DISEASES OF WOMEN

CHAPTER I

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 (colored 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.

This constant change creates a problem in anatomical description. Ordinarily we visualize anatomical structure as a stable and relatively fixed factor in the body. Thus it becomes an island of dependability in the fluctuating sea of physiological actions and reactions. But here our island of dependability shifts from week to week, with resulting confusion as to the boundries between anatomical structure, physiological change, and pathological development. Witness the difficulties of uterine specimen interpretation in the laboratory, some of which difficulties baffle even the specially trained and experienced gynecological pathologist. 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.

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

*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—Gould's, Keating's, Dorland's). A few authorities differ, some favoring soft g and long y, and others favoring hard g and long y.

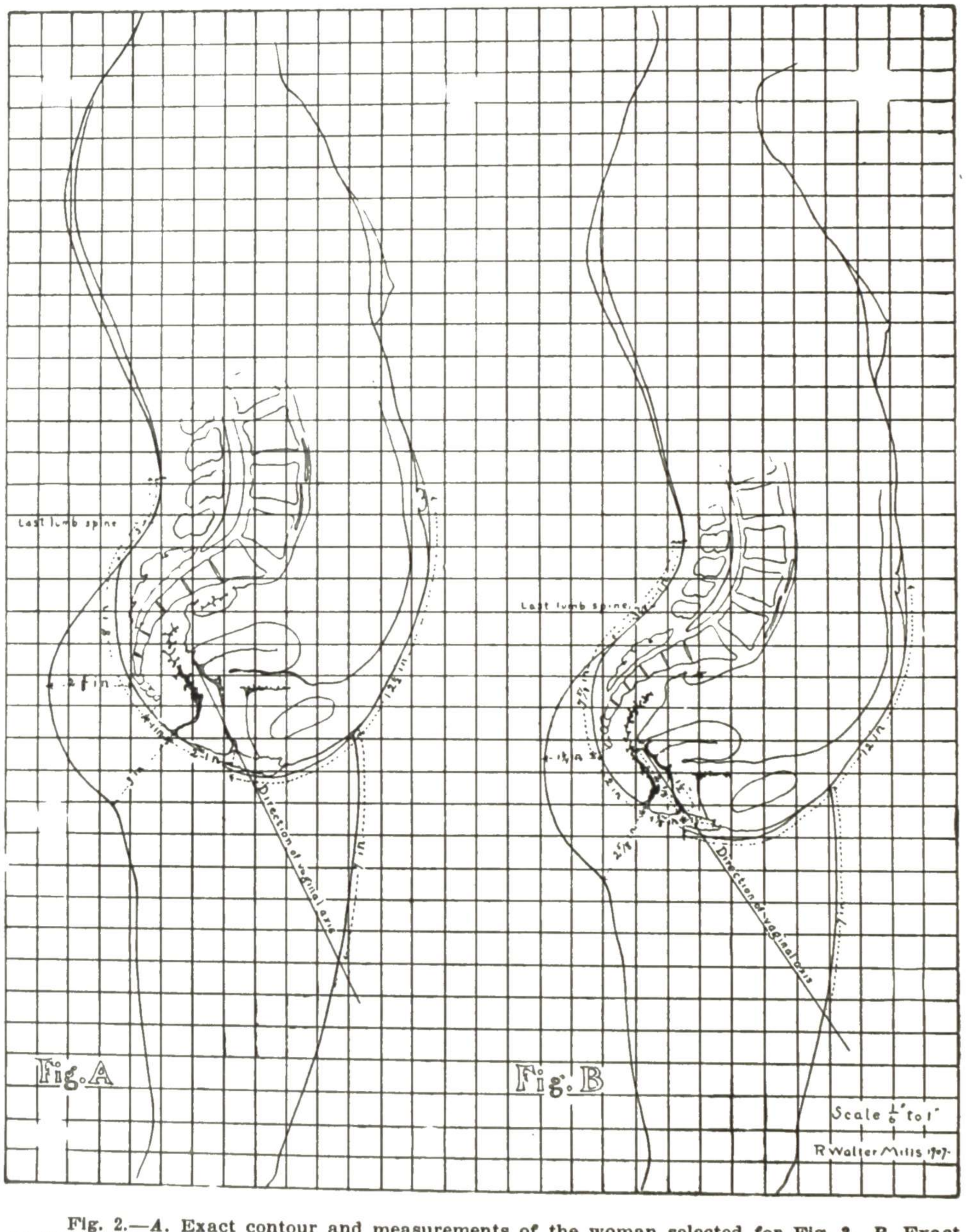

Fig. 2.—*A*. Exact contour and measurements of the woman selected for Fig. 3. *B*. Exact contour and measurements of another model, presenting a more pronounced lumbar and abdominal curve. The small squares represent one-inch squares at life size. (R. Walter Mills.)

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 in. (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.

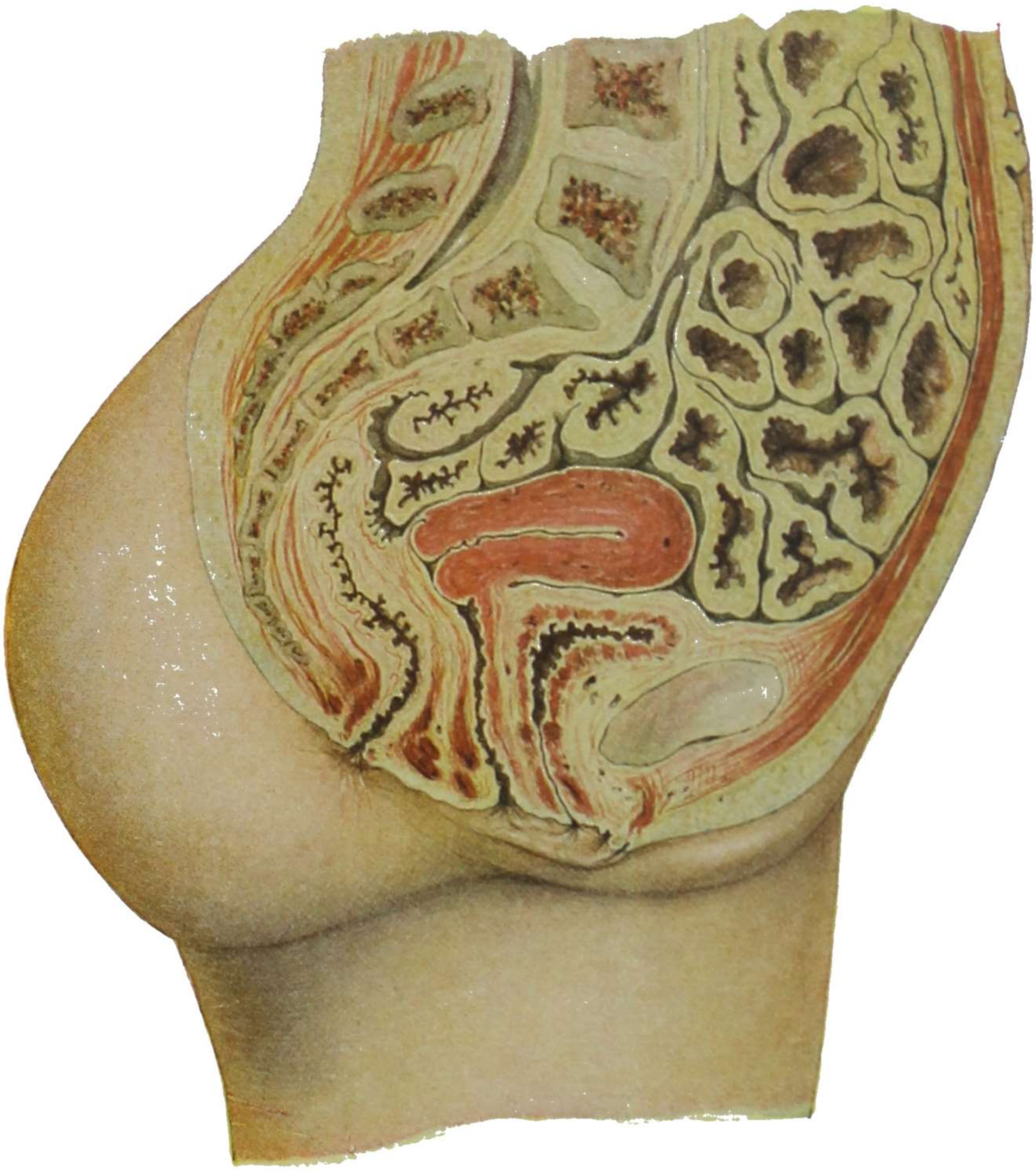

FIG. 3.—ANTEROPOSTERIOR SECTION OF PELVIS (SEMIDIAGRAMMATIC).

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.)

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.

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 hipbones, the sacrum, and the coccyx. Each hipbone (os innominatum) 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.

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 (become larger and smaller) 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 XIII). The anatomy and physiology (supporting

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. (Kelly—*Gynecology*. D. Appleton-Century Company.)

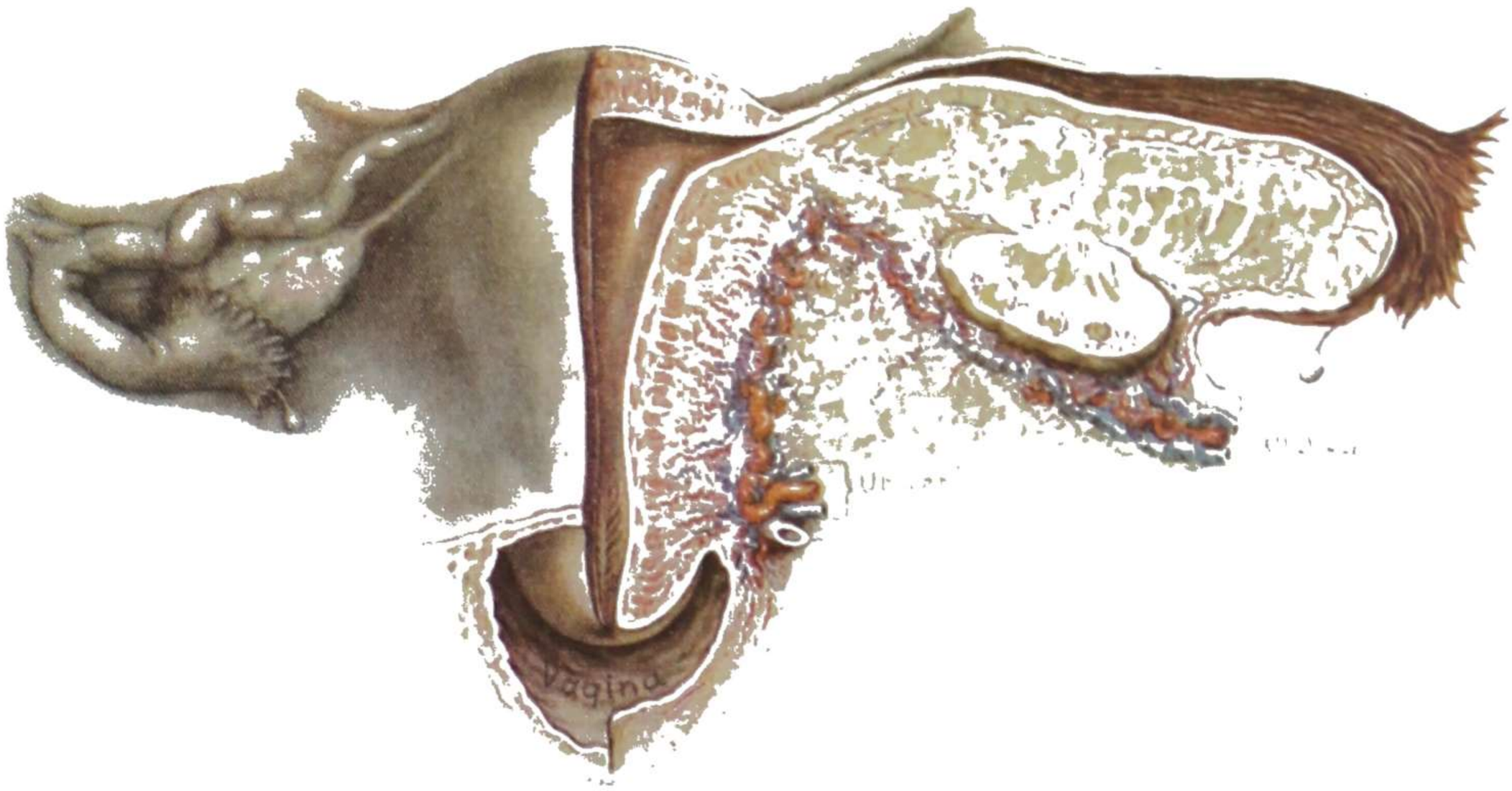

Fig. 6.—View from behind, showing on the left the relations of ovary and fallopian tube and posterior surface of uterus. On the right is a section of the uterus, tube, ovary, and broad ligament, showing the relations of these various structures and their blood supply.

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).

action) of the pelvic floor are best discussed in connection with relaxation and other damage to those structures and will be found in Chapter V.

In taking up the anatomy and physiology of the pelvic organs we begin with the most important, namely, the ovary. All other parts of the genital tract are dependent on the ovary for their structural development and physiologic activity. The structure and physiology of the ovary must be known before there can be an understanding of the physiologic changes in the other organs, for example, in the uterus or the tubes or the vaginal mucosa. Therefore the *order* of consideration in this chapter will be: ovaries, uterus, tubes, pelvic peritoneum, pelvic connective tissue, vagina, and external genitals.

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 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.

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 connective tissue. It contains no follicles, but it contains remnants of the tubular structure which in the male develops into the testicle.

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 remains of the germinal epithelium from which ova and graafian follicles were formed by infoldings. It is supposed that ova and graafian follicles are formed also from the ovarian mesenchyme in the substance of the ovary, as mentioned later.

In structure the ovary is simply a collection of ova, or microscopic eggs, supported and held together by the connective 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 connective 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. This connective tissue constitutes the ovarian stroma, or interstitial tissue, and is peculiar in that it is exceedingly rich in cells, which are packed so closely together that in an ordinary microscopic preparation the tissue seems to consist nearly altogether of dark-staining nuclei. Near the periphery of the ovary the connective tissue fibers become more numerous and the nuclei fewer, so that there is here a rather dense capsule. This fibrous capsule of the ovary is known as the "tunica albuginea." It is simply a condensation of the ovarian stroma and serves to protect the deeper structures. Outside of this fibrous layer lies the epithelial covering already mentioned.

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. 10. As the follicle develops, the single layer of cells lining it proliferates and the lining becomes many-layered, as in the follicle at the bottom in Fig. 10.

The follicles formed from the germinal epithelium on 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 (or supporting) ova secrete estrogen which aids progesterone in causing the progestational changes. These 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 from indifferent cells 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 gives 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

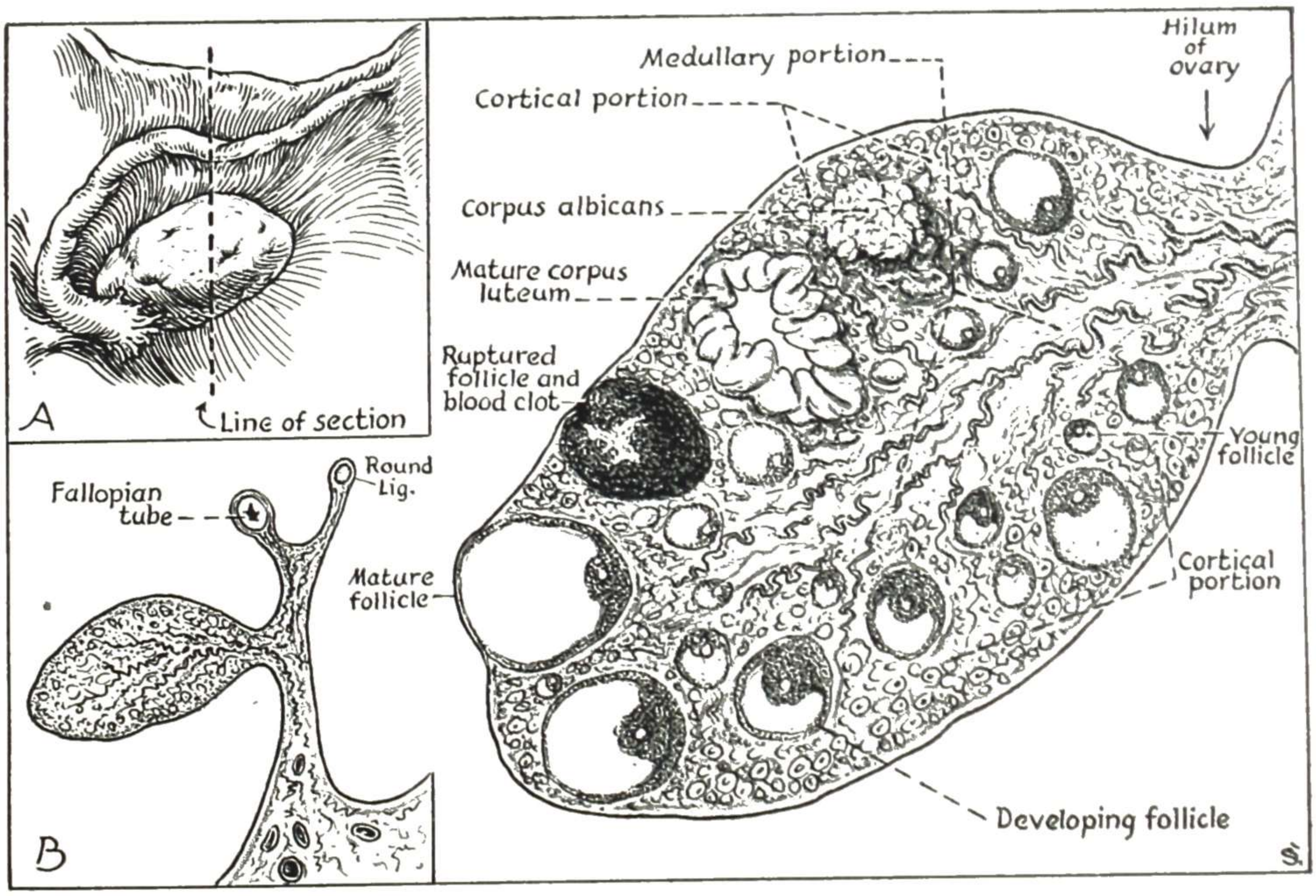

Fig. 7. Fig. 8.

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.

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 reproductive life of the average woman."

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.

Fig. 9.—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.

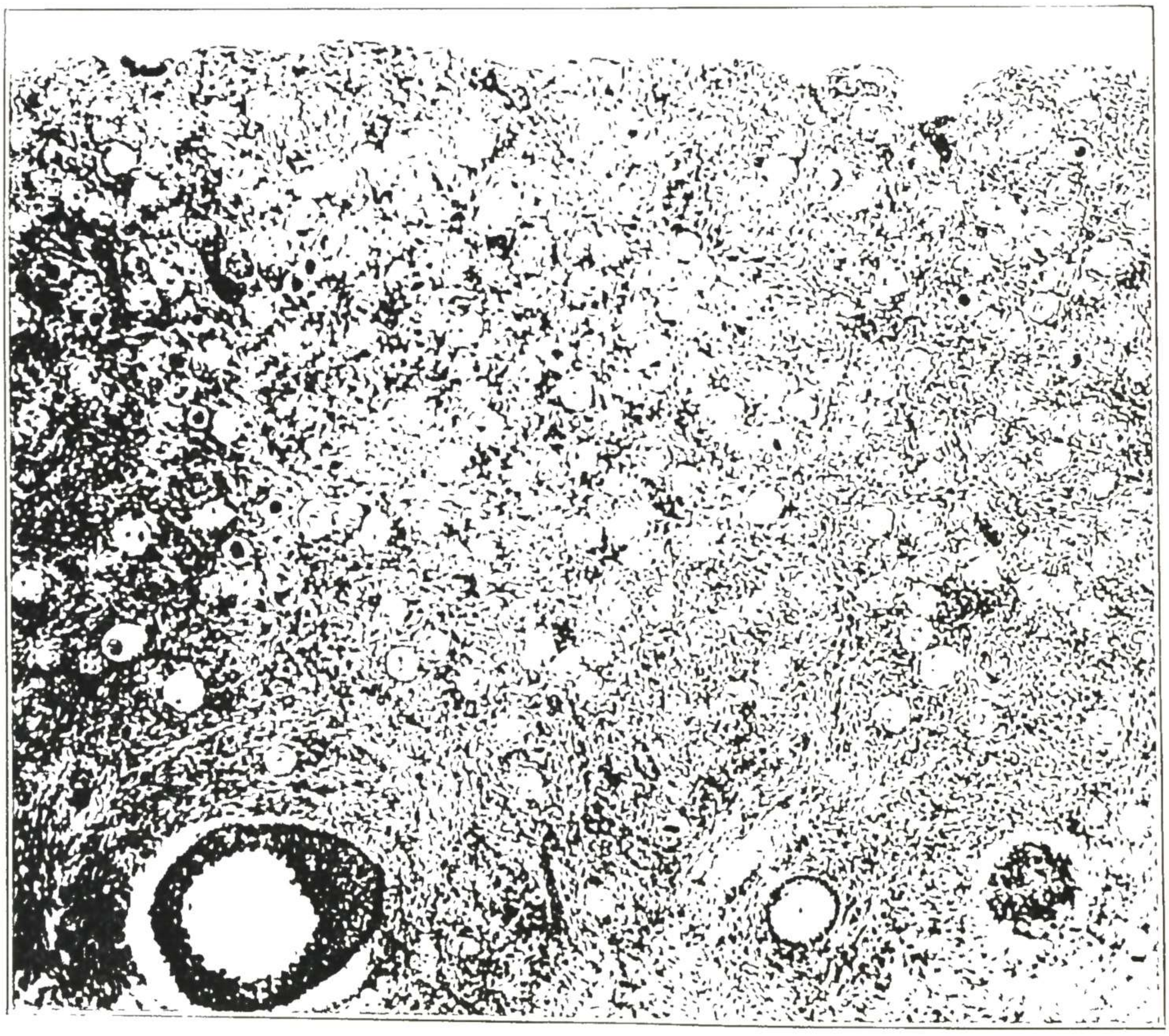

Fig. 10.—Photomicrograph of the cortical portion of ovary of a two-year-old child. Notice the large number of primordial follicles, embedded in a stroma which is characteristically ovarian. Note the large developing follicles in the deeper portion of the section. Gyn. Lab.

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 (Fig. 11). Under high power the secreting cells are seen in typical gland formation (Fig. 12).

The recent corpus luteum is a prominent structure in the ovary, as shown in Fig. 13. 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.

