringhaus, in describing the cycle, speak of a period of tissue loss (comprising the first day or two of bleeding), a period of re-epithelization (two days), and a pre-ovulatory "proliferative" period (ten to twelve days) in which the follicular hormone effect becomes fully developed. Markee designates the first ten days as the "rest" period.

In the early growth stage the growth is due chiefly to the action of estrone. By the end of the first week of this period there has been rapid growth of the endometrium, which becomes greatly thickened and somewhat edematous. There are numerous mitotic figures in the stroma and glandular epithelium. The straight glands become elongated but the lumen is still round and regular, as shown in Figs. 71 and 72. The epithelial cells lining the glands are inactive as far as secretion is concerned and the nuclei are still basal, and no glycogen or mucin is present. Small granules are seen in the nucleus and cytoplasm of the glandular epithelium, indicating early enzyme activity. In the early part of this stage the interstitial tissue of the stroma is dense, but later it becomes progressively looser as the intracellular fluid appears.

LATE GROWTH STAGE ("LUTEAL PHASE").—The typical features of this stage are shown in Figs. 73 to 78. In this latter part of the period of growth, after ovulation and corpus luteum formation, the influence of progesterone on the endometrium becomes manifest. Evidence of this progesterone effect is that the nuclei in the glandular epithelium are pushed from their basal position toward the center by masses of glycogen, leaving a clear area between the base of the cell and the nucleus. This change starts at the mouth of the gland and proceeds toward the deeper portion, but leaves the deep end unaffected.

The epithelial cells lining the glands become taller and taller and there is a decrease in the number of mitotic figures, and in two days the glycogen begins to migrate toward the lumen end of the cells. The position of these masses of glycogen can be clearly shown by special staining. Soon they appear as protrusions of the cells into the lumen of the glands, preparatory to the secretion of the glycogen into the lumen. This projection of glycogen from the cell ends gives a ragged frayed appearance, characteristic of this process and shown well in Fig. 76. The nucleus becomes basal after full secretion starts. Mucin appears in the lumen later than the glycogen, and it has never been found within the secreting cells. As the glands grow in this stage they become coiled and tortuous and irregular, as shown in the illustrations.

PREMENSTRUAL STAGE.—In this stage there is a marked increase in the tortuosity of the glands and rapid growth of their epithelial lining. This rapid epithelial growth causes crowding, hence tufts of cells are pushed into the glandular lumen, giving the typical "saw-tooth" appearance, as shown in Figs. 77 and 78.