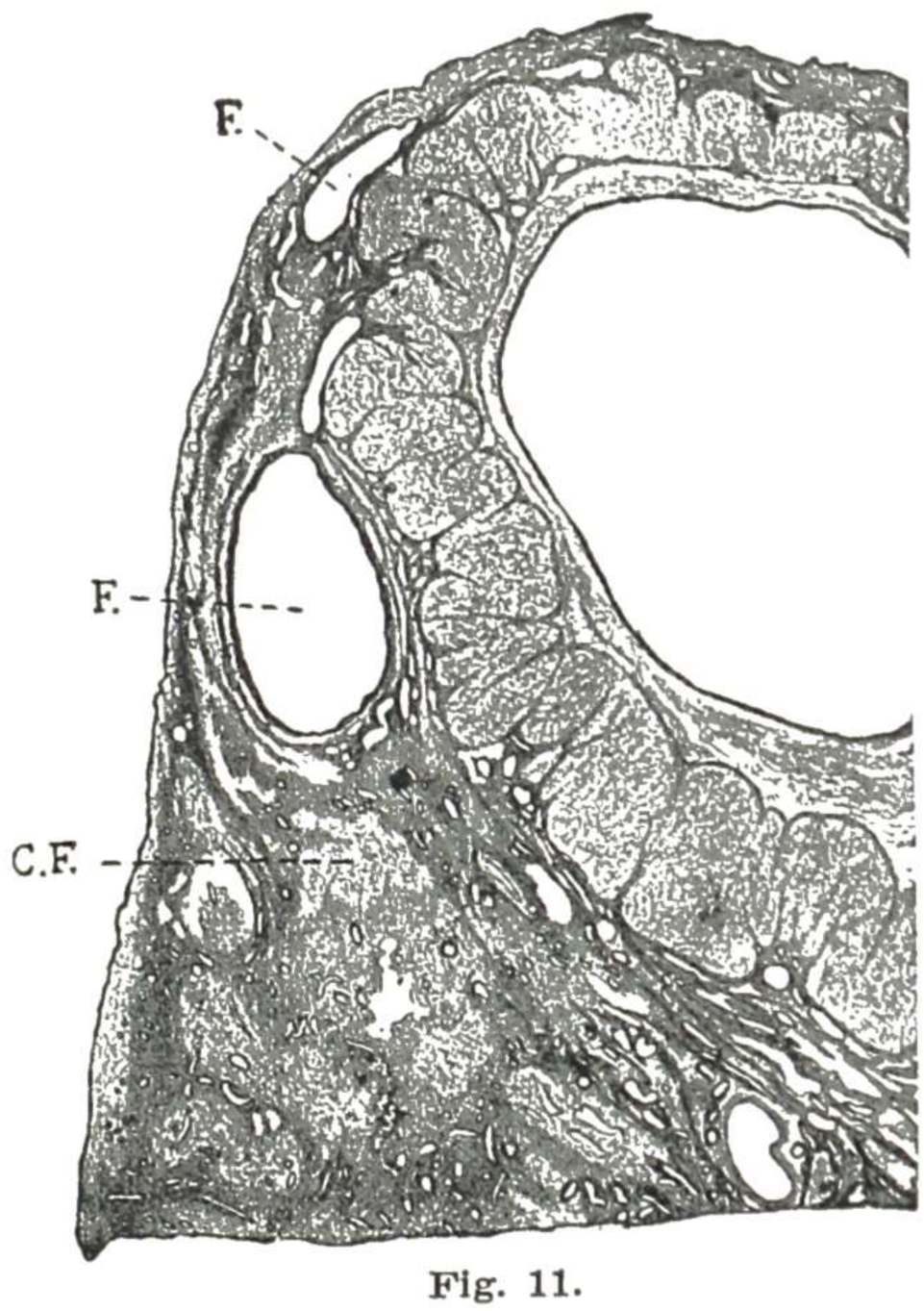

Fig. 11.

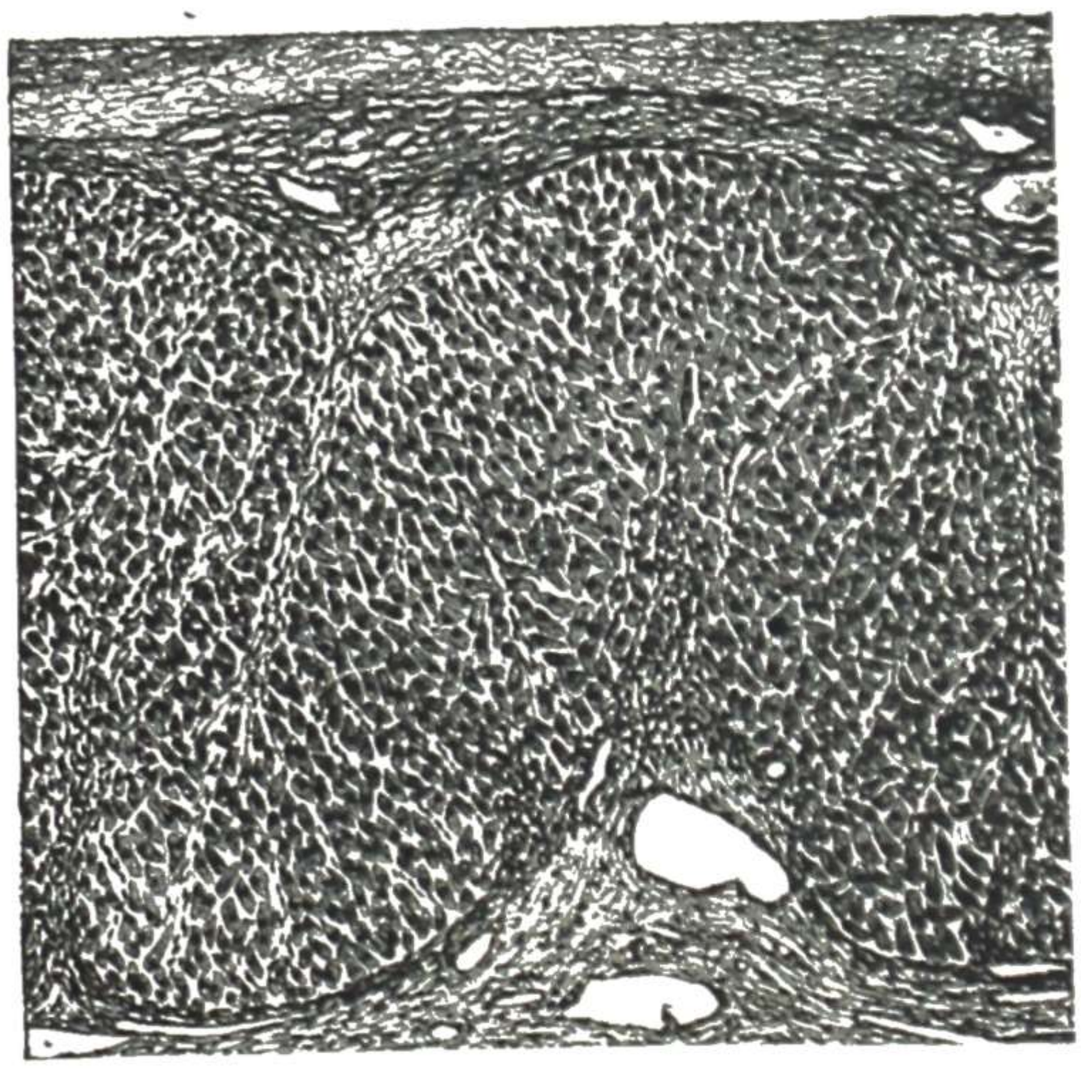

Fig. 12.

Figs. 11 and 12.—Corpus luteum. Fig. 11, Section through a corpus luteum, low power, showing the distribution of the layer of luteum cells, as a wavy wall about the cavity. Fig. 12, High power of the luteum layer, showing details of the cells. (Williams—*Obstetrics*, D. Appleton-Century Company.)

The lutein 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** (white body, 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 for months before retrograde changes set in.

The senile ovary is made up largely of old corpora lutea with resulting hyaline areas (Fig. 14). The follicles disappear and the stroma becomes more or less fibrous (Fig. 15).

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

A. *B.*

Fig. 13.—*A*, Ovary with recent corpus luteum at left end. *B*, Ovary sectioned showing what a prominent structure the recent corpus luteum is in the ovary. Gyn. Lab.

Fig. 14.

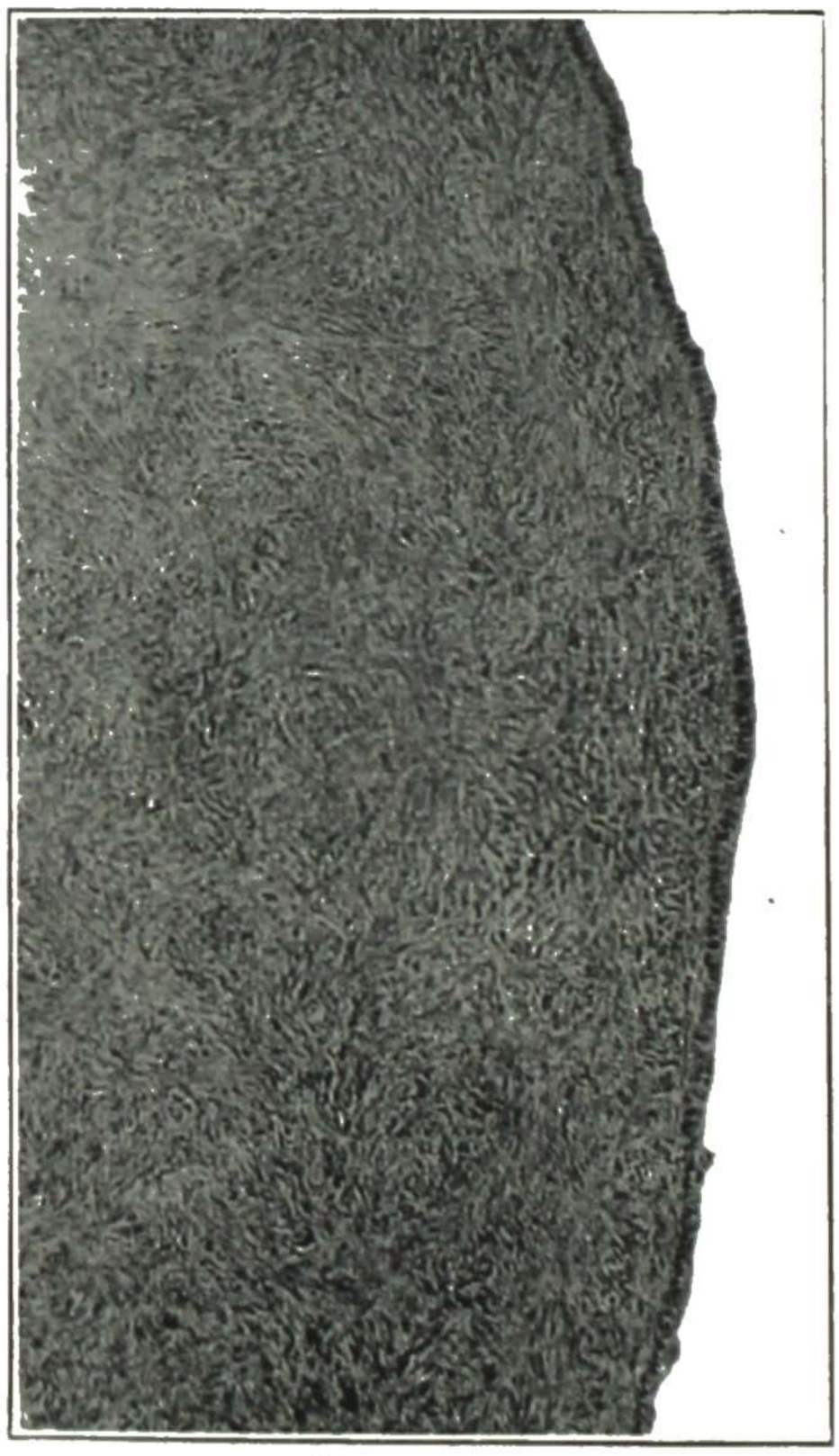

Fig. 15.

Figs. 14 and 15.—Senile ovary. Fig. 14, Section of the entire ovary. Notice the masses of hyaline material, due to merged corpora albicantia, and also the thickened vessel walls. Fig. 15, 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.

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 cyst or pseudomuci-

nous cyst or endometrial cyst or granulosa-cell tumor or even a tumor of male sexual cells (arrhenoblastoma).

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.

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. Consequently, in salpingectomy with preservation of the ovary, care must be taken to avoid occluding this arch in order to maintain good blood supply to the preserved ovary. 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 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. 67 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. 68 to 73).

PHYSIOLOGY

of Ovary

The ovary has two functions. One is the formation and discharge of 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.

OVULATION

Ovulation is the term applied to the maturing and discharge of an ovum. The progressive stages in ovulation, together with associated changes in the uterus and in hormonal levels, are shown in Fig. 1 (colored Frontispiece). The three steps, follicle formation and maturation and rupture with discharge of ovum, are indicated diagrammatically in Figs. 16, 17, and 18.

In man the future primordial cells which are to form the gonad become differentiated early in embryonal life. These large cells finally lodge in the region of the future gonad. As embryonic development progresses, there are periods in which these so-called primordial germ cells, which are now 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 Winivarter, 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

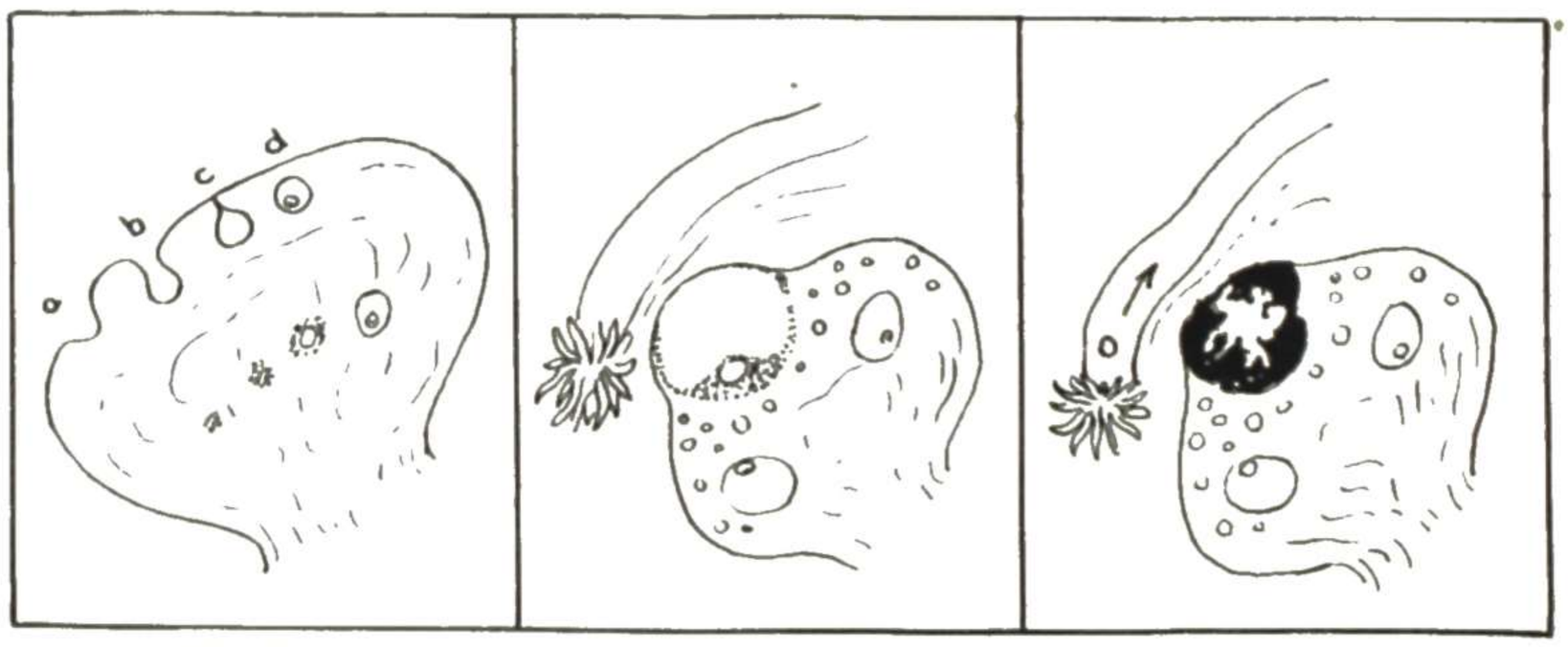

Fig. 16. Fig. 17. Fig. 18.

Fig. 16.—Diagrammatic illustration of the two methods of oogenesis. At *a*, *b*, *c*, *d*, various stages of the infolding of the germinal epithelium are seen. In the deeper portion of the ovary follicles are shown developing from the ovarian mesenchyme in this locality.

Fig. 17.—Ripened follicle at the surface of the ovary just before ovulation.

Fig. 18.—Follicle ruptured and corpus luteum of proliferation remaining. The ovum is seen in the tube on its descent to the uterus. (Crossen—*Synopsis of Gynecology*, The C. V. Mosby Company.)

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.

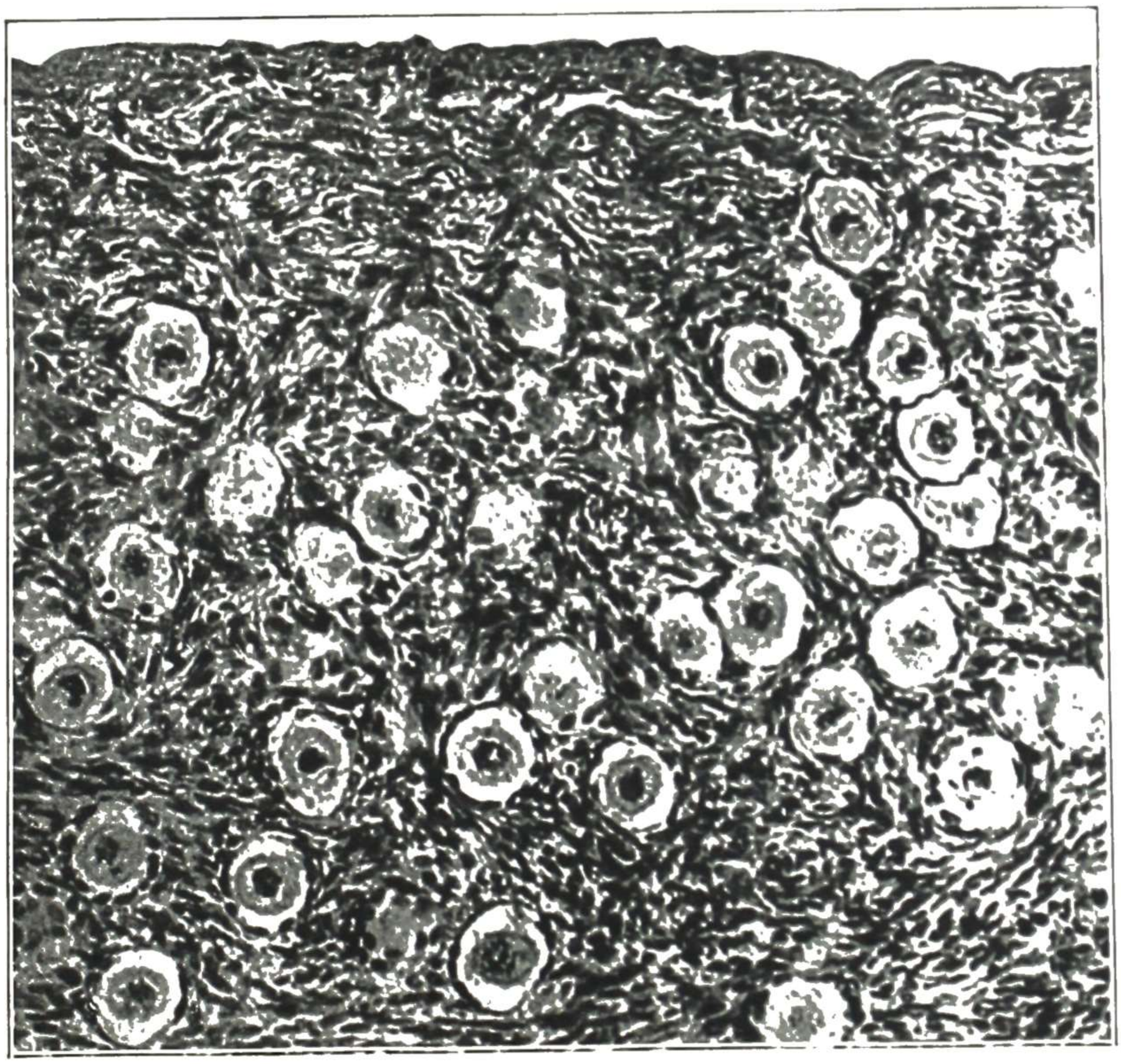

Fig. 19.—Primordial follicles. High power. Photomicrograph from ovary of child. Gyn. Lab.

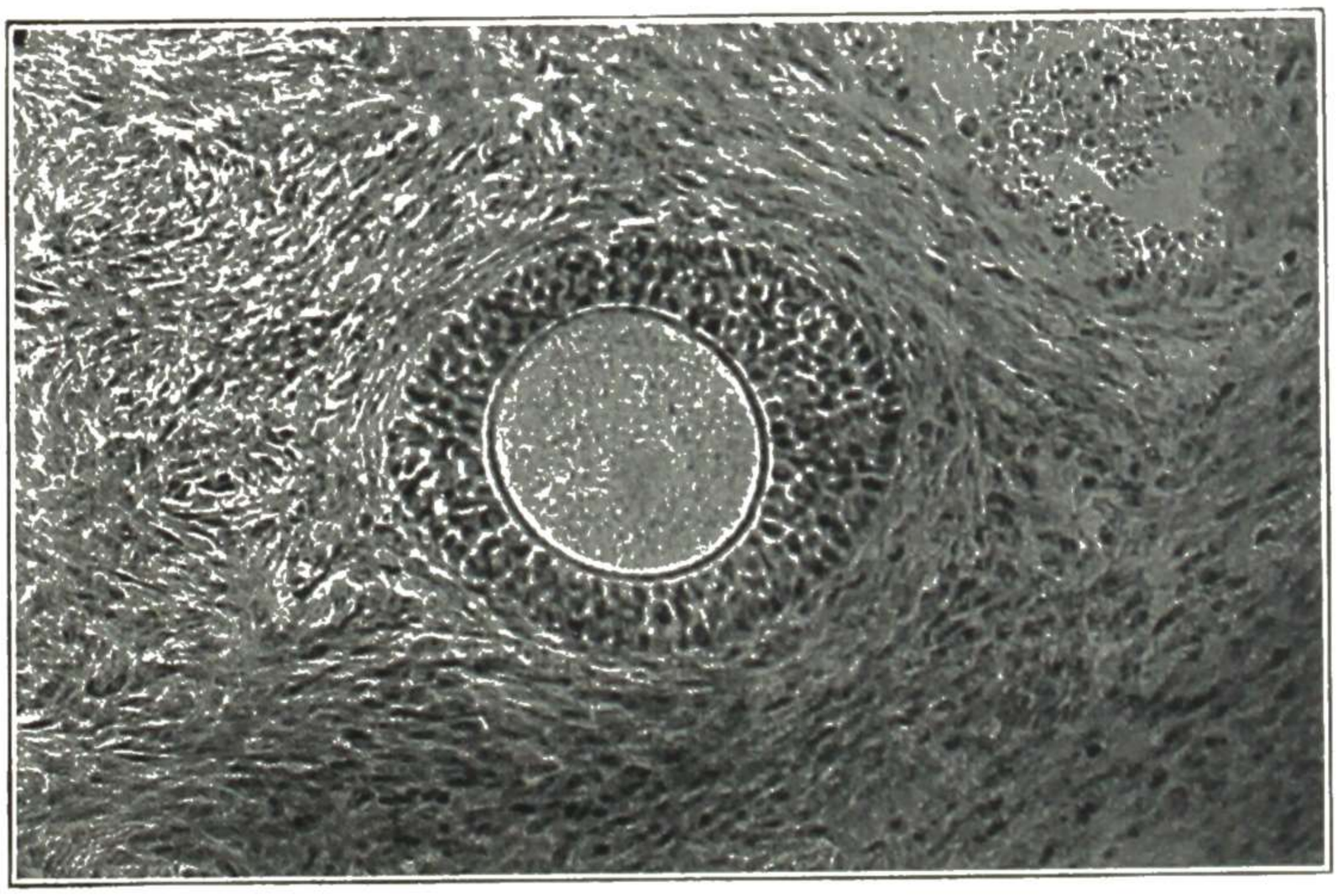

Fig. 20.—Adult ovary. Field showing a small follicle with contained ovum. Gyn. Lab.