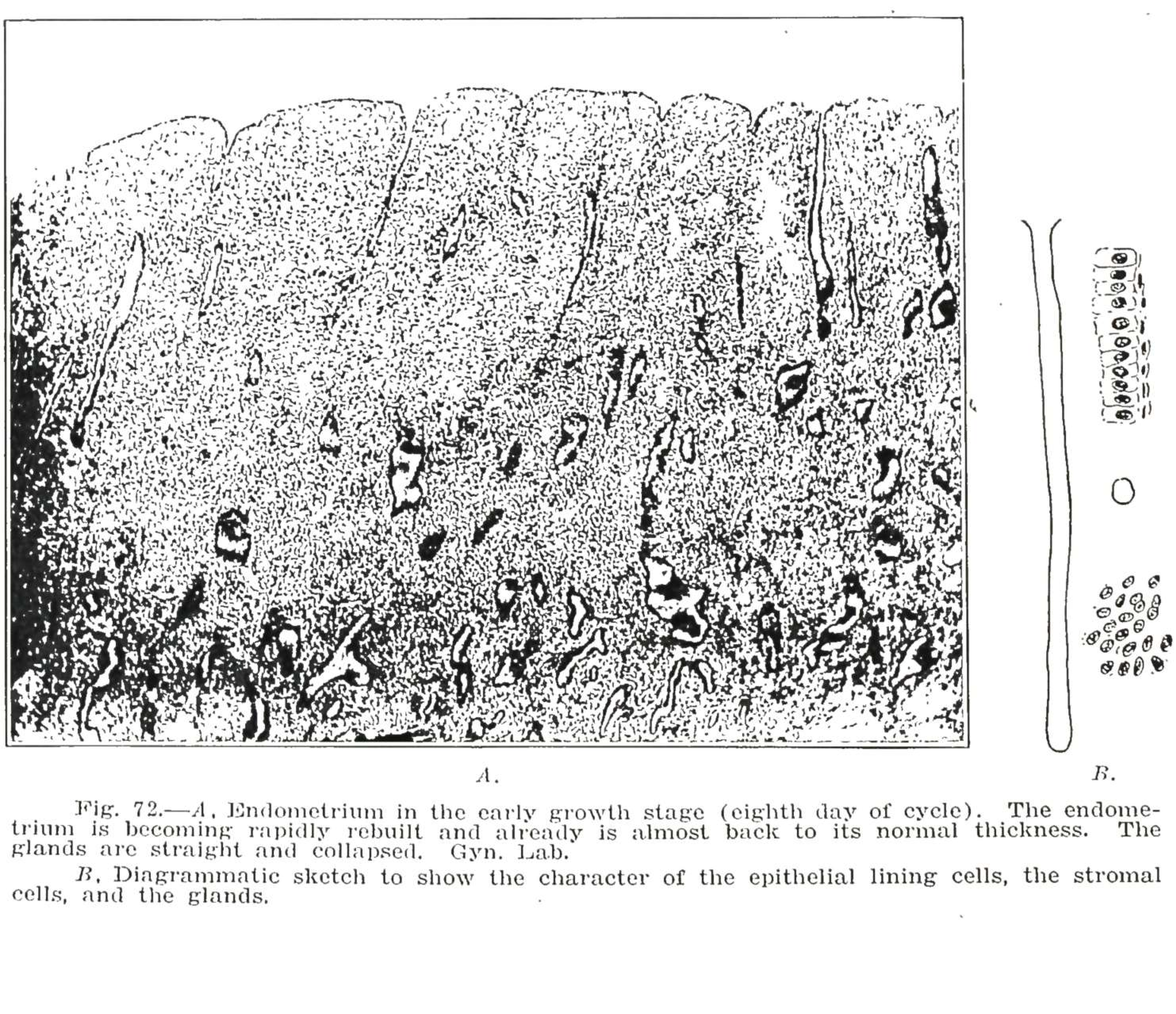


A. *B.*

Fig. 71.—*A*, Early growth stage a little later than Fig. 70. Note the beginning regeneration of the surface epithelium at the right upper corner. Gyn. Lab.

B, Showing the general character of the glands, short, straight, narrow, with a round lumen. The lining cells are cuboidal with central nuclei. The stromal cells are closely packed, with very little cytoplasm.

The detailed diagrammatic drawings in Fig. 71, *B* and also those in Figs. 72, *B*, 73, *B*, and 77, *B* are modified from drawings by Novak (Am. J. Obst. & Gynec.) whose studies and writings have greatly assisted in the classification of these complicated endometrial changes.

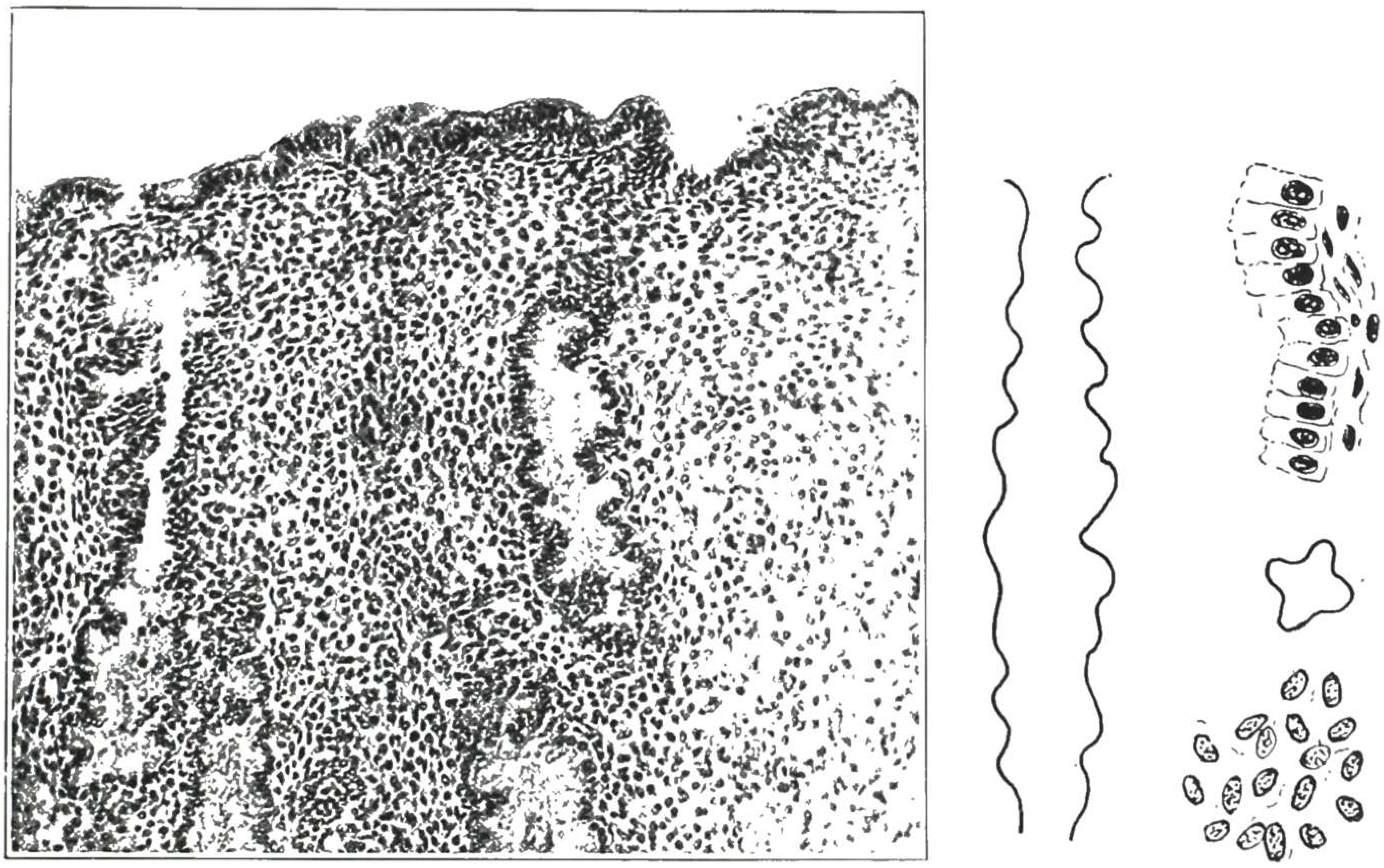


A. *B.*

Fig. 72.—*A*, Endometrium in the early growth stage (eighth day of cycle). The endometrium is becoming rapidly rebuilt and already is almost back to its normal thickness. The glands are straight and collapsed. Gyn. Lab.

B, Diagrammatic sketch to show the character of the epithelial lining cells, the stromal cells, and the glands.

In the middle portion of the endometrium the growth and tortuosity of the glands are so marked that the stromal cells are forced toward the surface, forming there a compact layer. By this process the endometrium becomes divided into three zones: the superficial "zona compacta," where the stroma



A. *B.*

Fig. 73.—*A*, Endometrium in the late growth phase. (Twelve to twenty-five days after the first day.) The endometrium is back to its normal height. The glands are beginning to become tortuous and they are filling with secretion. The stromal cells, particularly those near the surface, are increased in size and varied in shape. These are due to the beginning action of progestin, secreted by the corpus luteum since the time of ovulation. Gyn. Lab.

B, Diagram showing the characteristics of the late growth stage. Irregular gland becoming dilated with secretion, epithelial cells lining the gland are enlarged and secreting, stroma cells enlarged.