"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."

More recently Fischell and also Politzer have arrived at the conclusion that the ova and follicular epithelium and granulosa cells are formed in loco from the ovarian mesenchyme, from which likewise are formed the thecal and stromal tissues of the ovary. It is probable that both of the methods of ovum- and follicle-formation are present in the human being.

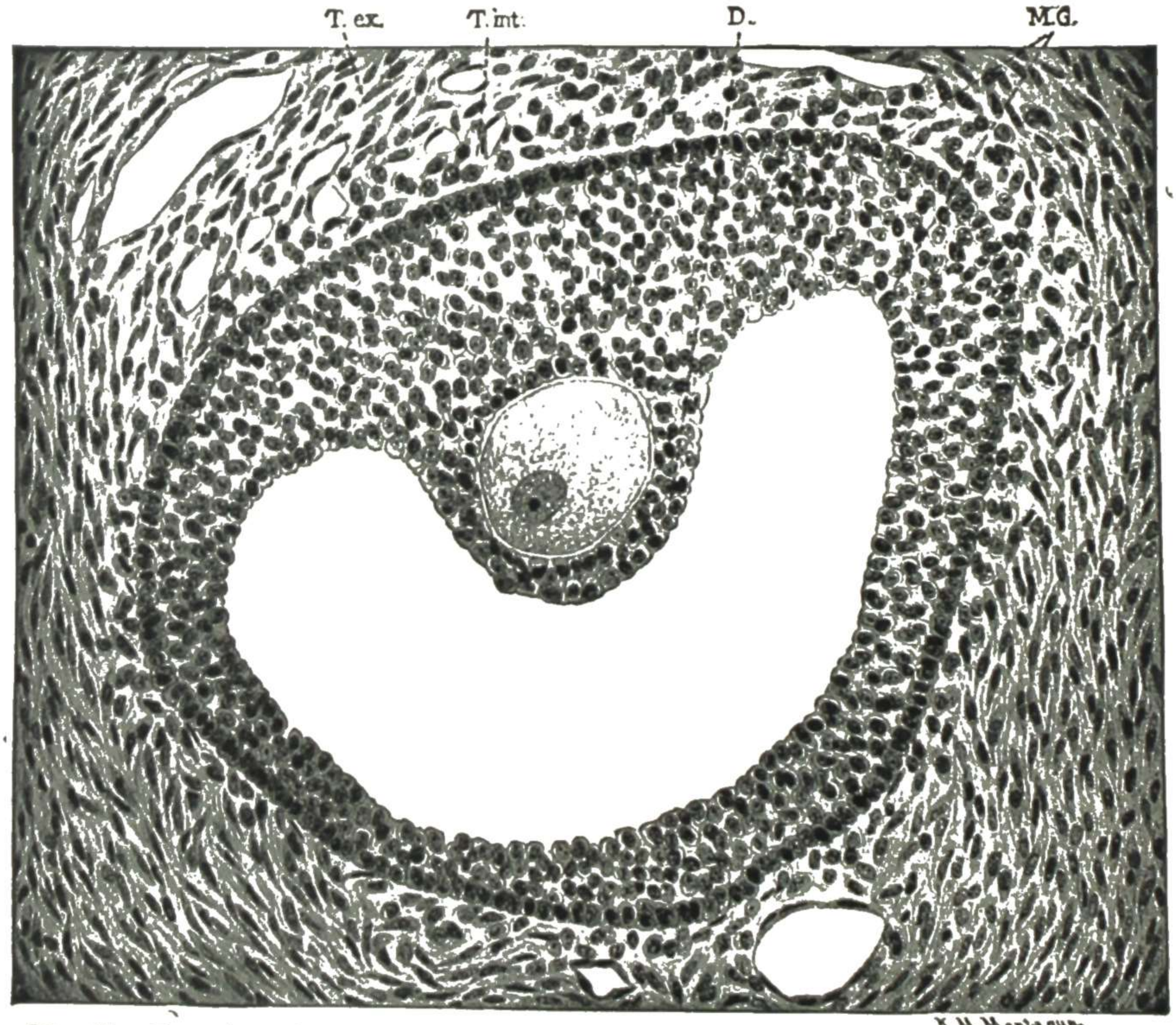

Fig. 21.—Drawing of a somewhat older follicle and contained ovum, to show the details of the follicular epithelium (membrana granulosa) and of the ovarian stroma, which is very rich in cells. The follicular cavity has begun to form. *M.G.*, membrana granulosa; *D*, discus proligerus; *T.int.*, theca interna; *T.ex.*, theca externa. (Williams—*Obstetrics*, D. Appleton-Century Company.)

The primordial **follicle** consists of an oocyte surrounded by a single layer of flattened epithelial cells (Fig. 19). As the child grows, the follicles develop further. In the adult, the first step toward a functioning follicle is the rapid proliferation of the epithelial envelope about the oocyte, which becomes several layers thick, as shown in Fig. 20. It is known that pituitary A (follicle-stimulating hormone) is one factor initiating this process of follicular development, but it is not known what causes this hormone to start functioning at this particular time.

In the developing epithelial layer, now called the **membrana granulosa,** a cleft appears and fills with fluid (Figs. 21 and 22). As this **liquor folliculi** increases, this cleft becomes a spherical cavity, as shown in Fig. 23. The fluid

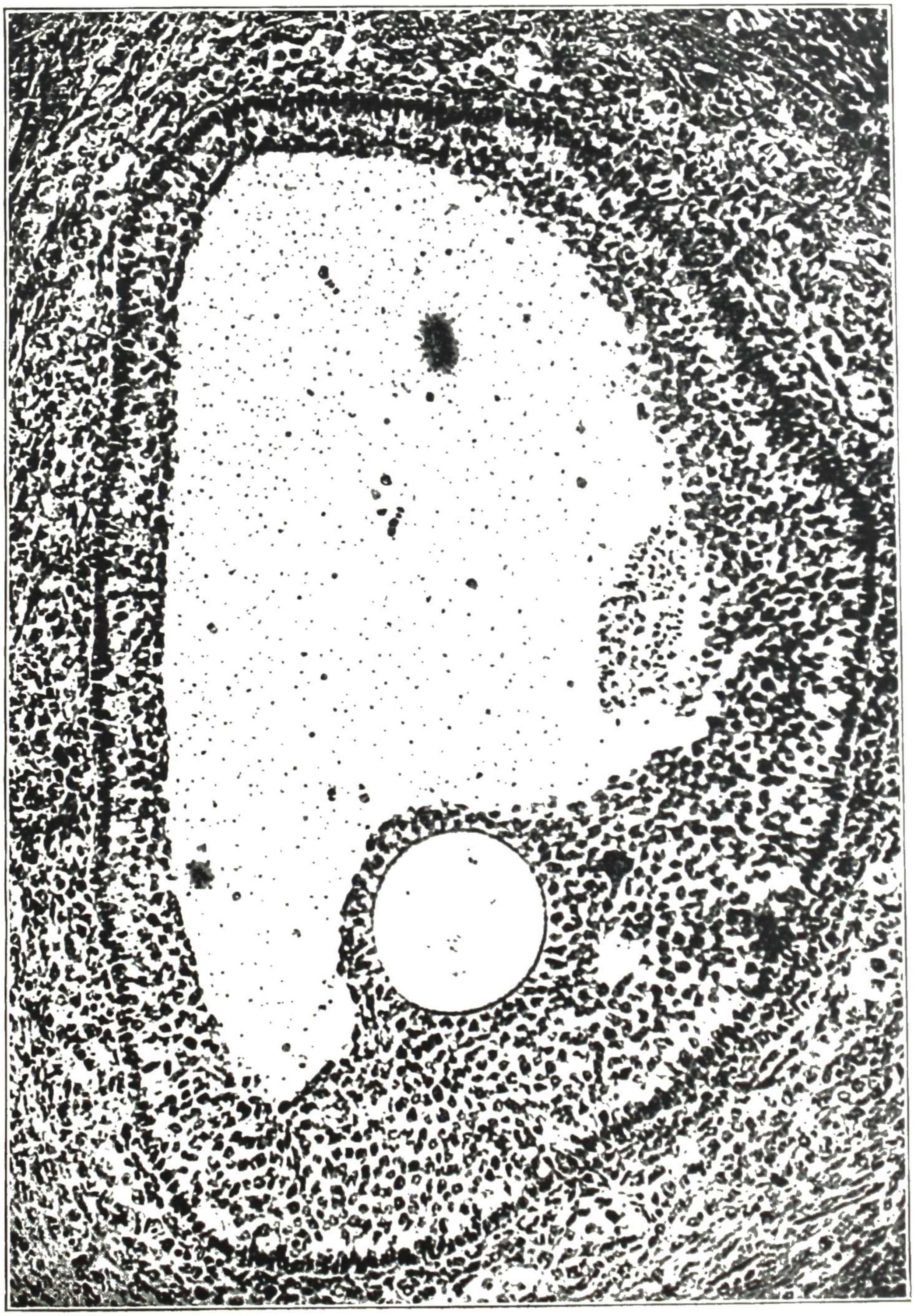

Fig. 22.—Photomicrograph of a growing follicle with the cavity still further developed. Fortunately the section passed through the ovum, showing that and the discus proligerus. Gyn. Lab.

is secreted by the granulosa cells. At one point the granulosa cells are heaped up into a mass which surrounds the ovum, as shown in Figs. 21 to 23. This projection is spoken of as the cumulus oophorus or discus proligerus.

Surrounding the follicle, even in the early stages, is a connective tissue 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 between the zona pellucida and the ovum.

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 millimeter 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. 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 remains of the nucleus wander to near the center of the cell, and the ovum assumes a resting state. It is then ready for impregnation. It is carried into the fallopian tube, and, if impregnation does not take place, it degenerates rapidly.

The work of Kurzrok, demonstrating an increase in F.S.H.* excretion about the middle of the cycle, leads him to conclude that F.S.H. is the stimulus causing rupture of the follicle. Frank noticed an increase in prolan A in the blood around the tenth to the twelfth day, and he also feels that it might be an important factor. **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. 24 and 25, show 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.

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*Pituitary A = follicle-stimulating hormone (F.S.H.).
Pituitary B = luteinizing hormone (L.H.).

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.

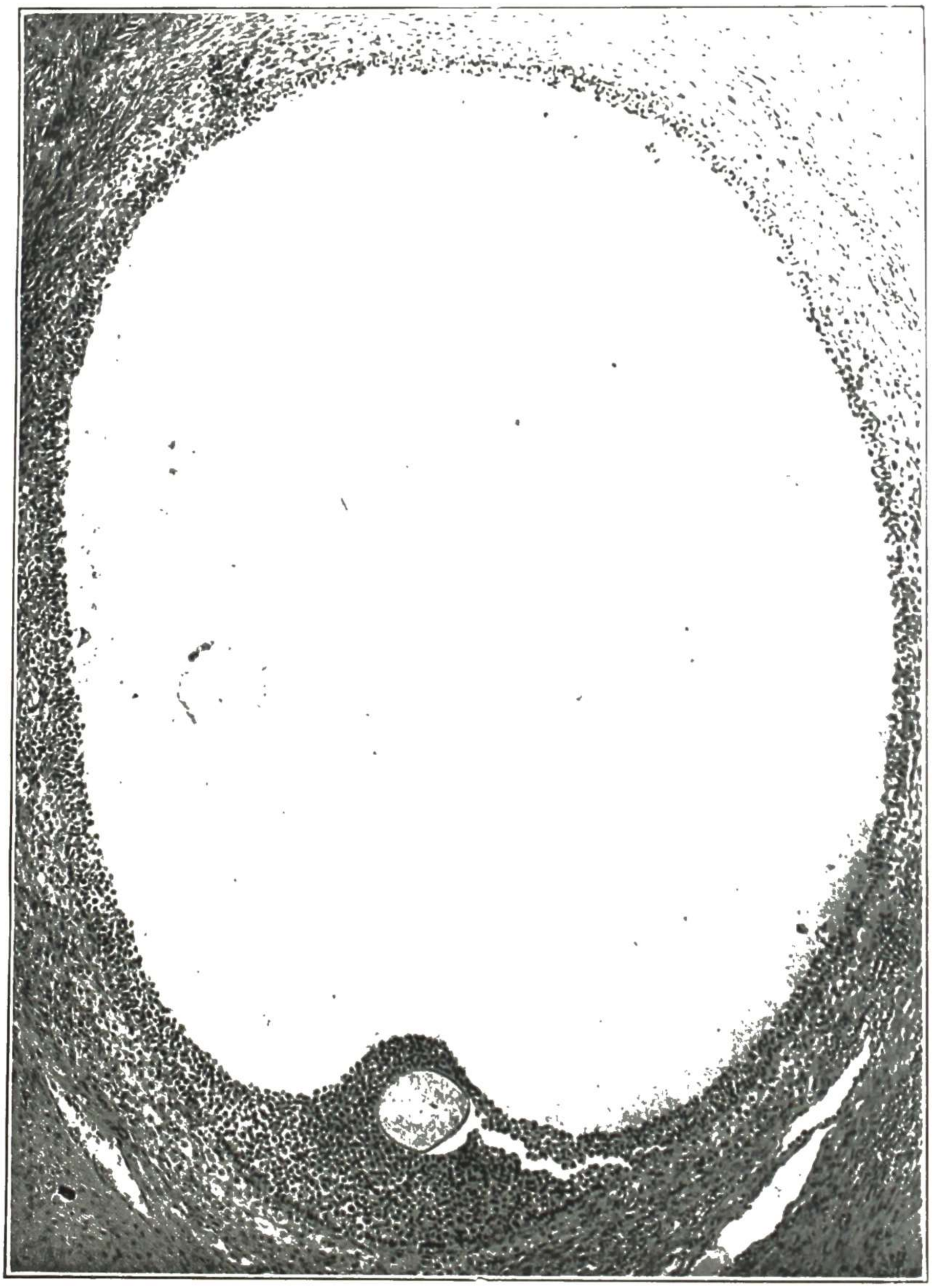
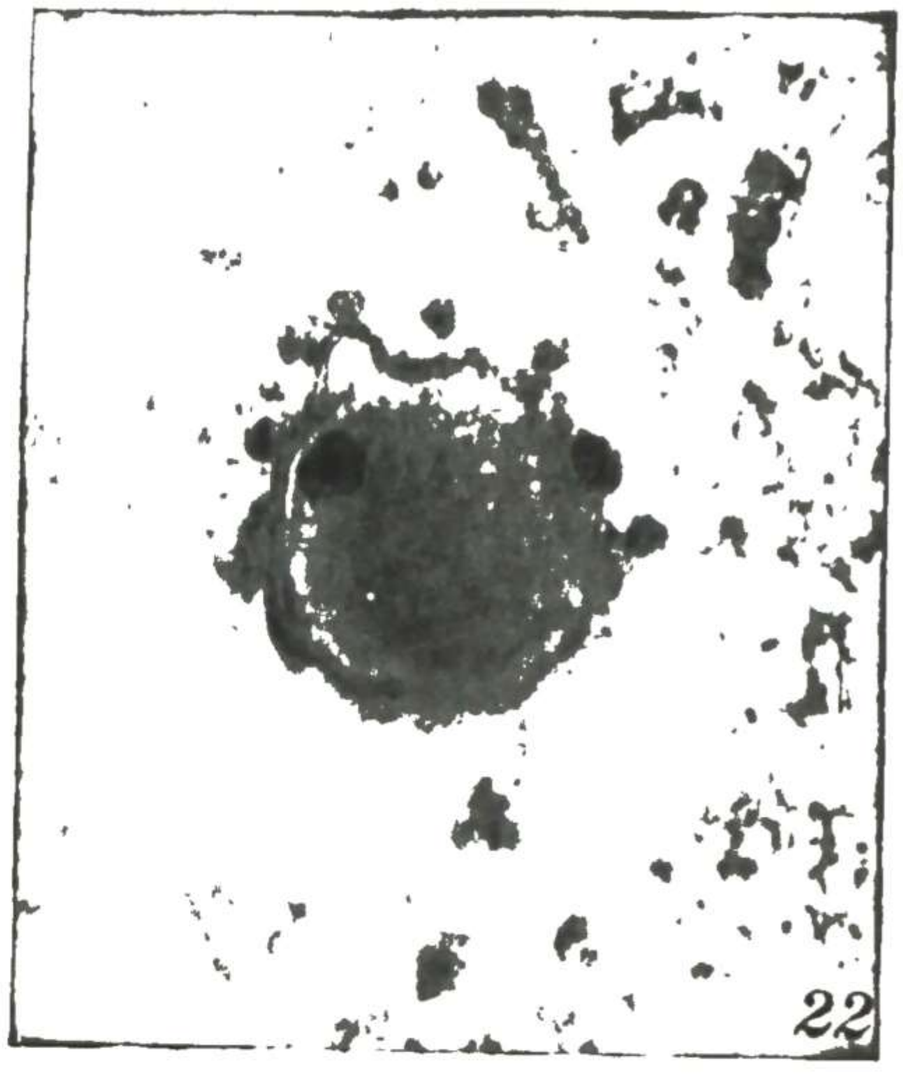


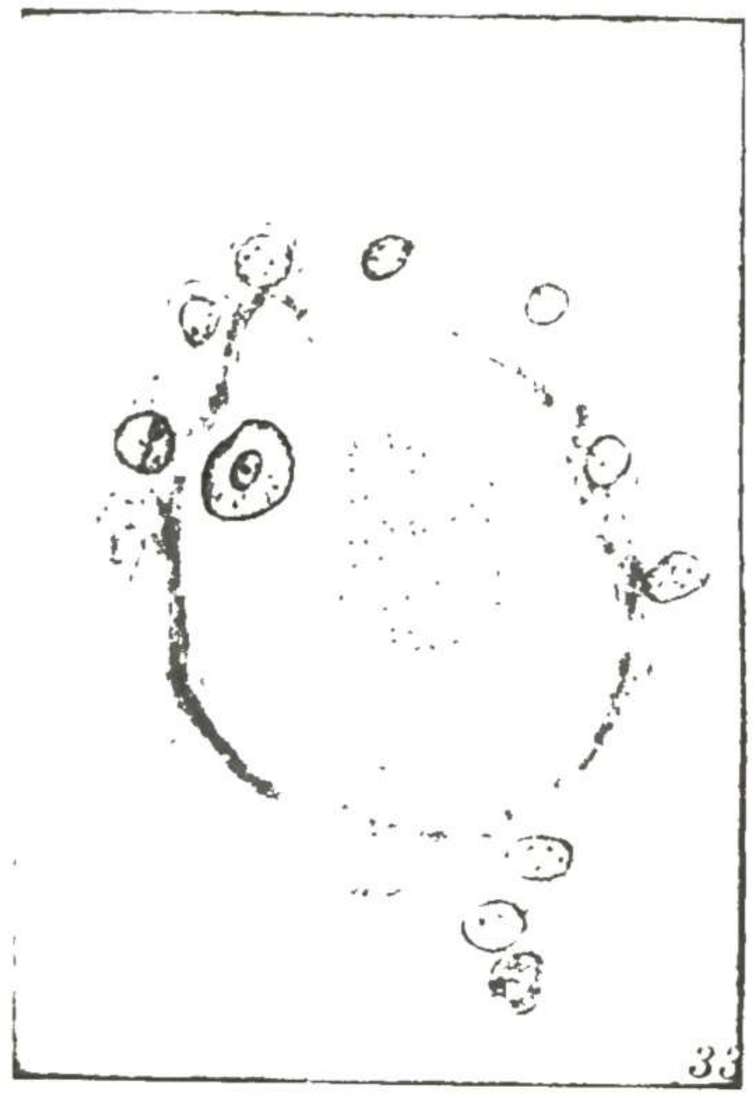
Fig. 23.—Photomicrograph of a follicle which is nearly mature, as indicated by the size of the cavity compared to the ovum. Gyn. Lab.

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. 26, 27, and 28 show the steps in the process.



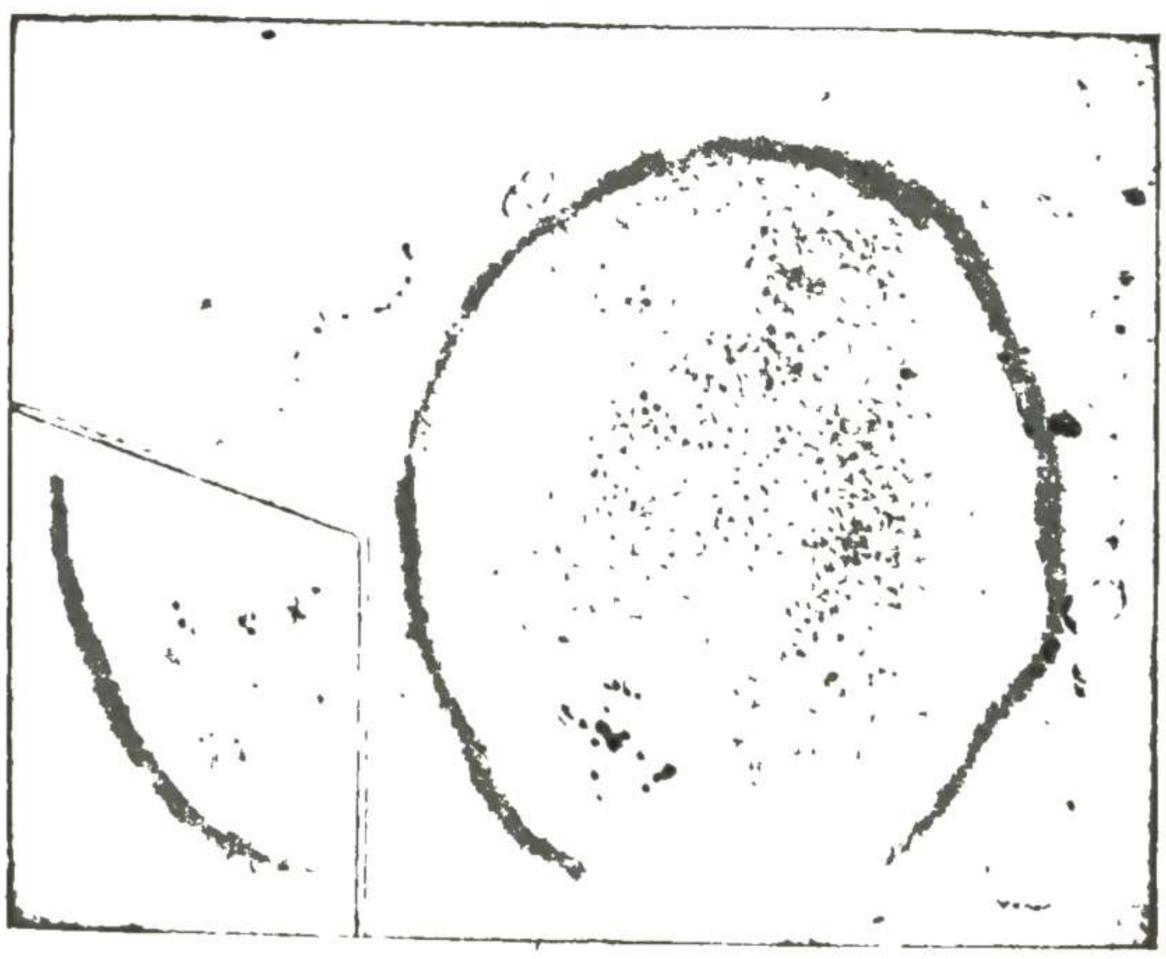
A.



B.

Fig. 24-*A* and *B*.—*A*, Twin human ovum recovered on the fifteenth day of the menstrual cycle. Ovulation probably occurred on the preceding day. The other twin ovum is shown in Fig. 25. This ovum was recovered from the left tube. *B*, Camera lucida drawing of *A*. Note the polar body at ten o'clock. (Figs. 24 and 25 are from a monograph by Edgar Allen, J. P. Pratt, Q. U. Newell, and J. L. Bland, published by The Carnegie Institution.)

A.



B.

Fig. 25-*A* and *B*.—*A*, Twin ovum to that shown in Fig. 24, recovered from the right tube. Chromosomes of the second maturation spindle were located at eight o'clock. *B*, Camera lucida drawing of *A*.

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. (c) 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. Cervical mucoid discharge is frequently seen at the time of ovulation. Séguy and Simonnet consider it a constant and dependable sign.

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.

3. On examination of the vaginal smear Papanicolaou found erythrocytes and a sudden increase in leucocytes in 31 per cent of his series of cases. Zuck and Duncan found that a rise of vaginal pH indicated ovulation.

4. Blood findings consist of a rise in estrin just before ovulation and there is an increase in prolan in the urine.

5. Premenstrual endometrial biopsy shows typical progestational effects, 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. Noyt and Meigs and also Hendrickson found some blood in the peritoneal cavity at ovulation time. It varied from a few cubic centimeters 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 women 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 F. 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 smear will be given under Vagina.

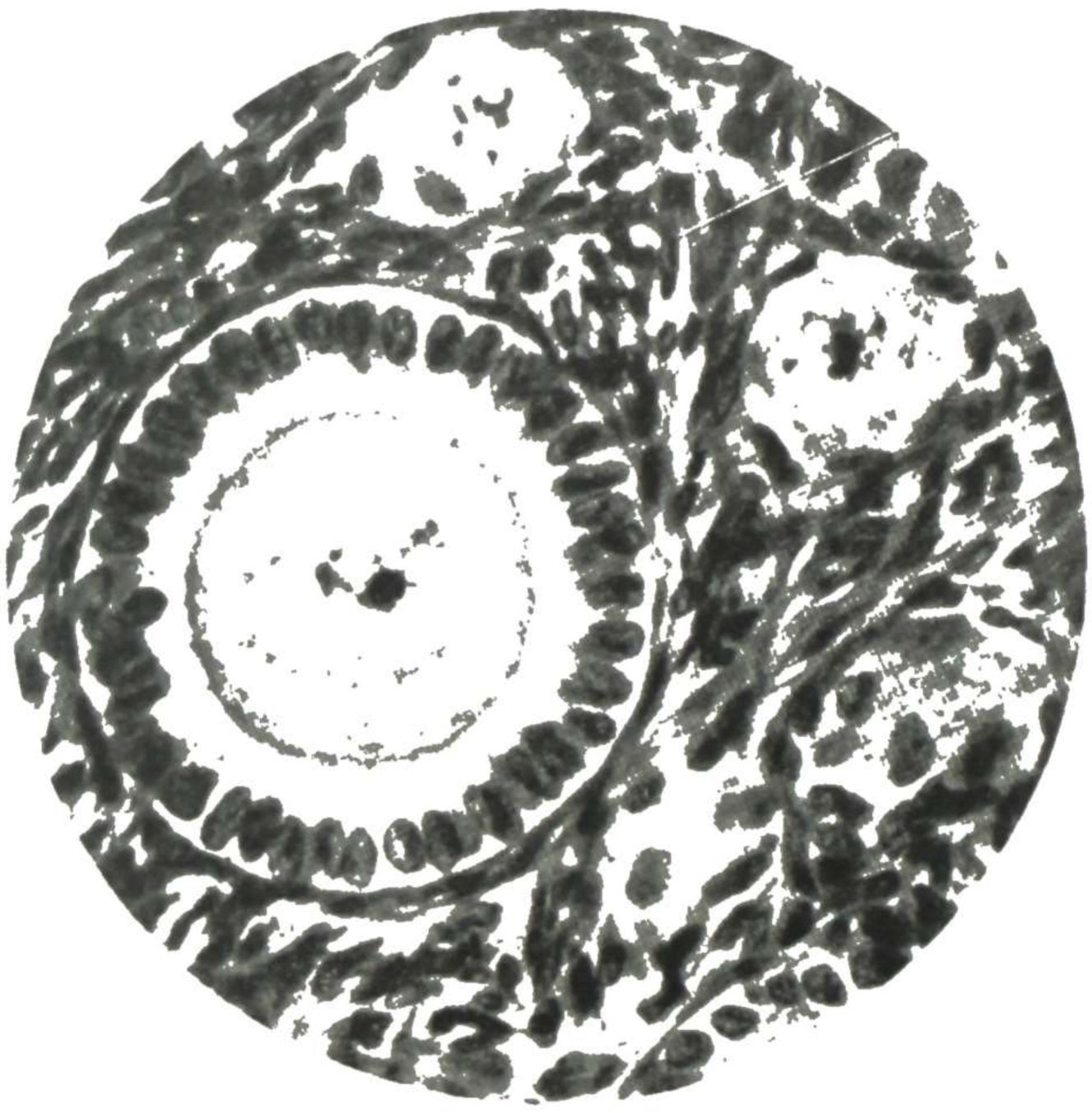


Fig. 26.—Theca interna cone, first stage. Triangular thecal wedge, indicated by line, pointing toward ovarian surface. No theca layers around follicle otherwise, one layer of granulosa cells. Small follicle of a rabbit (×325). (Strassmann—Am. J. Obst. & Gynec.)

Fig. 27. 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). (Strassmann—Am. J. Obst. & Gynec.)

After ovulation the **corpus luteum** is formed under the influence of pituitary B which is the luteinizing 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.

Fig. 28.—Theca interna cone, third stage, and granulosa cone, coinciding axis pointing toward ovarian surface. Streamlined adaptation of stroma. Ascending follicle of a cow (×80). (Strassmann—Am. J. Obst. & Gynec.)

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. 29 to 31 show corpora lutea in this early stage. Fig. 32 shows the three layers of the wall of an unruptured follicle—membrana granulosa, theca interna, theca externa—and Fig. 33 shows the corresponding layers in the wall of a corpus luteum in the stage of proliferation.

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 theca.

At the same time endothelial cells, from the vessels of the theca interna, push in between the granulosa cells centrally to the lumen of the corpus and form new capillaries in the epithelial zone.

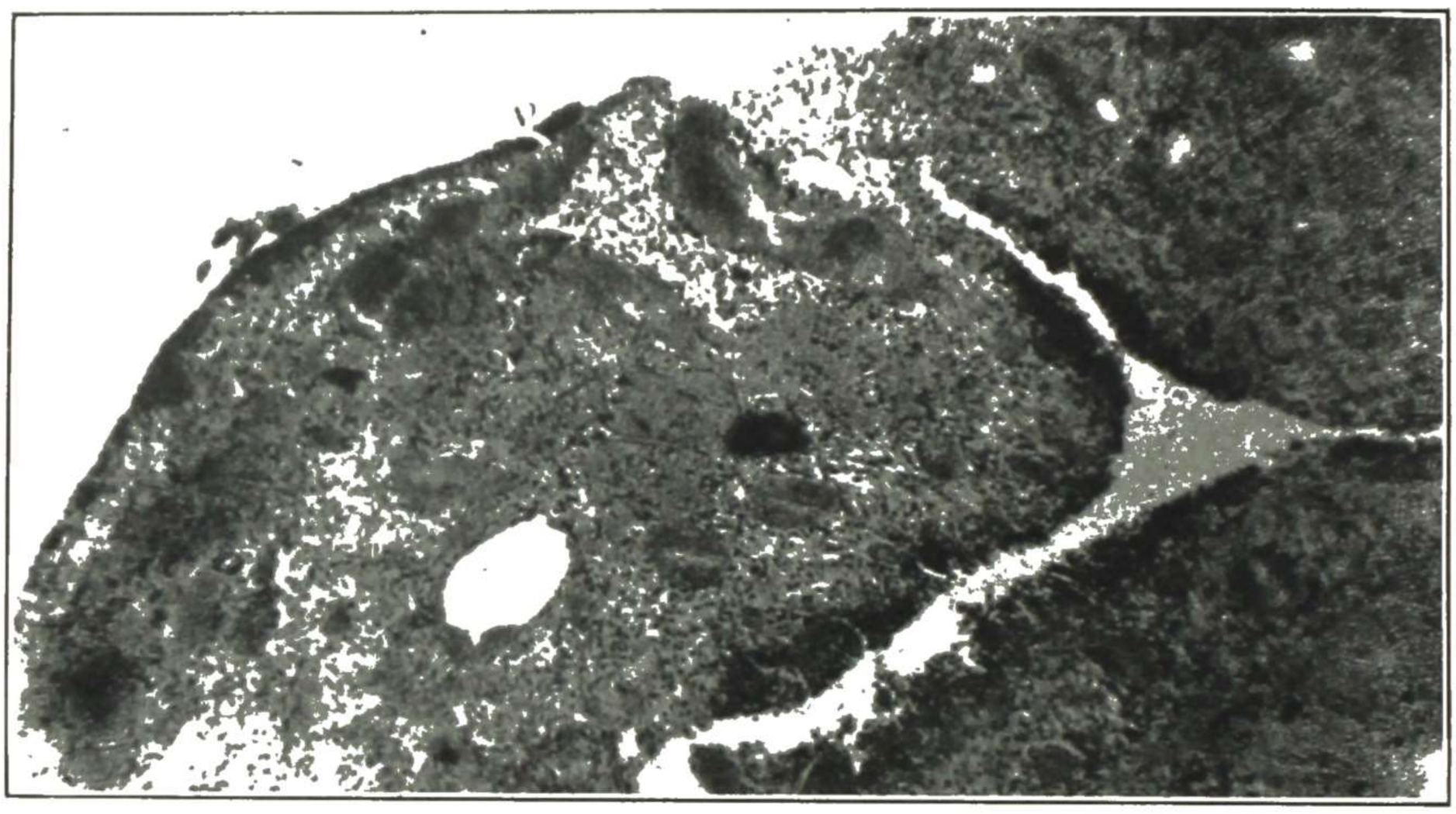


Fig. 29.—Recently ruptured follicle showing rupture point with plug already formed in the opening. This is now a corpus luteum of proliferation. Gyn. Lab.

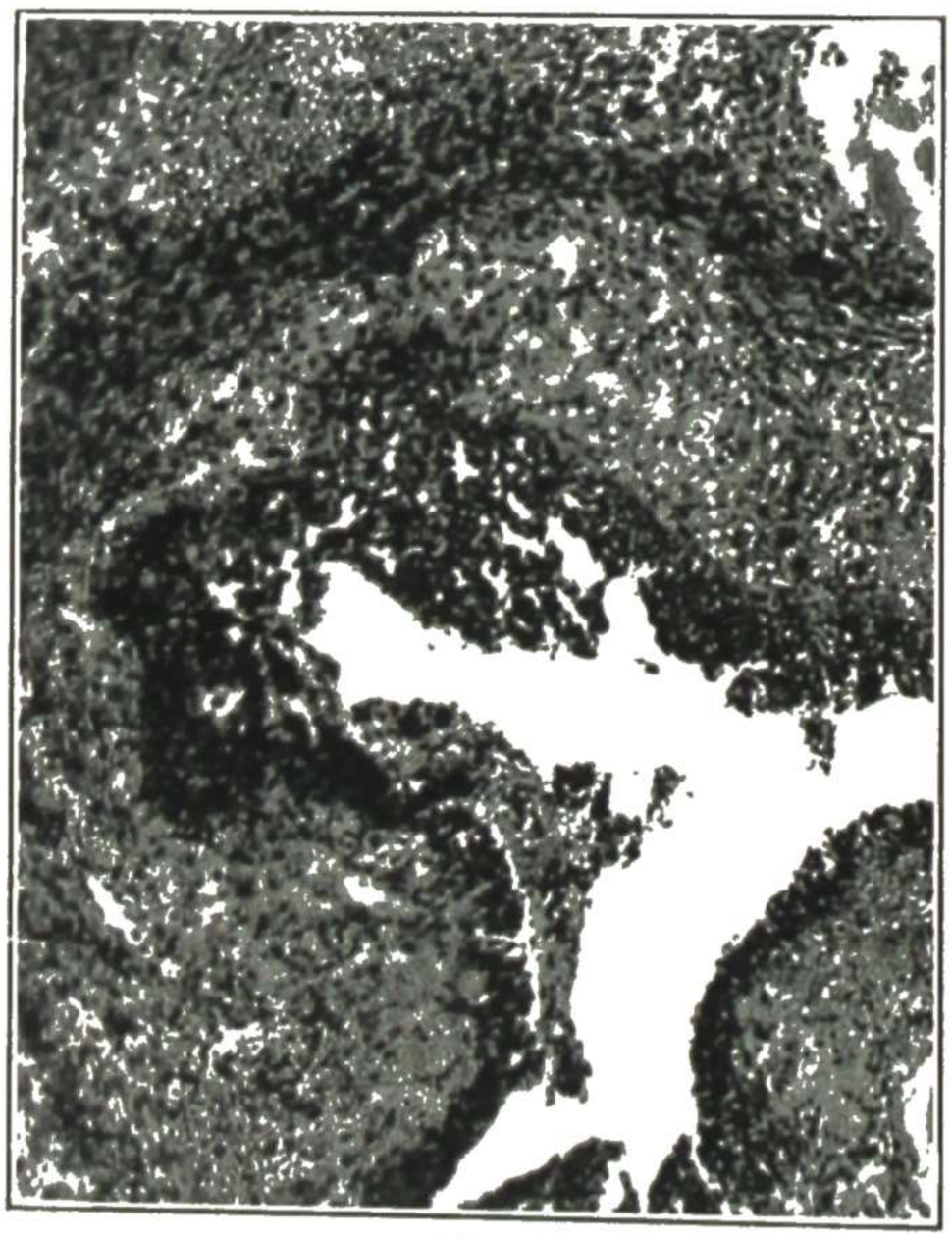


Fig. 30.

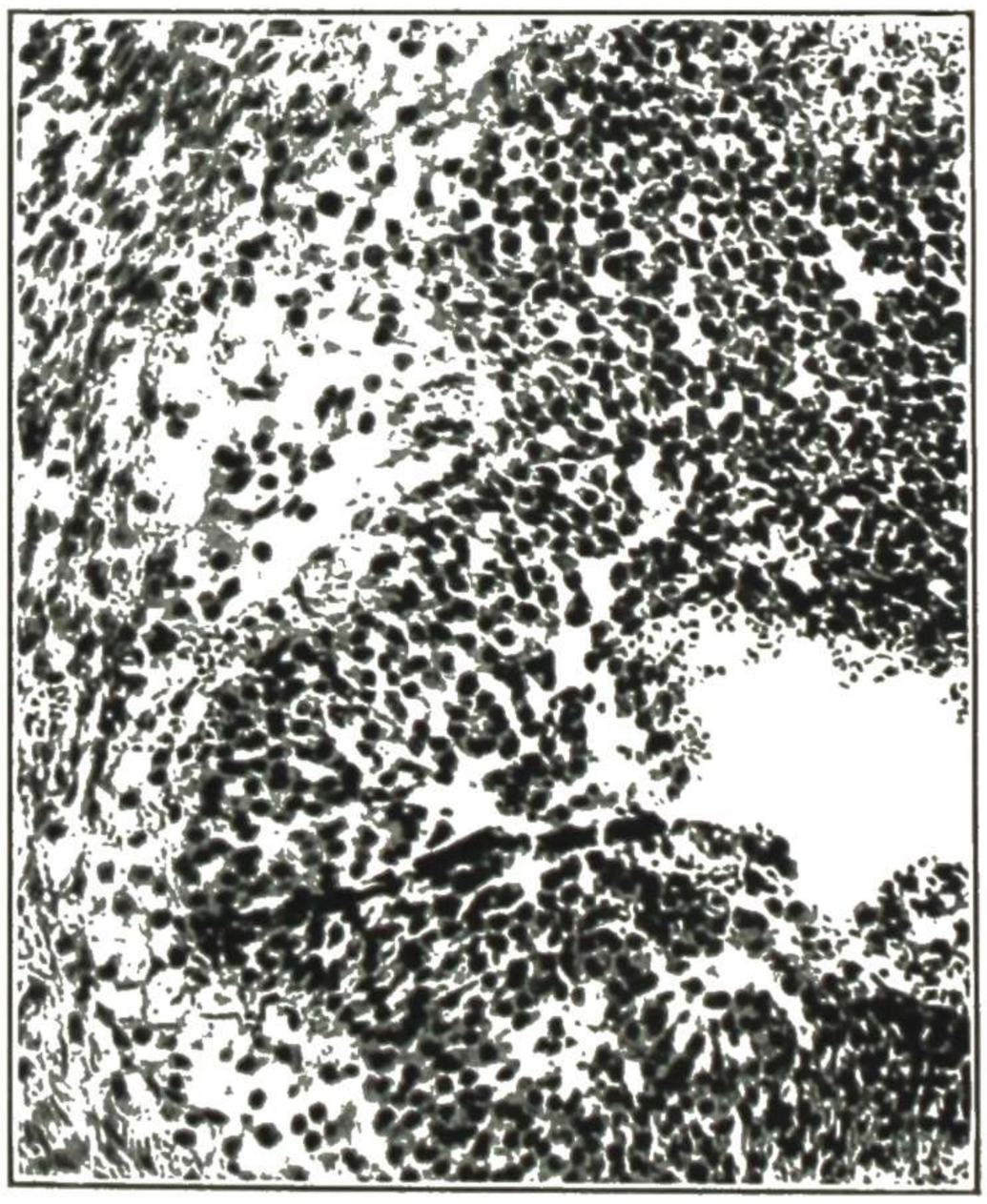


Fig. 31.

Fig. 30.—Corpus luteum of proliferation showing the arrangement of the three layers: theca externa, theca interna, and granulosa cell layer. Gyn. Lab.

Fig. 31.—Higher power of Fig. 30, taken from an area at the extreme left end of the wall. Gyn. Lab.

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

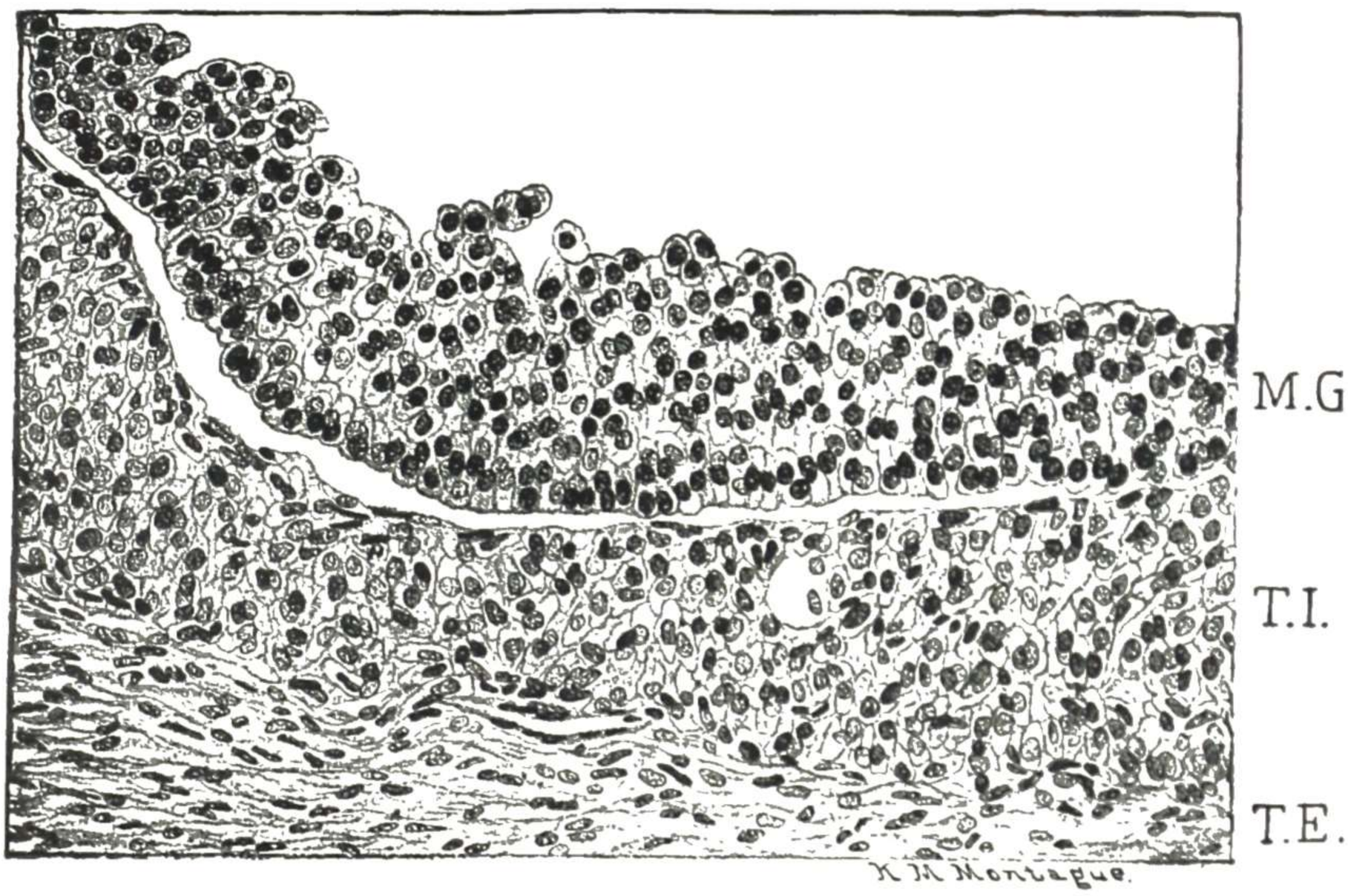


Fig. 32.—Lining of follicle before rupture. *M.G.*, membrana granulosa, the cells of which later form the lutein cells; *T.I.*, theca interna; *T.E.*, theca externa. (Williams—*Obstetrics*, D. Appleton-Century Company.)