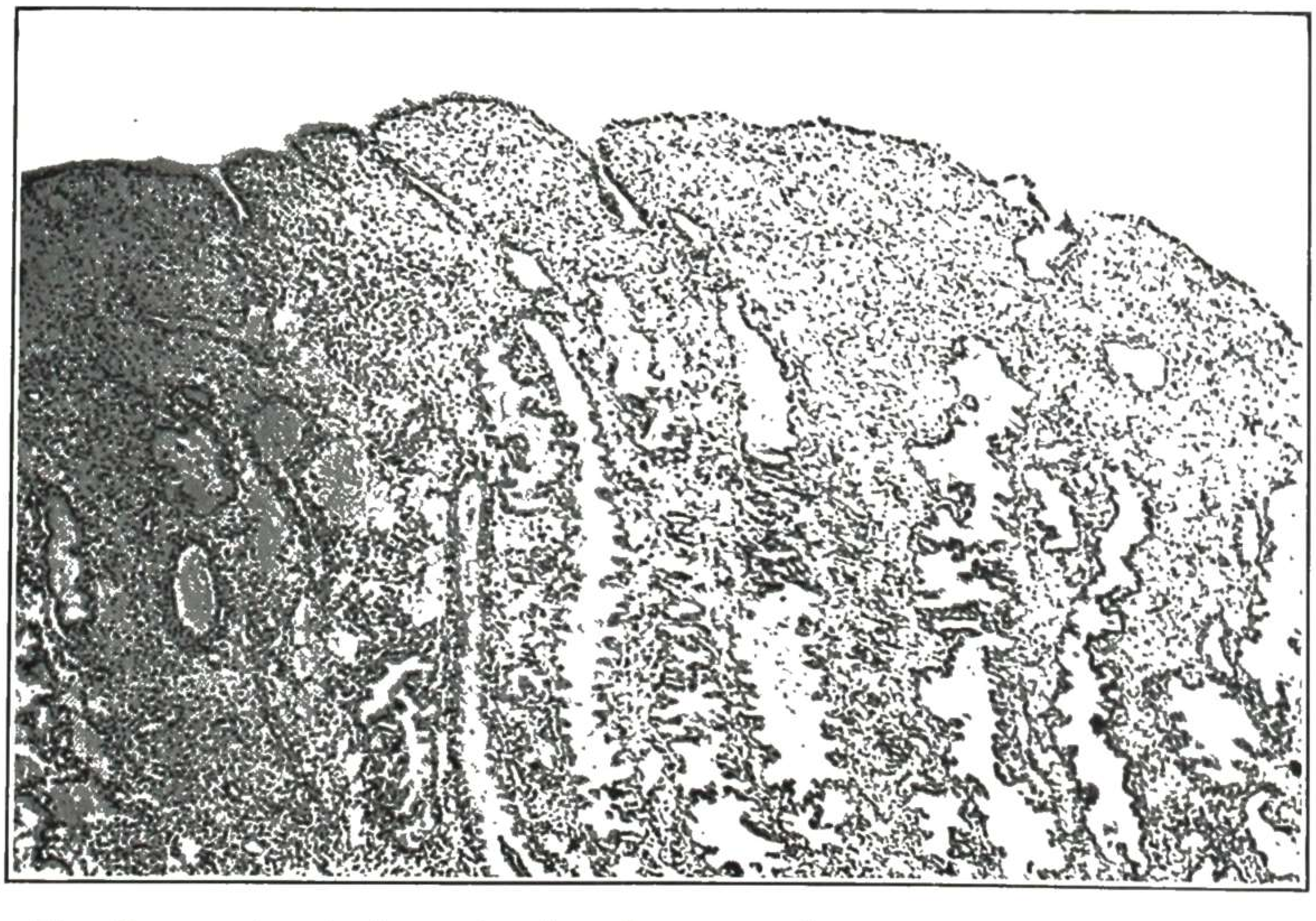