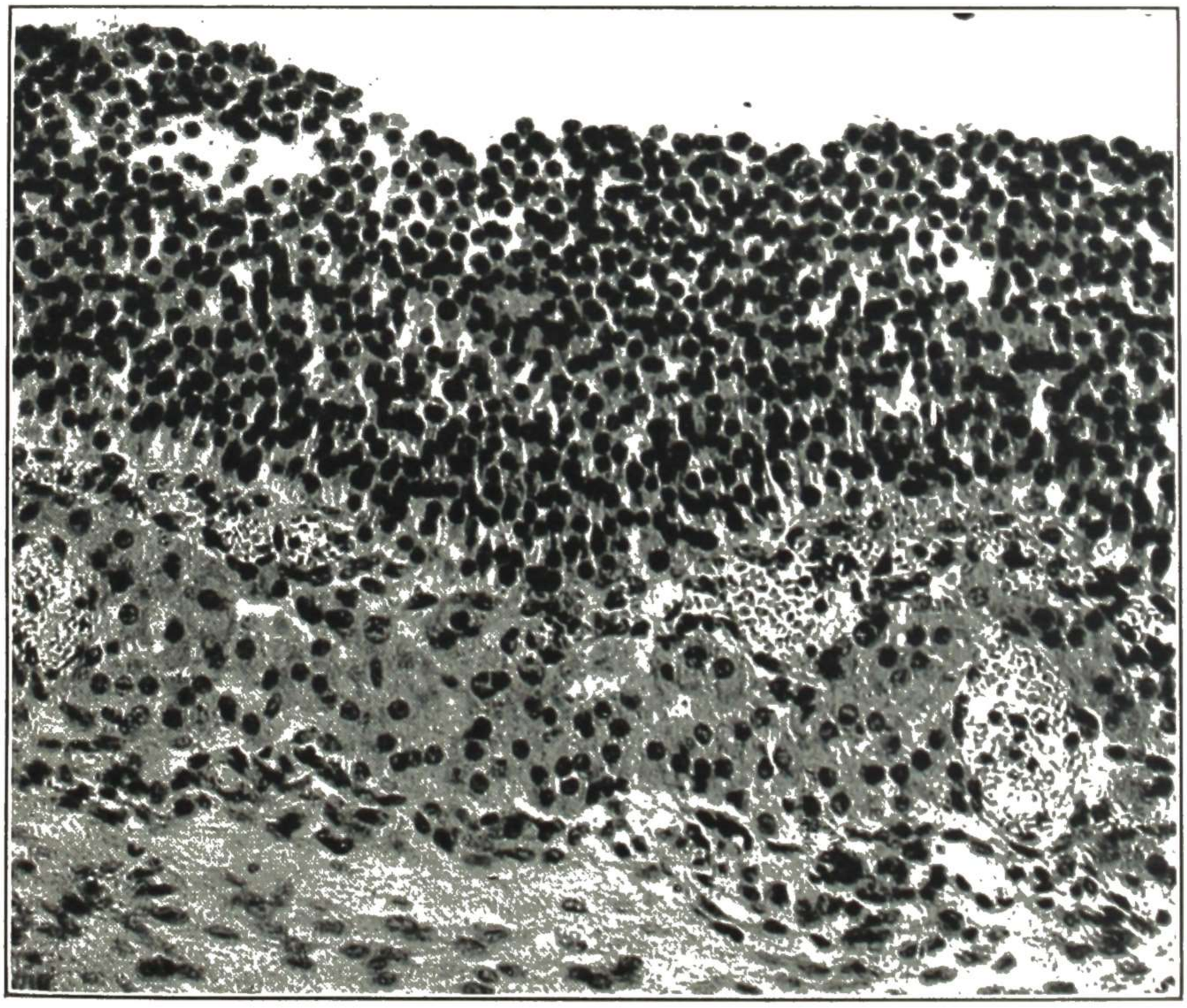


Fig. 33.—Photomicrograph, corpus luteum of proliferation. High power, showing the cellular characteristics of the three layers. Notice the large theca interna cells filled with light staining lipoid substance. The capillaries of the theca interna are widely dilated and filled with blood cells. The sharp 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.

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.

3. The stage of Maturity (twenty-third to twenty-sixth day). The completion of vascularization and the forming of the dividing line between the lutein layer and the contents of the lumen indicate that the corpus luteum has reached the stage of maturity (Fig. 35). Its function as an endocrine gland is now most evident, and it gives off its hormone into the blood stream instead of into the cavity. Fig. 36 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 (Fig. 37) 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.

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 Figs. 38 and 39. 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.

ENDOCRINE RELATIONS

Concerned in Ovarian Function

The ovary has another function entirely distinct from that of supplying ova and yet intimately associated with it, namely, the endocrine function. It has been clearly demonstrated that this endocrine function of the ovary is under the control of the hormones of the anterior lobe of the pituitary gland. The pituitary-ovarian relationship is the essential factor which determines in the girl the growth and development of the reproductive organs occurring at puberty. The development of the secondary sex characteristics, both physical and psychic, is also due to the action of these hormones. Opinion is divided as to whether the ovaries exhibit any endocrine function before puberty.

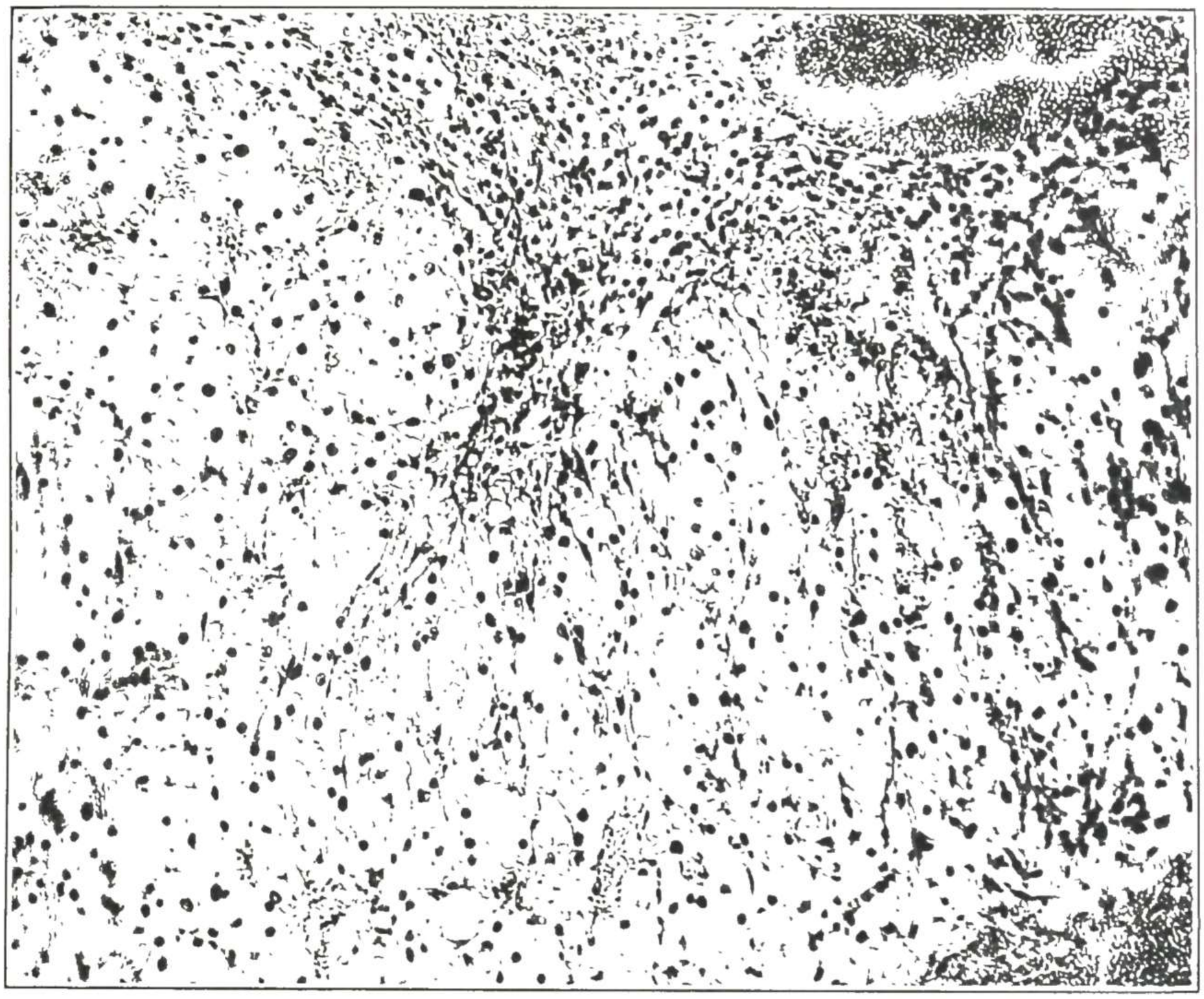


Fig. 34.—The theca interna cells have diminished in size due to a loss of their fat content. The capillaries of the theca interna are seen invading the granulosa layer, the cells of which have assumed a lutein character. In this luteinized layer the blood cells can be seen in capillaries and also lying 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.

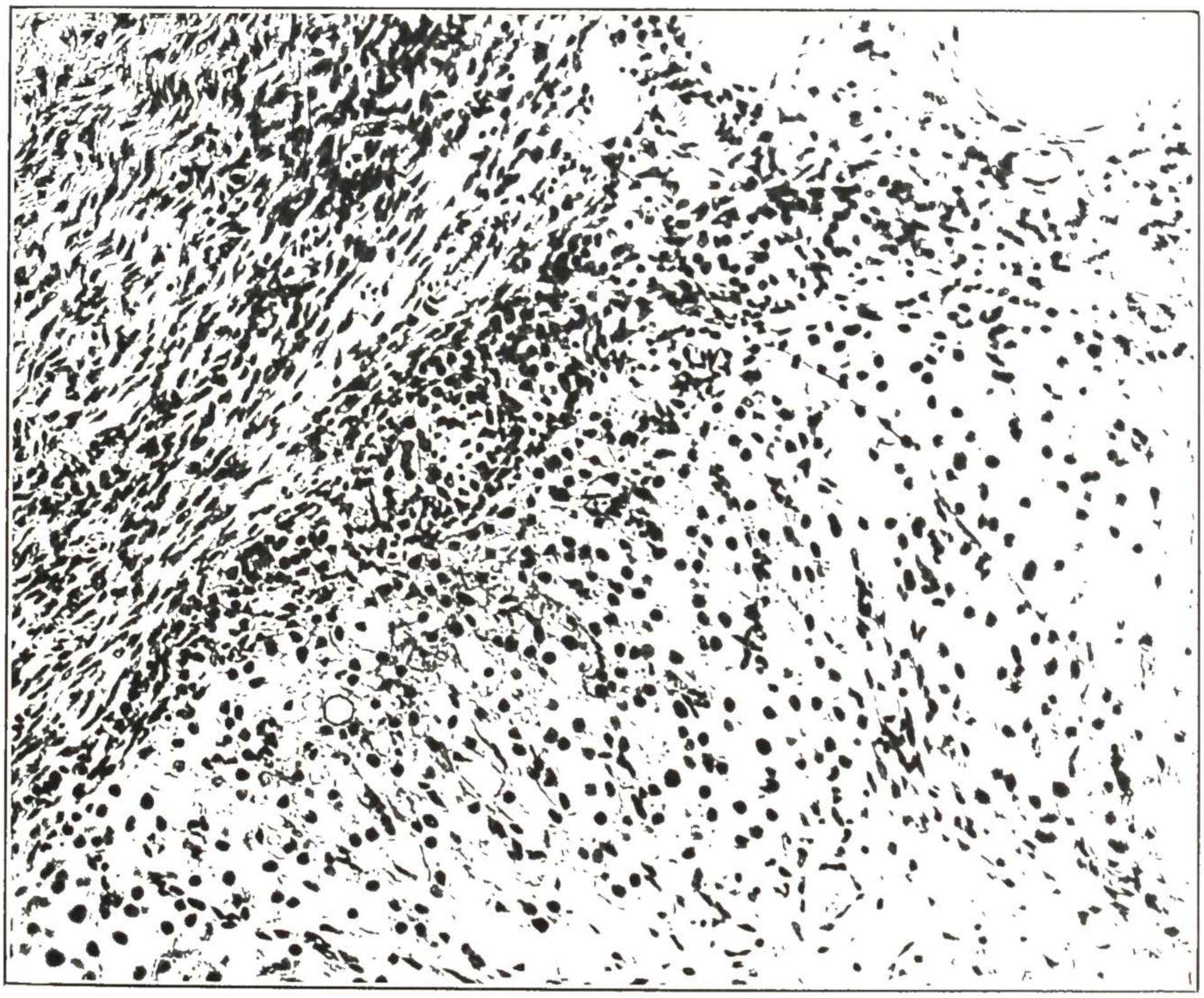


Fig. 35.—Corpus luteum of maturity showing area of the upper wall near the center of the figure. Note the zone of connective tissue separating the lutein layer from the cavity. Gyn. Lab.

Tandler and Cross hold that they have been able to demonstrate differences in the two sexes long before the onset of puberty. Novak, however, takes the opposite view, stating not only that there is no endocrine function before puberty, but also that there is no ordinary tissue growth of the uterus and ovaries from birth to puberty, such as is seen in other structures of the developing child.

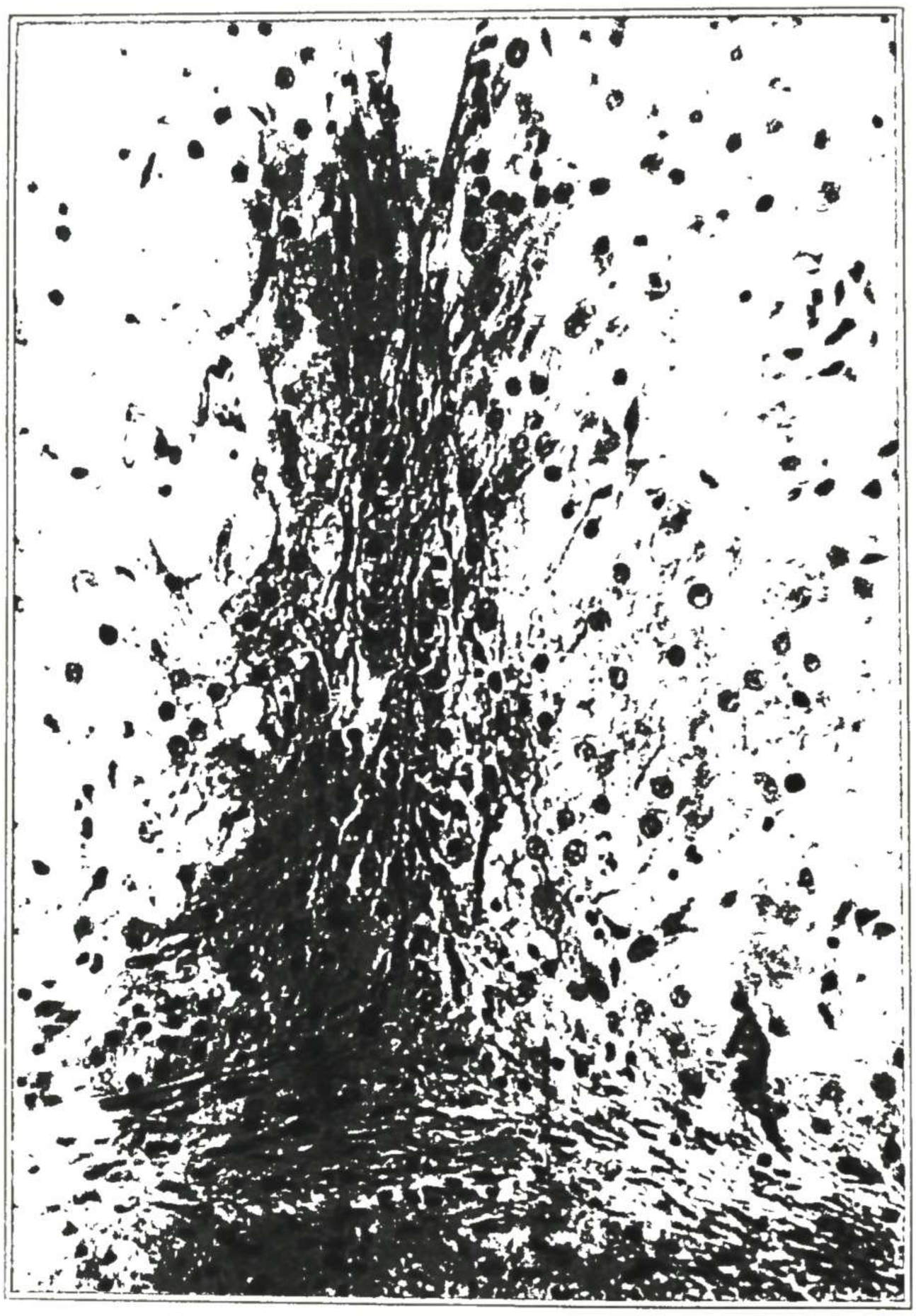


Fig. 36.

Fig. 37.

Fig. 36.—Corpus luteum of maturity, very high power, showing the septum formed by the theca interna (paralutein) cells. A large capillary is seen in the septum near the upper edge of the figure. The connective tissue cells lining the cavity are seen at the bottom of the figure. Gyn. Lab.

Fig. 37.—Normal adult ovary, showing a corpus luteum. Notice what a large part of the ovary is occupied by the corpus luteum. Gyn. Lab.

A concise summary of the known **endocrine relations** concerned in ovarian function will be given first. Later, a summary of the established facts concerning the various hormones, together with some of the steps in the development of this knowledge, will be given under the individual hormones.

With the onset of puberty and menstruation, a cycle of changes is set up involving the anterior pituitary and ovary and uterus, as indicated in Fig. 40. The factors initiating the onset of these cyclic changes are as yet not clearly understood.

Frank has shown that small doses of estrogen stimulate the pituitary gonadotropic function while larger doses inhibit it, hence it is possible that as adolescence approaches, the estrogen from the partially developed follicles at first stimulates and then, as the amount of estrogen increases, inhibits the production of the gonadotropic hormone. This gonadotropic hormone is the product of the basophilic cells in the anterior pituitary. In this summary the gonadotropic hormones directly from the pituitary are designated pituitary A or F.S.H., and pituitary B or L.H.

As shown in Fig. 40, pituitary A starts the follicle ripening and incites the granulosa cells to produce estrogen which in turn induces the growth phase of the endometrium. After full development of the follicle, ovulation occurs and a corpus luteum is developed from the ruptured graafian follicle. The

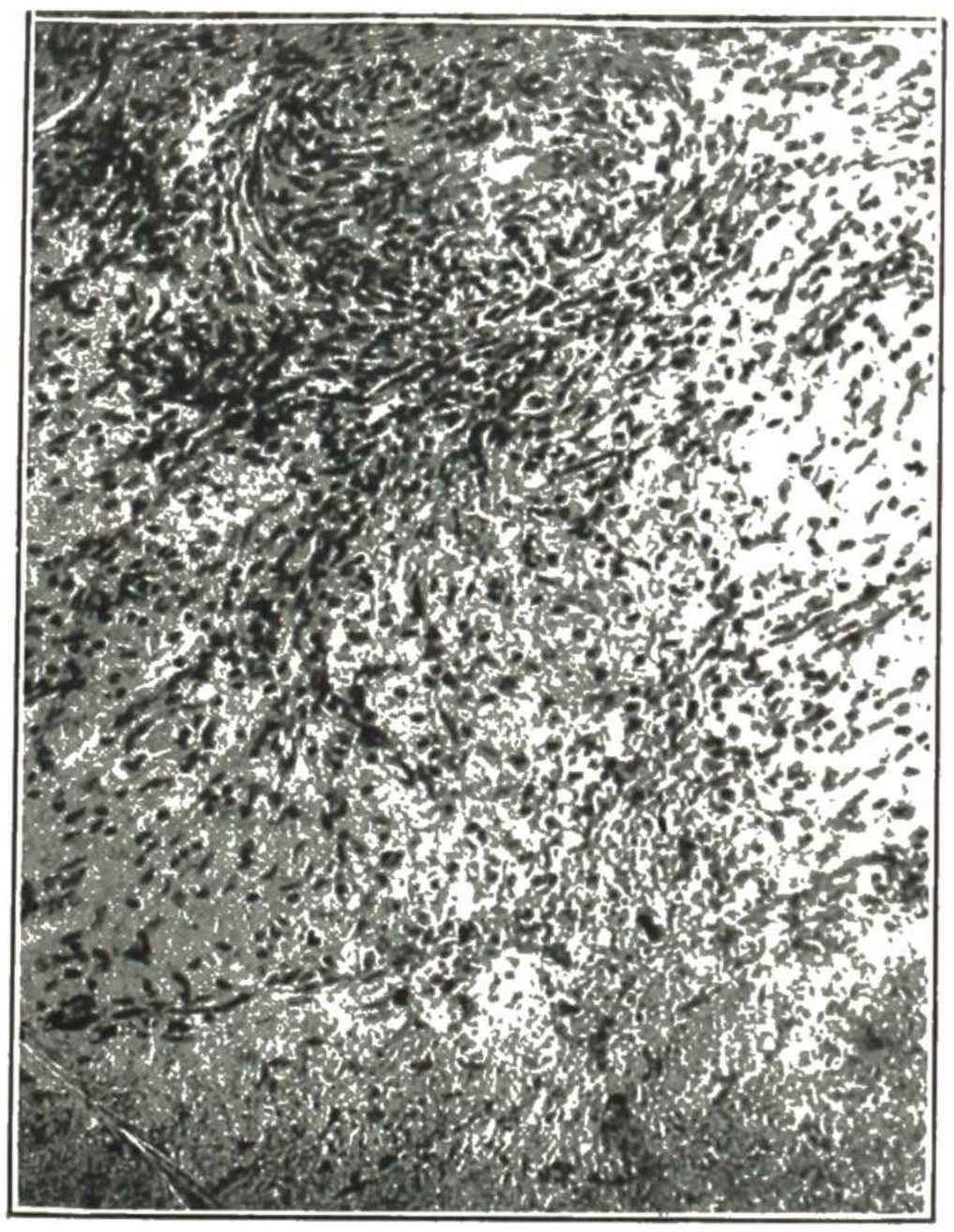


Fig. 38.

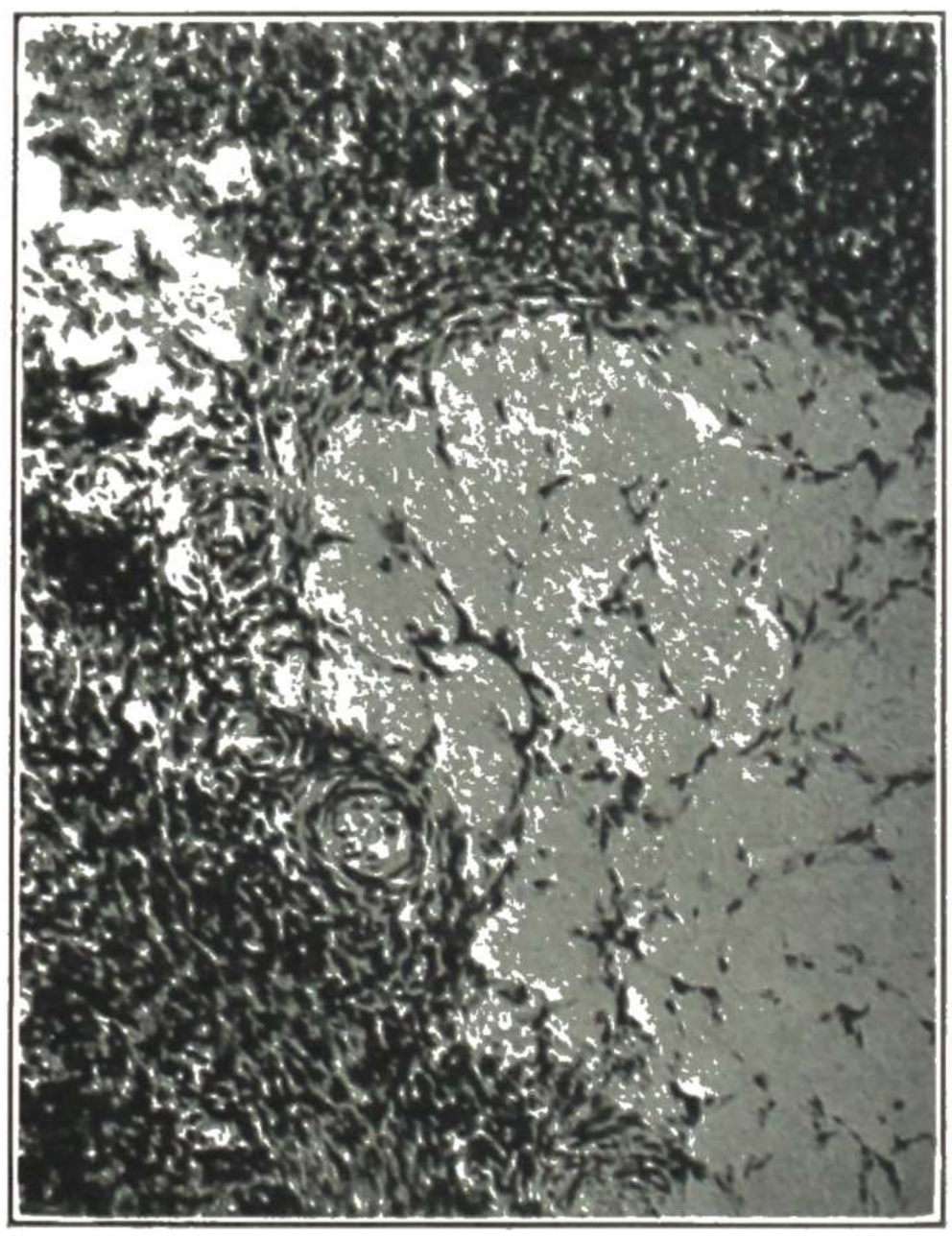


Fig. 39.

Fig. 38.—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. Gyn. Lab.

Fig. 39.—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.

action of pituitary B luteinizes the granulosa cells and incites them to produce the progesterone which, in conjunction with estrogen, causes the premenstrual or secretory phase of the endometrium.

The amount of the follicular hormone formed increases rather steadily through the cycle, reaching its highest peak just before menstruation. There is a slight drop in the blood estrogen at the time of ovulation. Estrogen inhibits the production of the gonadotropic hormone of the anterior pituitary. Consequently, as the level of estrin rises in the blood, there is a corresponding decrease in the secretion of pituitary A and B. When this decrease in the amount of the gonadotropic hormones becomes so marked that it is insufficient to maintain the corpus luteum, the latter undergoes retrogression. This results

in a cessation of estrogen production. The sudden withdrawal of estrin and progesterone causes a breaking down of the built-up endometrium, resulting in a flow of blood and débris (menstruation). The decrease of estrin in the blood now removes the inhibition on the anterior pituitary, allowing the basophilic cells to produce the gonadotropic hormone again. This stimulates a new follicle to develop, initiating a new cycle.

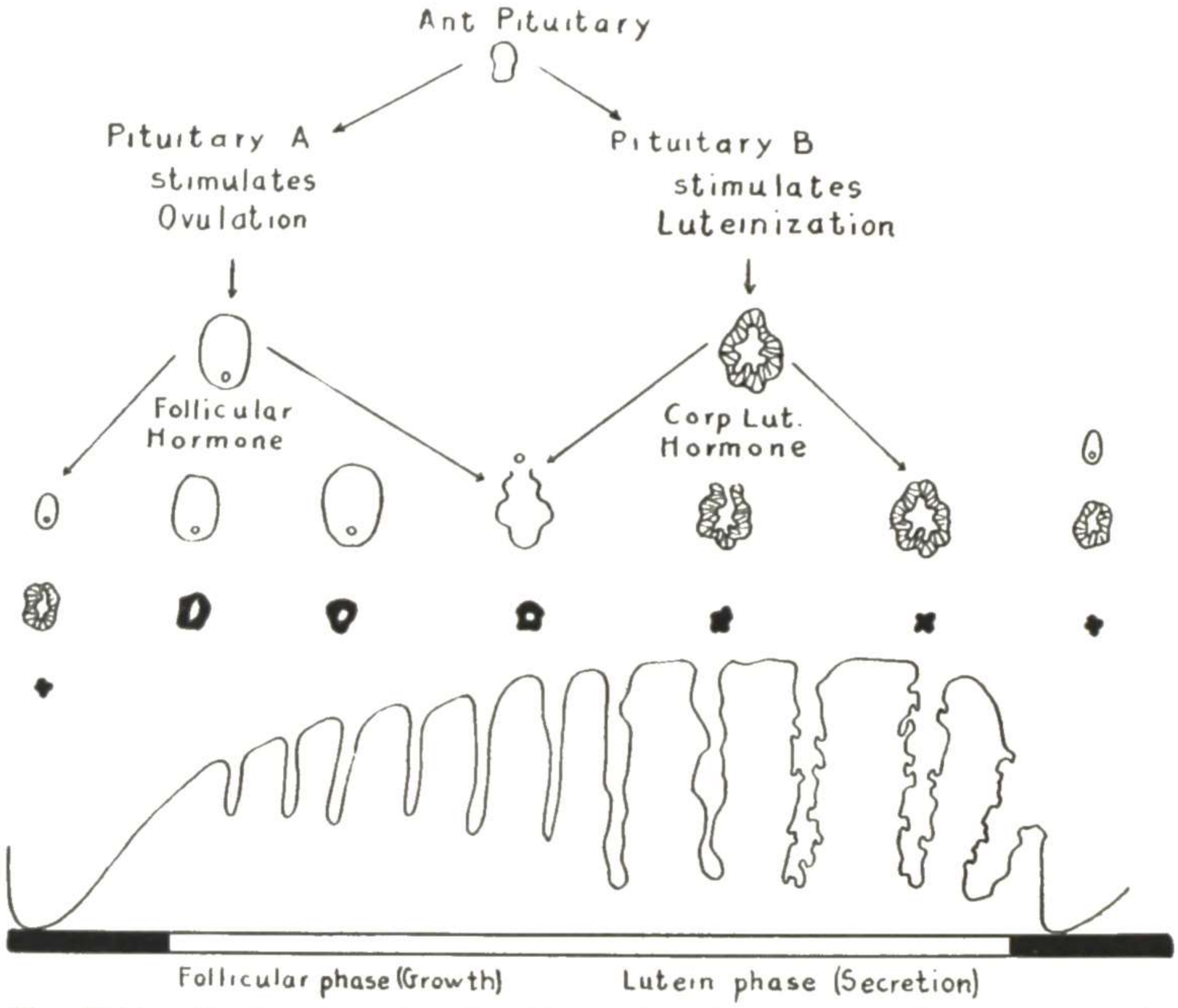


Fig. 40.—Schematic drawing showing the various hormones acting on the endometrium in their time relation. This represents a nonfertile cycle. (Crossen—*Synopsis of Gynecology*, The C. V. Mosby Company.)

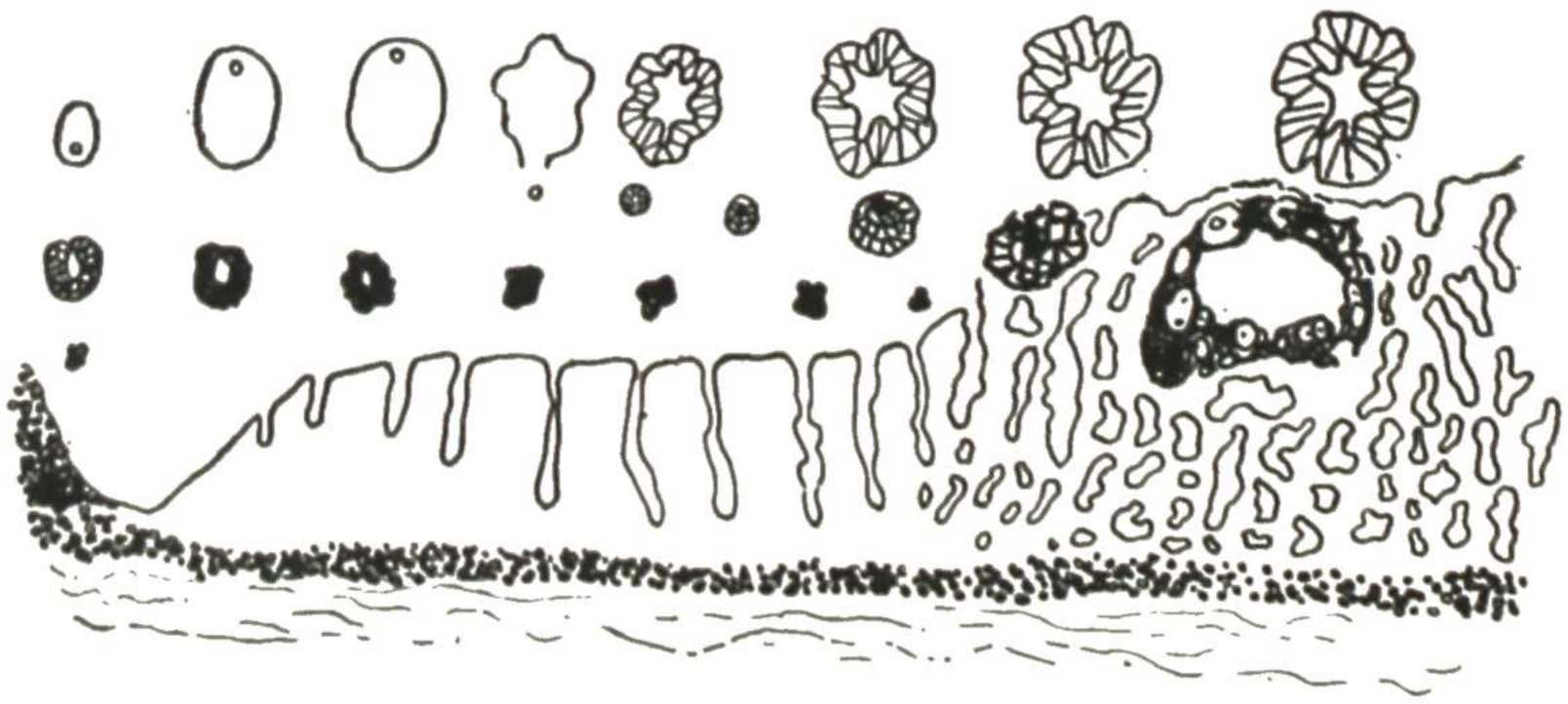


Fig. 41.—This represents the events occurring when pregnancy ensues. Ovum embedded, decidua formed, and corpus luteum enlarged and active. (After Schröder.)

In the event of pregnancy (Fig. 41) hypophyseal suppression persists, and the cyclic activity is held in abeyance throughout the gestation period. The corpus luteum continues to enlarge and its hormone, together with estrin, prepares the endometrium for the reception and the embedding of the fertilized ovum. A new factor is introduced in pregnancy, namely, the placenta. Collip and others have shown the placenta to be a very important source of the follicular hormone and of a hormone similar in some respects to the gonadotropic

hormone of the pituitary. The corpus luteum hormone was obtained from the placenta by Adler. The placenta probably takes over the production of progesterone after the third month of pregnancy, and the amount increases up to the end of the ninth month. The placental hormones will be discussed in more detail later.

OVARIAN HORMONES

The fact that the **gonads** were endocrine organs was first proved in 1849 by Berthold. He showed that the secondary changes caused by castration of cockerels could be avoided by implanting the removed testicle in the castrate. Very little was added to this knowledge until 1896 when Knauer showed that implantation of the ovary in castrates prevented atrophy of the uterus. In 1900 Halban demonstrated that the anatomic and physiologic development of the genital organs are governed by the endocrine function of the ovary. He caused normal puberty changes in immature castrated guinea pigs by implanting of ovaries subcutaneously. In 1904, the importance of the ovarian interstitial tissue was brought out by Limon. In successful ovarian grafts the follicles usually degenerated, showing that the success is not entirely due to the ova-producing mechanism. Adler in 1912 was the first to cause sexual activity in castrated females by injecting aqueous extracts of ovarian tissue and Iscovesco was the first to obtain an active alcoholic ovarian extract.

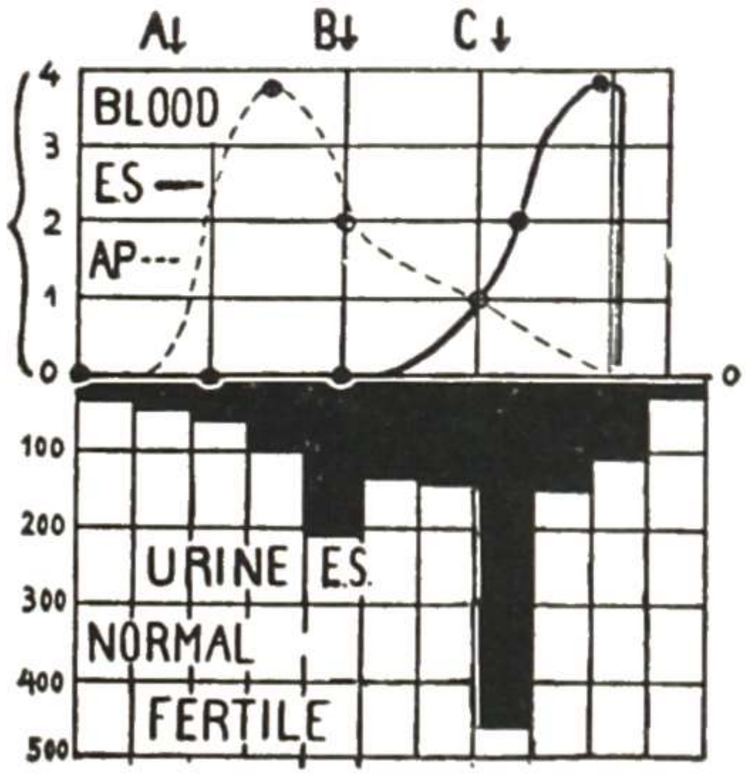


Fig. 42.

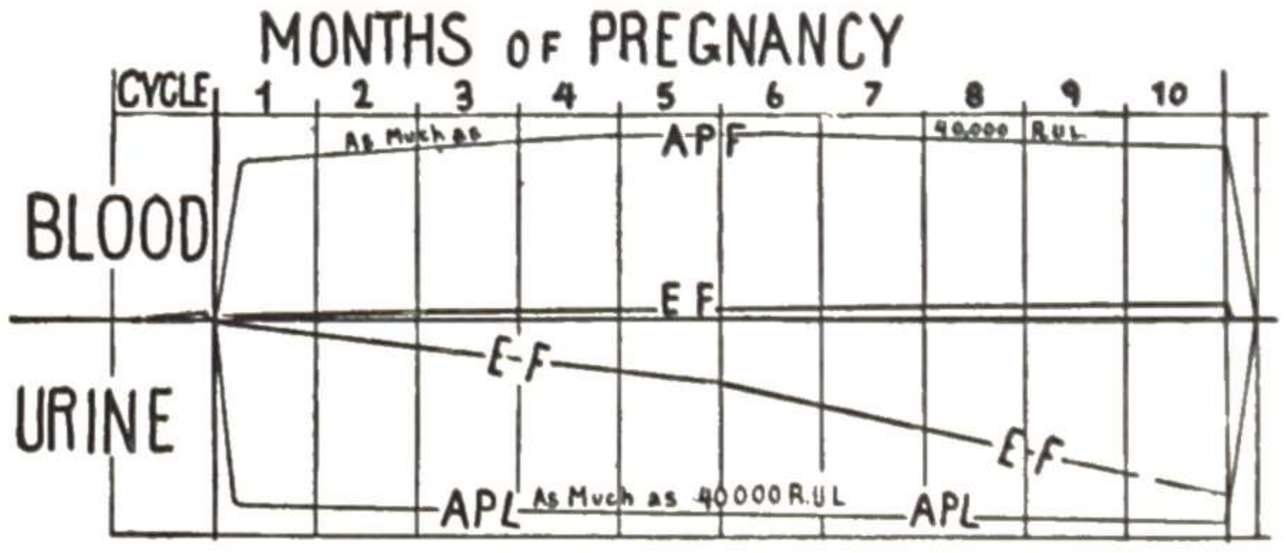


Fig. 43.

Fig. 42.—Hormone cycle (female sex hormone and anterior pituitary) of normal fertile menstruating woman. (Frank—*J. A. M. A.*)

Fig. 43.—Stupendous increase of hormone production and excretion produced by pregnancy. Not to scale—the cyclic readings are exaggerated, the pregnancy curve is reduced. (Frank—*J. A. M. A.*)

Follicular Hormone

New impetus to the study of the ovarian hormones was added by the discoveries of Stockard and Papanicolaou. They ascertained that ovulation in guinea pigs is accompanied by marked hypertrophic changes of the vaginal epithelium, which are easily detected by microscopic examination of the vaginal smear. The importance of this discovery becomes obvious when one realizes that most of the subsequent research work on ovarian hormones was done in laboratory animals and estimation of results was dependent upon this test of function. This test was confirmed in other laboratory animals by Allen, Long and Evans, and by Pelkan. In animals that show periodic sexual exhibitions, as the dog and cat and pig, this test was not needed nor was it necessary in the monkey where menstruation occurs.

Later Allen and Doisy made the significant discovery that an extract of the follicular fluid, when injected into a castrated mouse, caused changes in the morphology of the vaginal epithelium and discharges indicative of estrus. They were the first to supply a simple specific biologic test for this estrus-producing hormone and to determine a standard unit. The latter represents the smallest quantity of the specific hormone capable of producing the vaginal changes referred to above. Frank discovered the presence of the sex hormone (estrin) in the blood of normal women. He found that the amount in 40 c.c. of blood in the normal menstruating fertile woman is less than one mouse unit until seven days before the period after which it rises rapidly and reaches its maximum, of about four mouse units, just before the period. With the onset of menstruation there is an abrupt fall of the hormone level in the blood to zero. He has also determined the excretion of this estrus-producing hormone in the urine during the normal menstrual cycle. He found an increase in excretion on about the tenth day, followed by a fall and a subsequent rise to a maximum on about the twenty-fifth day; the fall to zero occurred about three days after the onset of the period. The normal monthly output is from 1,200 to 1,500 mouse units, the maximum in a single day being about 450 mouse units. The charts by Frank show the blood and urinary levels during a normal cycle (Fig. 42) and also during pregnancy (Fig. 43).

It was discovered by Aschheim and Zondek that enormous quantities of this hormone are excreted in the urine of pregnant women, the concentration varying from 600 to 10,000 mouse units in every 1,000 c.c. of urine. The hormone was also found in the feces during pregnancy, in the blood of the newborn child, in the amniotic fluid, and in the saliva, breast milk, and blood of the mother. Its occurrence is not limited to the female, for it is found in men as well as in women; nor is it found only in the animal kingdom, for it has been extracted from potatoes, wheat, sugar beets, yeast, and petroleum.

Hormone storage does not occur in the body, so the response of an organ depends upon the maintenance of a minimum hormone level or threshold dose for a period of time sufficient to give the response.

There has been much investigation to determine the sites in the ovary for formation of hormones. In a review of these investigations Corner concluded that, notwithstanding the large amount of investigative work, information as to the sites of estrogen formation is not yet complete. The general conclusion seems justified that the estrogen found in the ovary and blood and urine of the non-pregnant female is probably formed by the theca interna of follicles of all sizes, and the estrogen found in the placenta and blood and urine of the pregnant female of certain species is produced in all probability by the placenta.

The isolation of the crystalline form of the follicular hormone was accomplished almost simultaneously by Doisy in this country and by Butenandt in Germany, in 1929. Doisy gave this pure product the name of theelin, and described it as ketohydroxyestrin. The present accepted designation is estrone or theelin. The hydrated form of theelin, estriol, is a trihydroxyestrin and differs from theelin in its estrogenic potency. Later, by hydrogenation of the ketohydroxyestrin molecule, a dihydro compound was formed possessing four times

the potency of theelin. This was called estradiol and it exists in the alpha and beta forms. This was accomplished by Schwenk and Hildebrandt. The chemical relationships are shown in Figs. 44 and 45.

More recent compounds are the benzoic monoester of *a*-estradiol and the *a*-estradiol dipropionate. The potency of these estrogens per unit weight is in the following order, beginning with the least potent, estriol, estrone, estradiol benzoate, estradiol dipropionate, estradiol. If they are considered for duration of effect, the sequence is estriol, estrone, estradiol, estradiol benzoate, and last estradiol dipropionate, having the most prolonged effect.

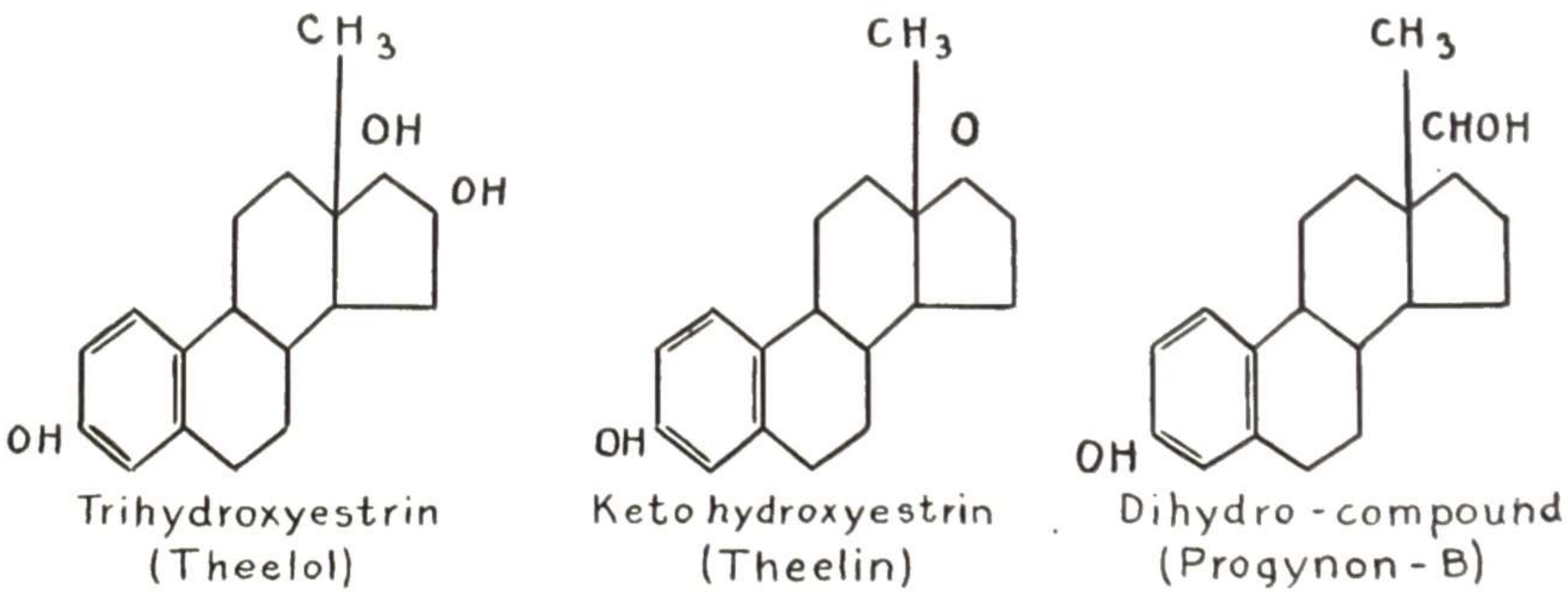


Fig. 44.—Chemical formulas of the various estrogenic substances.