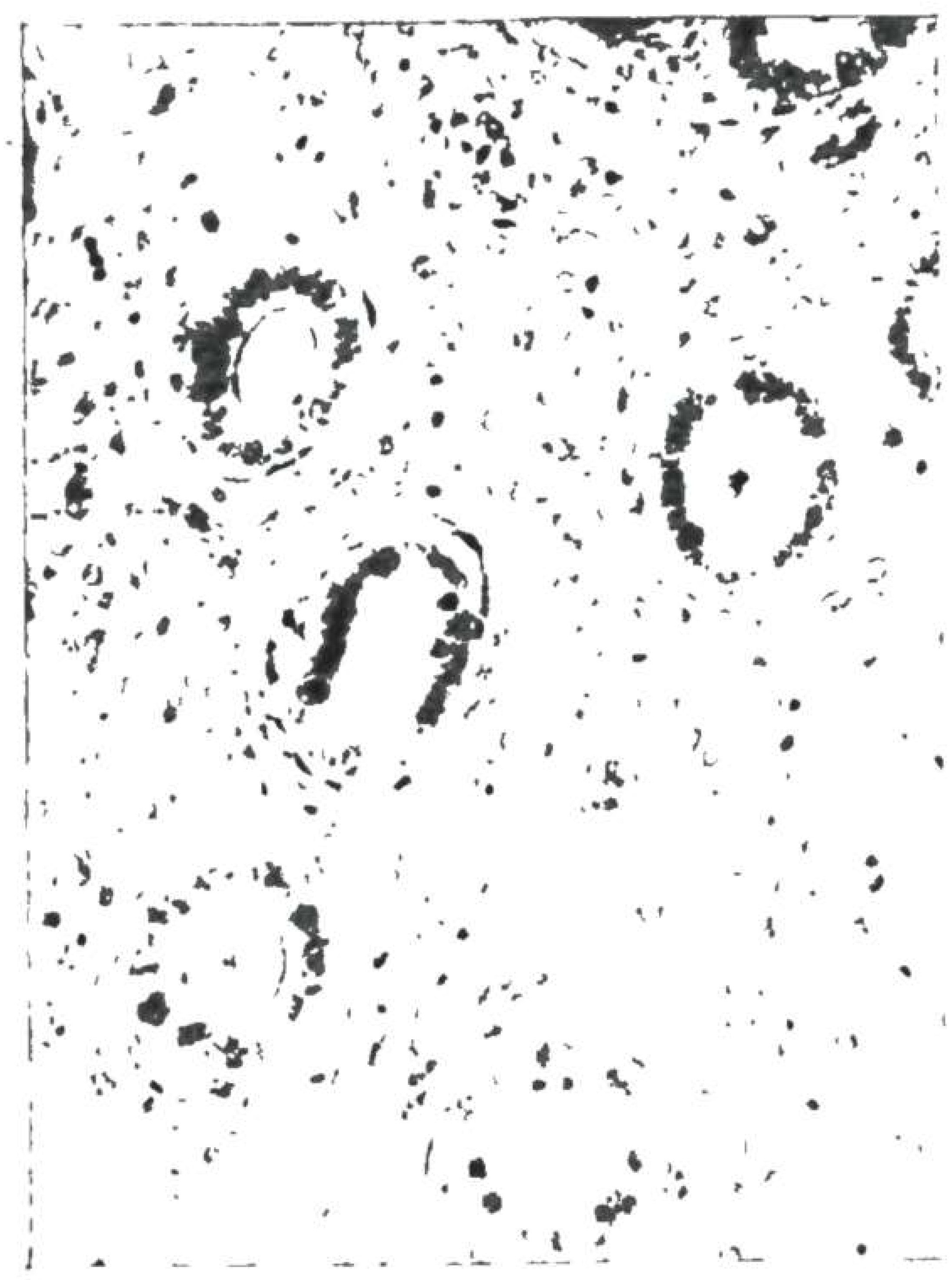
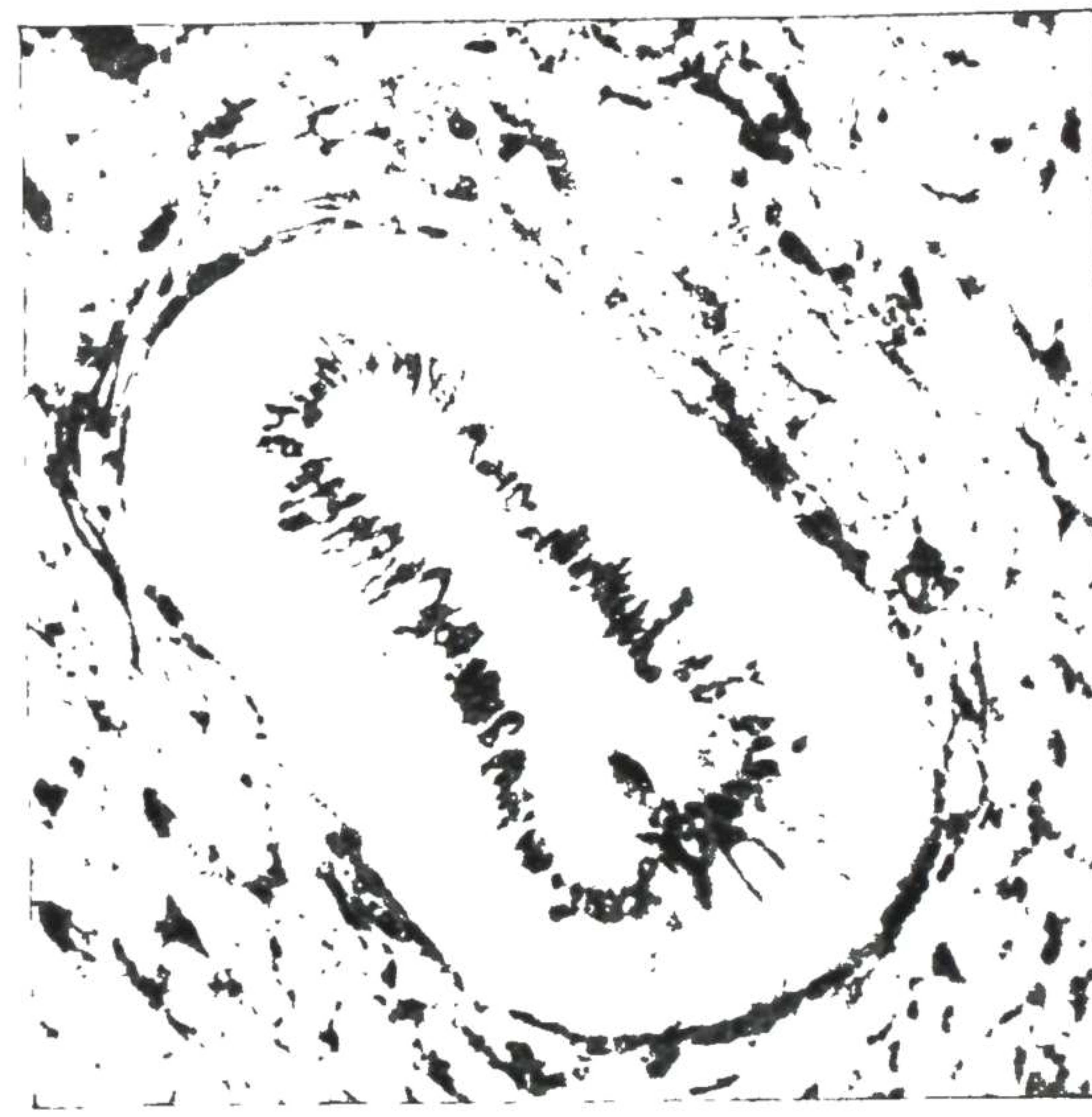