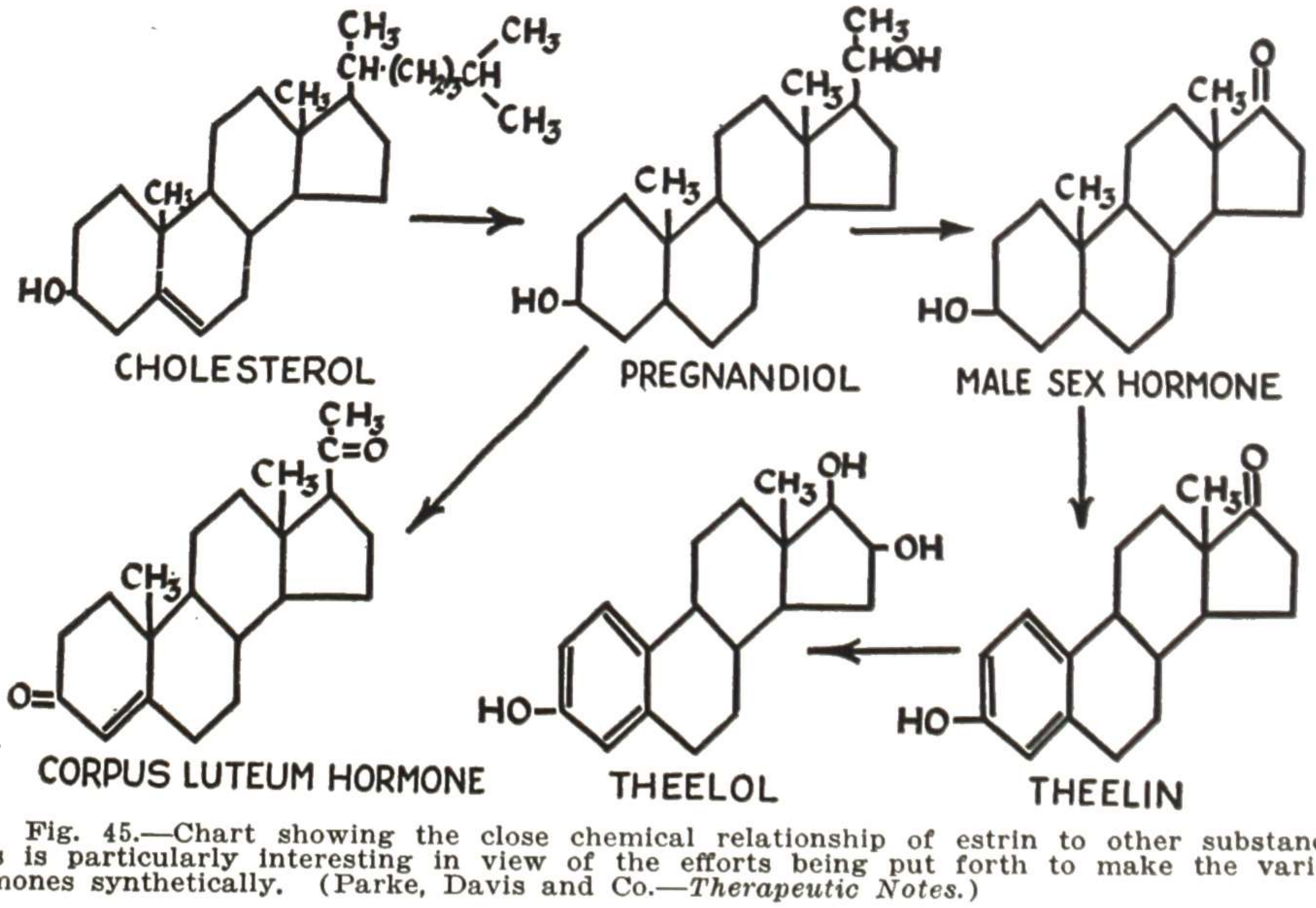


Fig. 45.—Chart showing the close chemical relationship of estrin to other substances. This is particularly interesting in view of the efforts being put forth to make the various hormones synthetically. (Parke, Davis and Co.—*Therapeutic Notes.*)

Stilbestrol, a synthetic substance related to the stilbenes, though not an estrogen, has been shown to produce many of the effects of the natural estrogens. It is inexpensive compared to the cost of the estrogens and is effective by oral administration. The disagreeable side-effects (nausea, dizziness, etc.) can usually be avoided by limiting the dose to 0.5 mg. daily, and giving it at bedtime. Two other synthetic preparations with estrogen effect are octofollin and hexestrol, supposed to have less of the disagreeable effects (see page 219).

An important recent accomplishment in the sex hormone field, from the chemical standpoint, was the synthetic creation of a natural estrogen from simple starting material. This was accomplished by Bachmann, who from simple materials made synthetic equilenin, which occurs as a natural estrogen in the urine of pregnant mares.

The Physiologic Actions of the Estrogenic Hormone
(Estrin, Follicular Hormones, Estrogens)
(Theelin or Estrone, Estriol, Estradiol, Estradiol Benzoate, Estradiol Dipropionate)

1. Promotes development of the secondary sex characteristics.

2. Promotes growth and vascularization of the uterus, controls the growth phase of the endometrium, and helps to control the progestational phase.

3. Produces estrus in normal or castrated, mature or immature, mice.

4. Inhibits the production of the gonadotropic hormone of the anterior lobe of the pituitary gland, by causing agranulation of the basophilic cells. In castrated animals the effect on these basophiles, explained under the gonadotropic hormone of the pituitary (Figs. 46 and 47), can be prevented by injection of theelin. In this indirect way it inhibits ovulation.

5. Withdrawal of the follicular hormone is thought to be one of the factors causing the onset of menstruation.

6. Contractions of the uterine and tubal musculatures are stimulated by estrin. It also sensitizes the uterine muscle to the action of pituitrin.

7. It inhibits the action of progestin on uterine and tubal muscle.

8. Hisaw and others produced uterine bleeding in castrated monkeys. The endometrium showed no premenstrual changes. They later used theelin injections followed by progestin and produced menstrual-like bleeding with progestational changes in the endometrium.

9. In monkeys and in human beings, excessive doses of theelin have caused hyperplasia of the endometrium.

10. It causes a marked elongation of the milk ducts of the mammary gland and an increase in the number of primary buds in the alveoli. The epithelium covering the nipple is also thickened.

11. It inhibits lactation by its inhibitory influences on the lactating hormone of the anterior lobe of the pituitary, and also by its local action on the breast. Both actions are present during pregnancy, where there is marked breast development and preparation for lactation but no lactation until withdrawal of theelin after the delivery of the placenta. Estrin may be a factor in the etiology of breast carcinoma.

12. Overholser and Allen produced atypical growth of cervical epithelium in monkeys by the prolonged administration of estrin in combination with chronic trauma. Loeb, Suntzeff, Burns and Moskop produced precancerous changes in the cervix of a mouse by estrogen administration. Later, Gardner, Allen and others produced cervical cancer in mice in the same way, and they

successfully transplanted these tumors in male and castrated female mice. Estrin may be a factor in the etiology of cervical carcinoma.

13. Estrin passes through the placenta into the fetal circulation and affects the genital organs of the fetus. The occasional finding of secreting breasts and uterine bleeding in the newborn is attributed to the sudden withdrawal of the maternal estrin at birth. A test for prediction of sex is based on the placental permeability to the male and female hormones.

14. Werner, and later Kaufmann, caused uterine bleeding in human castrates by huge injections of estrin, but curettage showed no premenstrual changes. Kaufmann gave from three to ten million international units over a period of months to five patients with primary amenorrhea, some with uteri smaller than a hazelnut. In these women he succeeded in causing the uteri to increase to normal size. Some of the patients had short periods of bleeding. Werner used theelin. Kaufmann used a dihydro compound (progynon B).

15. Kaufmann produced a typical Swiss-cheese hyperplasia in a human castrate by using huge estrin dosage. Crossen (R. J.) has produced advanced precancerous changes in the endometrial glands of an older mouse, using estrogen. Estrin may be a factor in the etiology of adenocarcinoma of the fundus. Nelson produced myoma in guinea pigs by estrogenic administration.

16. Kaufmann caused the formation of a premenstrual-like endometrium, in a human castrate by using estrin and progesterone. This is discussed under the corpus luteum hormone.

17. Werner attempted to cause lactation in human castrates by giving theelin, corporin, and prolactin in the proper sequence. He was unable to obtain lactation, although some of the women had marked enlargement of the breasts and felt as though they were about to lactate.

18. Estrin is responsible for the series of changes in the organism which tend to facilitate coitus and fecundation and to create a special state of libido, varying in degree according to the species.

19. It causes hyperemia of the nasal mucous membrane.

20. It increases the tone of the vesical muscle.

Corpus Luteum Hormone

The enthusiasm caused by Allen and Doisy's work led many workers in this field to forget the importance of the corpus luteum as an internal secretory organ. Some went so far as to claim that the follicular hormone was the only hormone of the ovary, and Frank suggested that it be called the female sex hormone. The fallacy of this idea will be shown by tracing the development of our knowledge of the corpus luteum hormone.

The first to suggest that the corpus luteum elaborated an internal secretion was Gustav Born. He noted that in placental mammals the corpus luteum reaches its peak of development at the time when the placenta is beginning to form, and from the first days of pregnancy a decidual reaction begins in the stromal cells of the endometrium. He suggested that the internal secretion of the corpus luteum prepared the endometrium for reception and embedding of the ovum. Born died before proving his theory, and the work was con

tinued by L. Fraenkel. In 1903, he proved Born's hypothesis conclusively by showing that in rabbits when the corpus luteum is cauterized or removed within six days after coitus (ovulation), pregnancy did not occur.

In 1907, Leo Loeb showed that the corpus luteum hormone sensitizes the endometrium so that irritation of any kind will cause decidual growth. Using guinea pigs, after an unfertilized ovulation (copulation with vasectomized buck), he inserted a foreign body into the uterine cavity on the day on which the embryos would have become implanted if the animal had been pregnant. In each case a tumor of decidual cells was formed at the site of irritation. This result could not be produced at any other time in the cycle, nor could it be obtained if the corpus luteum was removed or cauterized.

In 1929, Corner proved conclusively the dual secretory function of the ovary and established a test for the corpus luteum hormone. He removed the ovaries or cauterized the corpora lutea in rabbits from fourteen to twenty hours after mating, at which time the fertilized ova are in the tubes. No decidual changes occurred in the endometrium and none of the embryos lived after the fourth day. This demonstrated again the dependence of the endometrium on the corpus luteum for production of the premenstrual or progestational stage.

The following test for the presence of corpus luteum hormone was then proposed. A doe rabbit is mated and eighteen hours later is subjected to removal of both ovaries and to excision of a small portion of the uterus. Corpus luteum extract is then administered for five days and on the sixth day after mating the animal is killed, the embryos are recovered if present, and the uterus is examined microscopically and compared with the specimen removed at castration. With administration of the extract the uterus undergoes changes indistinguishable from characteristic progestational changes and identical with normal pregnancy of the fifth or sixth day. When the experiment was repeated, using follicular fluid instead of corpus luteum, no progestational changes occurred. W. M. Allen and Corner carried castrated rats to term, using corpus luteum injections, while the controls invariably aborted. Corner named this hormone progestin.

Hisaw in 1927 isolated a crystalline fraction from an extract of cow corpora lutea which causes relaxation of the pelvic ligaments characteristic of pregnancy in guinea pigs. He also has isolated a noncrystalline fraction which causes the characteristic progestational changes in the endometrium. Hisaw named the former relaxin and the latter corporin.

Certain other facts pertaining to the ovarian hormones are of interest. That the corpus luteum has an inhibiting effect on menstruation has long been known clinically. Its removal at operation during the premenstrual phase causes precipitate menstruation. Persistent corpora lutea in cows prevent ovulation and cause sterility, both of which are corrected when the corpus luteum is destroyed. Estrus and ovulation can be prevented experimentally by injection of extract of the corpus luteum. It is evident then that estrogens and progestin have antagonistic effects, though they are synergistic when used in proper time-relation in promoting normal ovulation and menstruation.

This teamwork between the follicle hormone and the corpus luteum hormone has been demonstrated in numerous ways. Corner and Hartman, working separately, found that in primates there are two types of cyclic uterine bleeding, one in which ovulation does not occur, and one in which ovulation takes place and a corpus luteum is formed. With the former type there are no premenstrual changes in the endometrium while with the latter type, where a corpus luteum is present, typical premenstrual changes occur. They injected an estrogenic hormone into castrated monkeys and caused endometrial bleeding, but there was no premenstrual proliferation (lutein phase) of the mucosa. Hisaw next sensitized the mucosa in castrated rats by follicular injections and followed this with a series of corpus luteum injections (progestin), and in this way caused typical premenstrual-like proliferation of the mucosa. Hisaw and Leonard sum up the situation thus: "The function of the follicular hormone seems to be that of putting the uterus in the proper physiologic condition so it can respond to the corpus luteum hormone. Neither of these substances can produce progestational proliferation in the castrate uterus when given alone. If, however, it is first brought into condition typical of estrus through the injection of follicular hormone, and is followed immediately by corpus luteum treatment, progestational-like proliferation results."

According to Llinás, the evolution of the corpus luteum depends on whether pregnancy occurs or not. In any case it is divided into two stages: (1) an anabolic stage or stage of development which, in woman, lasts twelve days in the corpus luteum of menstruation and from three to four months in the corpus luteum of pregnancy, and (2) a catabolic stage or stage of regression which in pregnancy lasts until delivery.

During the anabolic stage of the corpus luteum certain changes take place in the genital organs which tend to favor the reception, implantation, and nutrition of the fertilized ovum.

During the catabolic stage of the corpus luteum all of the changes in the genital organs disappear and the organs return to normal. This regression occurs rather suddenly, and in woman and certain anthropoids is responsible for the menstrual flow due to the shedding of the congested mucosa.

During the first three months of pregnancy the corpus luteum determines the maintenance of the ovum in situ, and after that the placental progesterone takes over this function.

Progesterone has been extracted from the placenta, corpus luteum, and adrenal cortex. It was crystallized almost simultaneously by Willard M. Allen, Butenandt, and several others. It has never been secured in the urine, but it is thought that pregnandiol glycuronidate represents the end product of its secretion.

The Physiologic Actions of the Corpus Luteum Hormone (Progestin, Progesterone)

1. Together with estrin it controls the secretory or premenstrual phase of the endometrium and prepares it for the reception and embedding of the fertilized ovum.

2. It is essential for the conservation of early pregnancy before the placental progestin is present. The anabolic phase of the corpus luteum lasts during the first three or four months of pregnancy, after which time the placenta supplies the progestin.

3. It has been shown independently by Loeb, Papanicolaou, and Macht that it inhibits ovulation. It is thought by some that this action is an indirect one accomplished through inhibition of the anterior pituitary gland. Moore states that the direct evidence of the action on the pituitary gland is lacking.

4. It inhibits the contraction of the uterine muscle and maintains it in the state of comparative quiescence during pregnancy. It also inhibits tubal contractions, being antagonistic in its action to estrin and pituitrin in both tubal and uterine effects.

5. Corner and W. M. Allen have produced a premenstrual-like endometrium in castrated rabbits by using estrin and progestin in the proper sequence; this had previously been done in castrated monkeys by Hisaw and others.

6. It stimulates the development of the mammary gland beyond the degree secured by estrin, the chief effect being on the acini.

7. According to G. Van S. Smith, it is needed for the conversion of estrone to estriol for excretion by the kidneys.

8. Progesterone is probably excreted as pregnanediol glucuronide as observed by Vennig and Browne.

9. When supplied, it can prevent estrogen-withdrawal bleeding.

10. Progesterone-withdrawal bleeding occurs with a shorter latent period than does that from estrogen withdrawal. It may be delayed by estrogen administration.

Demonstration of the effect of the corpus luteum hormone on the human endometrium in the castrate resisted all efforts until Kaufmann's work in 1932. He succeeded in producing a premenstrual-like endometrium in a human castrate by using in their proper sequence estrin and the corpus luteum hormone. In forty cases of secondary amenorrhea he produced menstrual-like bleeding by the same means.

In the castrate case the total amount of estrogen used was 1,000,000 international units. In order to get the concentration needed in a small dose of liquid for hypodermic use, he used the dihydro compound obtained by hydrogenation of the ketohydroxyestrin (Schwenk and Hildebrandt). He used 35 rabbit units of progestin in the form of proluton.

In the first trial, curettage was done without waiting for menstruation, and a typical premenstrual-like endometrium was obtained. The experiment was repeated without curettage, and the bleeding started two days after the last injection of the corpus luteum hormone. Pieces of the discharged endometrium showed markedly convoluted glands, and an abundance of glycogen was demonstrated in the glandular epithelium, indicating that the glands were in a condition of marked functional activity.

In the cases of secondary amenorrhea the following plan was used: on the first, fourth, eleventh, and fifteenth of the month 50,000 mouse units of progynon were given intramuscularly. This was followed on the nineteenth, twentieth, twenty-second, and twenty-third days of the month by 10 rabbit

unit doses of progesterone (corpus luteum hormone). Menstrual-like bleeding always occurred within a few days after the last injection. W. M. Allen has shown that a similar effect can sometimes be obtained by the use of progesterone alone.

The very important question arises here as to whether the help given these patients assisted them to ovulation and corpus luteum formation and resulting menstruation (normal preparation for pregnancy) or only to nonovulation bleeding. Probably some of the patients attained to ovulation and others did not—a vital difference in trying to overcome sterility. This brings up the problem of determining in a given case, under treatment resulting in a bloody flow at times, whether or not ovulation is taking place. It also emphasizes the need of a distinctive term for nonovulation bleeding, instead of confusing it with menstruation, which has long implied, and should continue to imply, ovulation and corpus luteum formation with resulting preparation of the endometrium for pregnancy. This point is further considered under Physiology of the Uterus.

Male Hormone

Under gonadal hormones the androgens must be included. We now know that the ovary secretes some male hormone, and in both sexes hormones of the opposite sex are found in the blood and excretions. Hence these hormones are not sex specific. Some of the androgens and adrenal cortical extracts show estrogenic and progestational activity. These effects of the androgenic substances in the female rat are as follows: suppression of estrus cycles, increase in size of uterus, prevention of uterine atrophy after castration, and luteinization of the ovaries. In the monkey it inhibits menstruation, as it does also in the human subject. Some of the undesirable effects in the human being are deepening of the voice, enlargement of the clitoris, and excessive hair growth. Some of these actions are indirect, through inhibition of the pituitary.

GONADOTROPIC HORMONES

These two groups of hormones stimulate the gonads to functional activity and hence are referred to as the gonadotropins. First, there is the group derived from the anterior portion of the pituitary. These are found normally in the blood and urine of both men and women, and in increased amount after natural or artificial menopause. Second, there is the group derived from chorionic cells (placental hormones). These are found in the blood and urine of women with normal or abnormal pregnancy, and in the blood of pregnant mares.

Pituitary Gonadotropins

A great step forward in the knowledge of sex physiology was the demonstration of the fact that the anterior lobe of the pituitary gland controls ovarian function. Long and Evans had produced luteinized atretic follicles and delayed estrus and ovulation, by injections of alkaline extracts of beef pituitary. Smith and Engle caused true ovulation, with luteinization of atretic follicles coupled with growth stimulation to the degree of gigantism, by re-

peated anterior lobe pituitary transplants in immature mice. Aschheim and Zondek produced a predominance of luteinized atretic follicles and hemorrhagic follicles by implanting single grafts of the anterior lobe of the pituitary in immature mice. A separation of the anterior lobe extracts into follicle-stimulating and luteinizing components was first accomplished by Fevold, Hisaw, and Leonard.

It now seems well established that the basophilic cells of the anterior lobe of the pituitary elaborate the gonadotropic hormone. These cells, as well as the acidophilic cells, are formed by the process of granulation from parent nongranulated cells called the "chromophobes." Normally basophiles are being produced continually by the appearance of granules in the chromophobes and, simultaneously, the basophiles are being changed back into chromophobes by the disappearance of the granules, as indicated in Fig. 46. The

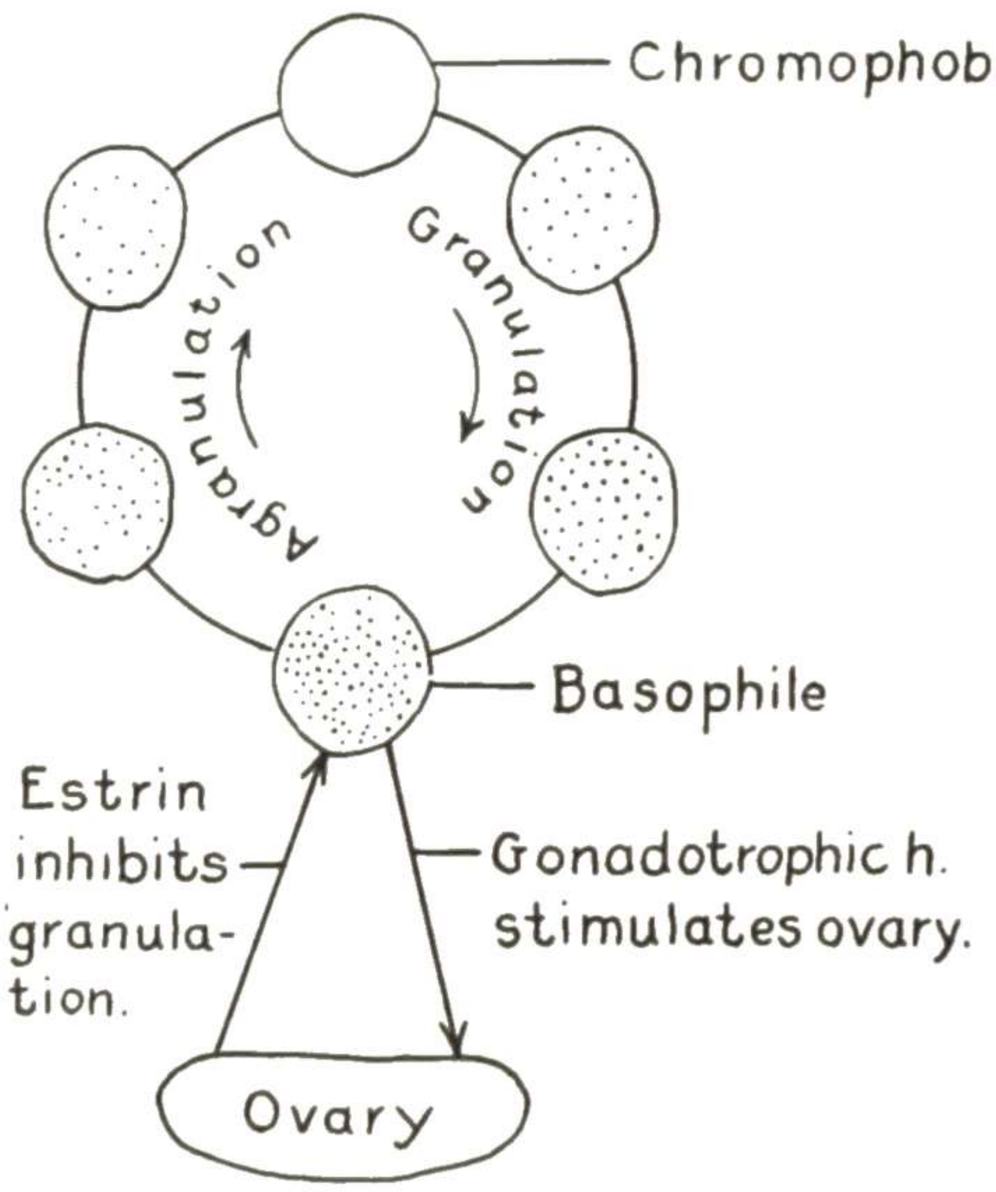


Fig. 46.