Fig. 74.—Premenstrual stage showing the upper layer of the endometrium. The saw-toothed edges of the glands are particularly noticeable in the section. The stroma is decidua-like. Gyn. Lab.

is fairly dense and the glands compressed and straight; the "zona spongiosa," composed of dilated coiled glands with very little between them, and the "zona basalis," containing the deep ends of the glands which are affected very little by the cyclic changes. These zones are well shown in the photomicro-



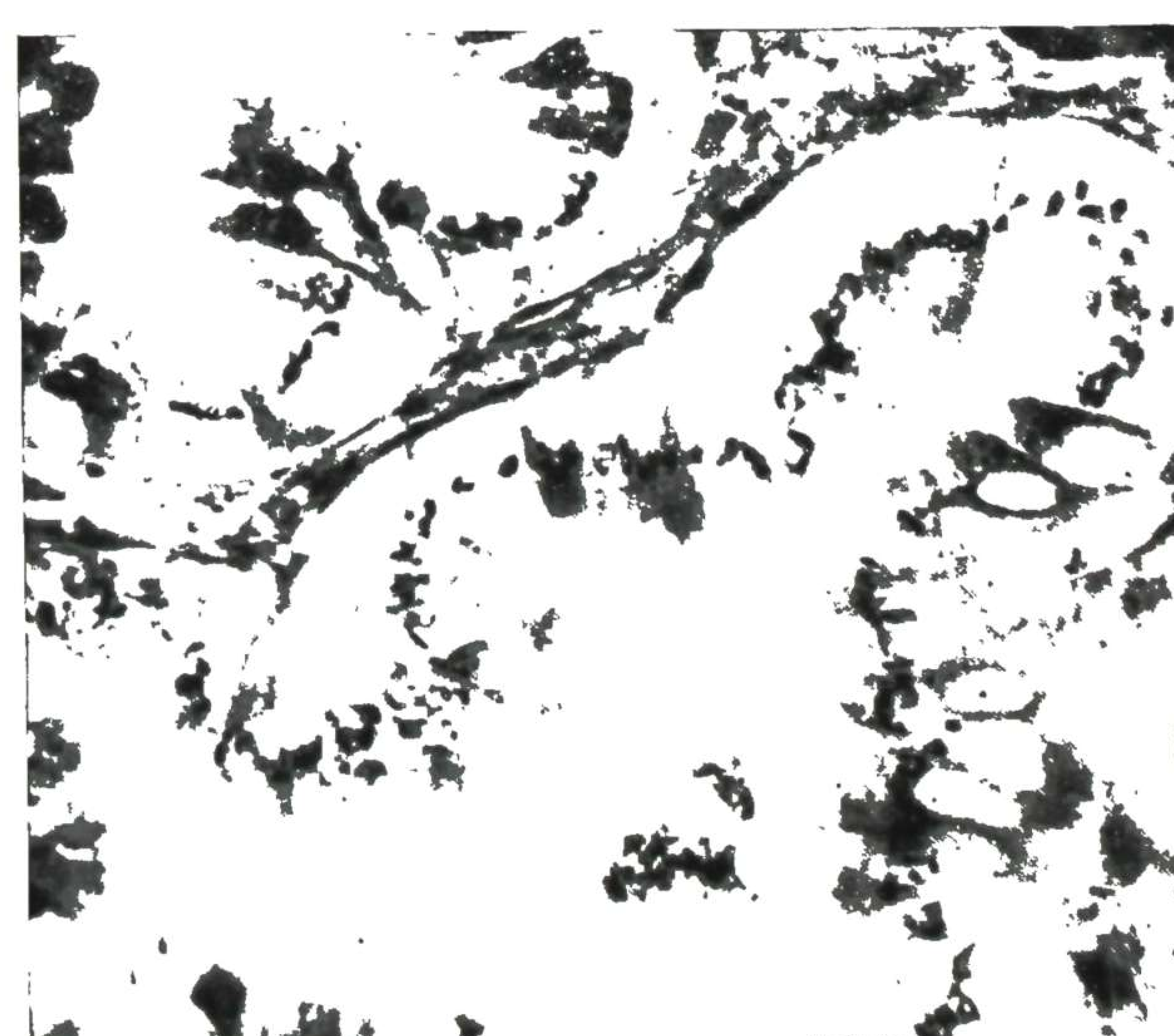
A.



B.

Fig. 75.—The follicular phase of the growth stage. *A*, Specimen from a patient on the sixteenth day of the cycle. The follicular effect is fully developed. Ovulation probably occurred about this time. (×140.) *B*, Special staining of gland, in follicular phase, to show Golgi apparatus. (×600.) (From Campbell, Lendrum, and Sevringhaus: Surg., Gynec. & Obst.)

A.



B.

Fig. 76.—The luteal phase of the growth stage. *A*, Specimen from same patient on the twenty-third day of the same cycle. The luteal effects are now well developed, but are still fairly early, as is evidenced by the presence in some places of a clear zone between the gland nuclei and the basement membrane. (×140.) *B*, Special staining of gland, in luteal phase, to show Golgi apparatus. (×600.) (From Campbell, Lendrum, and Sevringhaus: Surg., Gynec. & Obst.)