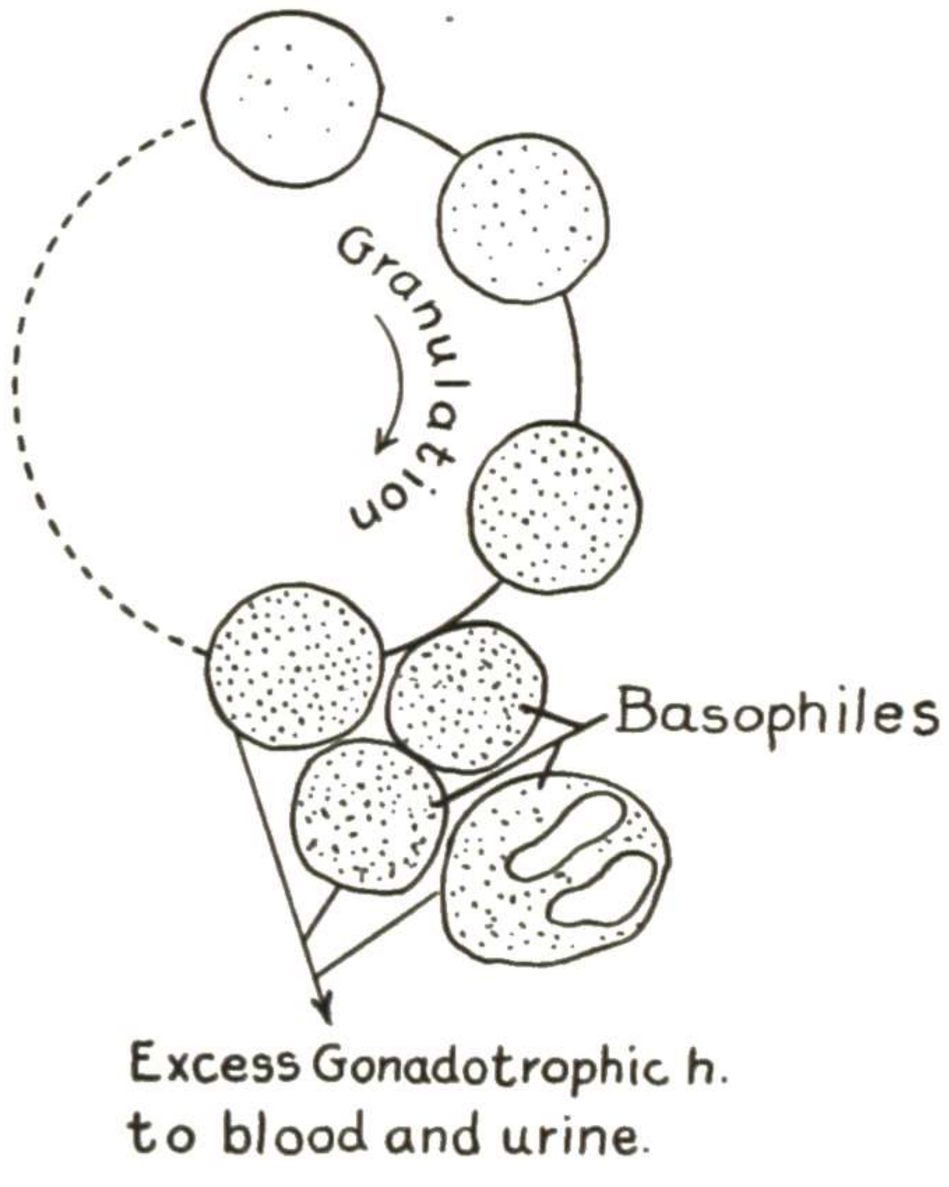


Fig. 47.

Fig. 46.—Normal cycle of the basophile in the anterior lobe of the pituitary gland. The basophile is formed by granulation of the chromophobe. The action of estrin inhibits granulation and initiates the process of agranulation, whereby the basophile is changed back to a chromophobe.

Fig. 47.—Basophilic cycle in the castrate. The estrin influence has been removed, hence excessive granulation and no agranulation are the result.

rate of granulation and degranulation is controlled by the estrin level in the blood. Removal of the ovaries removes this control of the balance in the rate of basophile formation and return to chromophobes, with the result that there is not only a more rapid granulation rate, with increased formation of basophiles, but also the ability to degranulate is lost. This marked change from the normal cellular cycle is indicated in Fig. 47. The basophiles not only increase in number but also increase in size and show a tendency to become vacuolated. As a result of this there is an increase in production of the gonadotropic hormone, especially the F.S.H. factor, with increased excretion in the urine. This is similar to the condition commonly found in the urine of women past the menopause.

The amount of the gonadotropic hormone in the blood as determined by Frank varies during the menstrual cycle, as is shown in the chart (Fig. 42). The increase to a maximum on the ninth day in the blood and the eleventh day in the urine (Kurzrok) would indicate a stimulation necessary for ovulation. Seidlin found that the gonadotropic hormones are metabolized by the ovary in vivo or in vitro and by no other tissue.

The weight of evidence at present is that there are two gonadotropic hormones of the anterior pituitary group—pituitary A and pituitary B. Shedlovsky and his associates have recently isolated the luteinizing hormone (B) in pure form and the follicle-stimulating hormone (A) in "almost" pure form.

Pituitary A (F.S.H.). This is the follicle-stimulating hormone which causes growth and development of the follicles and incites the granulosa cells and probably the theca interna to secrete estrogen. It does not, in its purest form, cause the follicle to become luteinized. Werner has shown that during the normal menstrual cycle there is a sudden transient increase of pituitary A in the urine at the mid-interval, evidently related to ovulation. In support of this idea Werner found pregnanediol in the urine two to five days following the increase of pituitary A. D'Amour feels that this pituitary A is the same as that which is found in menopause urine.

In the male, pituitary A stimulates the tubular elements of the testes.

Pituitary B (L.H.). This is the luteinizing hormone which acts on follicles, when ripened to a certain degree by pituitary A, and produces lutein changes leading to the secretion of progesterone. It augments the follicle-stimulating action so that the sum of the action of both together is greater than that of either used separately. It causes a rapid involution of existing corpora lutea.

In the male, pituitary B causes growth and functional activity of the interstitial tissue of the testes and stimulates growth of the accessory structures, the latter probably indirectly by its stimulation of androgen secretion.

Chorionic Gonadotropins

The chorionic gonadotropic hormones are of two kinds: (a) those present in the blood and urine of pregnant women and (b) those present in the blood of pregnant mares.

Human Chorionic Hormones. These appear in the blood and urine soon after the implantation of the ovum and the amount rises to a maximum in fifty to sixty days after the last menstrual period, after which there is a rapid fall to a lower level for the remainder of the pregnancy.

These gonadotropins differ from those of the pituitary group in that their ability to cause follicle growth and ovulation and luteinization, in laboratory animals (mice, rats, guinea pigs, rabbits), is dependent on an intact pituitary. They will not cause these changes in hypophysectomized animals unless treatment is given immediately after hypophysectomy while some of the actual pituitary secretion is still present.

The predominating effect of these pregnancy-urine hormones is luteinization in the laboratory animals mentioned. In monkeys and human beings these gonadotropins will not cause follicle growth or ovulation or luteinization even though the pituitary is intact.

The hormones obtained from human pregnancy-urine are similar to the gonadotropins of the anterior pituitary group, but not identical, for the pituitary must be present for them to operate in the laboratory animal experiments. The preponderating effect of these pregnancy-urine hormones is similar to that of pituitary B, whereas the effect of menopause-urine hormones (prolan A) is nearly altogether that of pituitary A.

Pregnant-Mare-Serum Hormones. The second type of chorionic gonadotropic hormones are present in the blood serum (but not in the urine) of pregnant mares. In laboratory animals this serum produces responses similar to those obtained by a combination of human pregnancy-urine and menopause-urine; that is, it produces follicle growth and ovulation and luteinization. In monkeys, which are different from the "laboratory" animals, this serum produces follicle stimulation and ovulation but no luteinization.

In human beings, Davis and Koff were able, in normally ovulating women, to produce ovulation at will by intravenous administration of forty to sixty units. So far it has not been proved to cause this effect in nonovulating women. The fate of the serum hormone after injection is not known, but it is not excreted in the urine. This hormone has been purified, and preparations of high potency are on the market.

OTHER HORMONES

From what has been said it is evident that the ovaries constitute an important coordinating unit in the great endocrine glandular system, all parts of which are interrelated. The ovarian-pituitary cycle will function normally, and thus induce and maintain normal genital development and activity, only so long as this entire system persists in a state of equilibrium effected by "interglandular reciprocity" and "chemical correlation" of all its members. Ovarian function, therefore, is very likely to be interfered with whenever this balance becomes disturbed through either hypofunction or hyperfunction of an individual gland. The glands principally concerned in this connection are the pituitary, thyroid, adrenals, and pancreas.

Pituitary Hormones

In the extensive and complicated endocrine system the pituitary gland exercises a major influence, indicated by the large number of hormones originating in its anterior and posterior portions. In addition to the gonadotropins, already described, the pituitary hormones of special gynecologic interest are the growth, thyrotropic, adrenotropic, lactogenic, and oxytocic.

Growth Hormone.—Long and Evans, in 1922, demonstrated the stimulating effect of the anterior pituitary on growth in normal rats. They succeeded in restoring normal growth in rats dwarfed by hypophysectomy by administration of anterior pituitary gland.

Although preparations of this hormone are not pure physiologically, they may now be freed sufficiently from contaminating hormones to produce normal growth while the thyroid and gonads and adrenal cortex remain atrophic. Evans states that it is probable that all forms of dwarfism are directly caused by inadequate pituitary function, regardless of the ulterior cause. Cretinic

dwarfs are the result of a depression of the pituitary function secondary to a thyroid deficiency. It can be corrected indirectly by administration of thyroid, with the consequent stimulation of the hypophysis, or directly by administration of anterior pituitary extracts of the growth hormone.

Thyrotropic Hormone.—In 1917, B. M. Allen showed that extirpation of the anterior lobe of the pituitary caused atrophy of the thyroid and the adrenals in amphibia. Administration of fresh bovine anterior pituitary in these amphibia caused repair and activation of the involuted thyroid and in some cases even produced hyperplasia.

The discovery of the thyroid-stimulating effect in animals was made by Loeb in 1929 and independently by Aron a little later. P. E. Smith found that the atrophy of the thyroid and adrenals caused by hypophysectomy in mammals could be corrected by replacement therapy. It is now known that these thyroid-stimulating effects are due to a specific hormone of the anterior pituitary, and this has been named by Wiesner and Crew the thyrotropic hormone.

A partial purification was first achieved independently by Junckmann and Schoeller and by Loeser in 1932. The thyrotropic hormone exerts its action only in the presence of the thyroid gland. It is not active by mouth and is destroyed by boiling. The administration of the thyrotropic hormone to normal animals results, in the course of a few days, in enlargement and hyperplasia of the thyroid. There is an increase in heart rate, exophthalmos, reduction in the iodine content of the gland, and a depletion of liver glycogen.

Adrenotropic Hormone.—For years clinicians have recognized that there was a definite relationship between certain adrenal lesions and certain types of precocious menstruation. Also secondary amenorrhea may be associated with adrenal hyperplasia, as emphasized by Cecil and others. Operations to remove the adrenal lesion usually reestablish the normal pelvic function.

As previously mentioned, P. E. Smith demonstrated that the atrophy of the adrenal cortex occurring after hypophysectomy could be prevented by intramuscular transplants of fresh hypophysis. Evans obtained the same results, using purified extracts.

Clinically, destruction of the hypophysis by disease causes atrophy of the adrenal cortex, while in functioning tumors of the pituitary (especially cases of acromegaly) hypertrophy of the adrenal cortex occurs.

Lactogenic Hormone.—The association of the mammary gland with pelvic function has always been evident, from the changes taking place with puberty, menstruation, pregnancy, and the menopause. The mechanism of this relationship was obscure until Stricker and Grueter reported lactation produced by the administration of anterior pituitary extract. Corner confirmed this work in 1930 and more recently the hormone has been studied in detail by Asdell, Nelson and Pfiffner, Gardner and Turner. In 1933, Riddle, Bates, and Dyskshorn published an article on "The Preparation and Assay of Prolactin—a Hormone of the Anterior Pituitary." Prolactin causes the onset and continuation of milk secretion after the breast has first been developed by estrin. Selye showed that a brief period of lactation will occur in hypophysectomized rats at parturition, so the anterior pituitary is probably not the only source of the lactogenic hormone. Werner was unable to cause lactation in castrate women

although the breast was first stimulated by injections of theelin followed by corporin, before the administration of the prolactin. Growth of the male breast and lactation have been accomplished by combined use of theelin and prolactin.

Pancreotropic Hormone.—Insulin is used for the relief of dysmenorrhea, and there may be some relationship between its action in this condition and its effect on the pituitary.

Oxytocic Hormone.—Pituitrin and similar acting preparations are from the posterior lobe of the pituitary. All the other hormones mentioned are from the anterior lobe.

Nongenital Hormones.—There are many hormones of the pituitary which are only indirectly concerned with the genital functions and therefore are not discussed in detail here. The importance of the pituitary in general endocrine control is indicated by the number and variety of its hormones, as shown in the accompanying table by Jores.

TABLE OF PITUITARY HORMONES (BY ARTHUR JORES)

HORMONE	SOURCE	REMARKS	AUTHORS
1. Oxytocic hormone	Posterior lobe	Successfully isolated	Dale, Kamm
2. (a) Blood pressure hormone	Posterior lobe	Identity questionable	Schäfer, Oliver, Kamm
(b) Intestinal hormone	Posterior lobe	Isolation not yet successful	
(c) Antidiuresis hormone	Posterior lobe		
3. Intermedin (Erythrophoric) hormone	Middle lobe	Successfully isolated	B. Zondek and Krohn
4. Melanophoric hormone	Basophile anterior lobe cells	Successfully isolated	Hogben, Winton, Jores
5. Growth hormone	Eosinophile anterior lobe cells	Successfully isolated	Long and Evans
6. Follicle-ripening hormone	Basophile anterior lobe cells	Successfully isolated	
7. Luteinizing hormone	Basophile anterior lobe cells	Identity questionable	Smith, Zondek, Aschheim
8. Thyrotropic hormone	Anterior lobe	Successfully isolated	Aron, Crew and Wiesner
9. Lipoitrin	Anterior and posterior lobes	Successfully isolated	Raab
10. Fat metabolism hormone	Anterior lobe		Anselmino and Hoffmann
11. Pancreotropic hormone	Anterior lobe		Anselmino and Hoffmann
12. Parathyrotropic hormone	Anterior lobe		Anselmino and Hoffmann
13. Adrenotropic hormone	Anterior lobe	Identical with the pigment hormone?	Smith, Anselmino, and Hoffmann
14. Contrainsulin hormone	Anterior lobe	Identical with the growth hormone?	Houssay and Unger, Lucke
15. Lactogenic hormone (Prolactin)	Anterior lobe		Lyons, Riddle

Since this table was published much investigative work has been carried on in various directions. A few items of interest in this field are that lactogenic, thyrotropic and chromatophoric hormones have been isolated from human pituitary glands (by M. Riley) and that purified factors of lactogenic, follicle-stimulating, luteinizing, thyrotropic, and growth-promoting hormones have been obtained (by Fevold, Lee, Milton, Hisaw, and Cohn).

Thyroid Hormone

The influence of thyroid extract on disturbances in pelvic endocrine function has long been known clinically. In fact, it was for many years the one glandular extract which seemed to give any consistent results. The exact mechanism of its action is still not known, but the effects obtained are probably due both to its general action on metabolism and to some action on the anterior pituitary.

Adrenal Cortex Hormone

In normal animals administration of the adrenal cortex hormone caused a slight decrease in the positive potassium balance, and in large doses it caused an increase in the reticulocytes. Removal of either the hypophysis or the adrenal gland leads to atrophy of the ovary. This is repaired by anterior lobe injections in the absence of the adrenals, but not by injections of adrenal cortex hormone in the absence of the pituitary.

This would indicate that the adrenal effect is indirect through the anterior pituitary. Evidence of direct action on the ovary, however, has been presented by Migliavacca. He gave adrenal cortical hormone to guinea pigs in which the pituitary had been inactivated by roentgen radiation, and succeeded in producing luteinization of the ovarian follicle. He concludes that this effect, which is the same as that of pituitary B, is a direct one by the adrenal cortex on the ovary. Hirsutism and virilism cannot be caused by injection of this hormone nor can such injection cause the condition of basophilia of the pituitary. It may be that the secondary changes which result with adrenal cortex lesions are due to another hormone or to a withdrawal of the cortical hormone.

L. R. Broster gives the following classification for the adrenogenital syndrome: Group I, in which there is adrenal pseudohermaphroditism, usually discovered at puberty because of primary amenorrhea; Group II, in which adrenal virilism appears after puberty with secondary amenorrhea; Group III, in which mild virilism, in association with other endocrine disturbances, especially those of the pituitary, occurs after puberty. The patients in the last group usually have excess fat. Excellent results were obtained by adrenalectomy in the Group II cases, but not in Groups I and III.

There is no satisfactory physiologic test for the hormone.

ANTIHORMONES

Other possible factors called antihormones should be mentioned before leaving the hormones. These are substances of unknown origin which appear in the serum of animals treated over long periods of time with anterior pituitary extracts. These substances seem to make the animal less responsive to the extracts, and the serum of animals which have been treated if injected into untreated animals makes the latter animals refractory to treatment with similar extracts. These antigonadotropic sera when administered to untreated animals prevent the action of endogenous gonadotropic hormones and have effects similar to hypophysectomy.

To account for these effects, Collip advanced the theory of antihormones. According to this theory the level of a hormone in the body is related directly to the level of the corresponding antihormone.

PUBERTY AND CLIMACTERIC

The development of the ovarian functioning elements has been described and illustrated. General physical growth takes place along with this ovarian growth, and when development is sufficiently completed ovulation begins. This is signalled in a general way by the beginning of menstruation. The latter part of the period of growth and the establishment of ovulation and menstruation is designated **puberty**. This is a general term used conveniently to cover the whole developmental picture at this age. The term **menarche** is used to indicate particularly the beginning of menstruation, which is considered further under Physiology of the Uterus.

After the allotted period for childbearing, the ovarian function declines. The decline is gradual, extending over some years like the development, and this time of readjustment is designated the **climacteric**. When the adjustment is sufficiently completed the menstrual flow ceases. The term **menopause** refers particularly to the cessation of menstruation, and is considered further under the Physiology of the Uterus.

The years of puberty and of the climacteric, being periods of adjustment to new conditions, are accompanied with some special stresses, an outward evidence of which is a certain instability of nervous reactions. Though usually not serious, various climacteric disturbances may be quite uncomfortable. The development of endocrine knowledge, however, and its application to therapy have reduced materially the discomforts of this readjustment period. The diagnosis and treatment of these manifestations are considered under Disturbance of Function (Chapter XVI).

THE PAROVARIUM

The parovarium is the remains of a fetal organ, the wolffian body, which helps to form the generative organs. It consists of a triangular group of tubules situated in that part of the broad ligament lying between the ovary and the fallopian tube. The apex of the triangle lies near the hilum of the ovary. Beginning near the hilum of the ovary, the tubules extend upward, almost parallel, or in a kind of fan-shaped formation, and enter a transverse tube. This transverse tube is called the "head tube," and it terminates in a small cul-de-sac near the fimbriated extremity of the fallopian tube (Figs. 48, 49). 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 remnants of the wolffian body which lies nearer the uterus is called the "paroophoron" (Figs. 48 and 49).

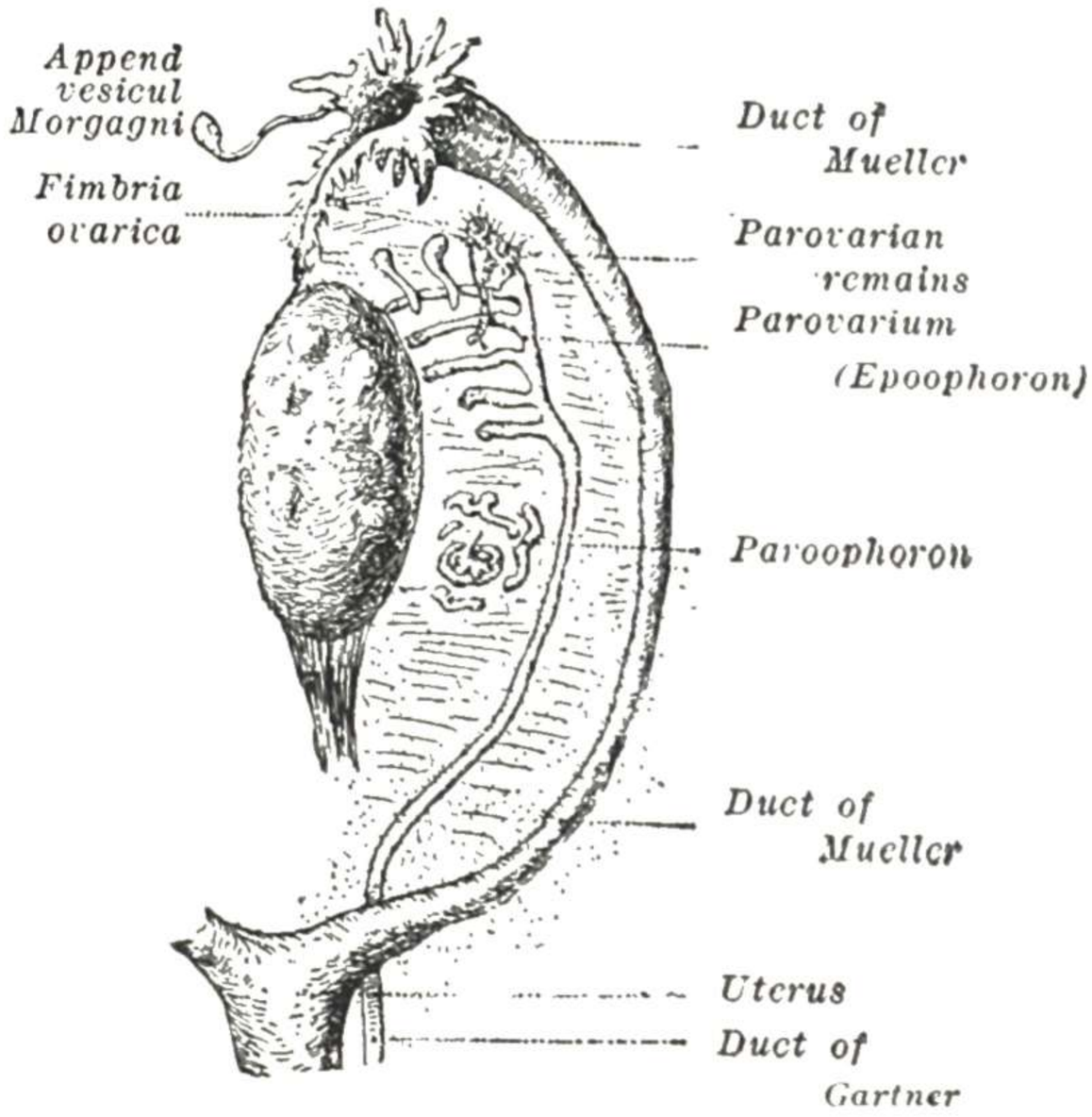


Fig. 48.—Embryonic genital organs, showing the parovarium and paroophoron, and their relation to the tube and ovary and duct of Gärtner. (Abel, after Kollman—*Gynecological Pathology*, William Wood & Company.)

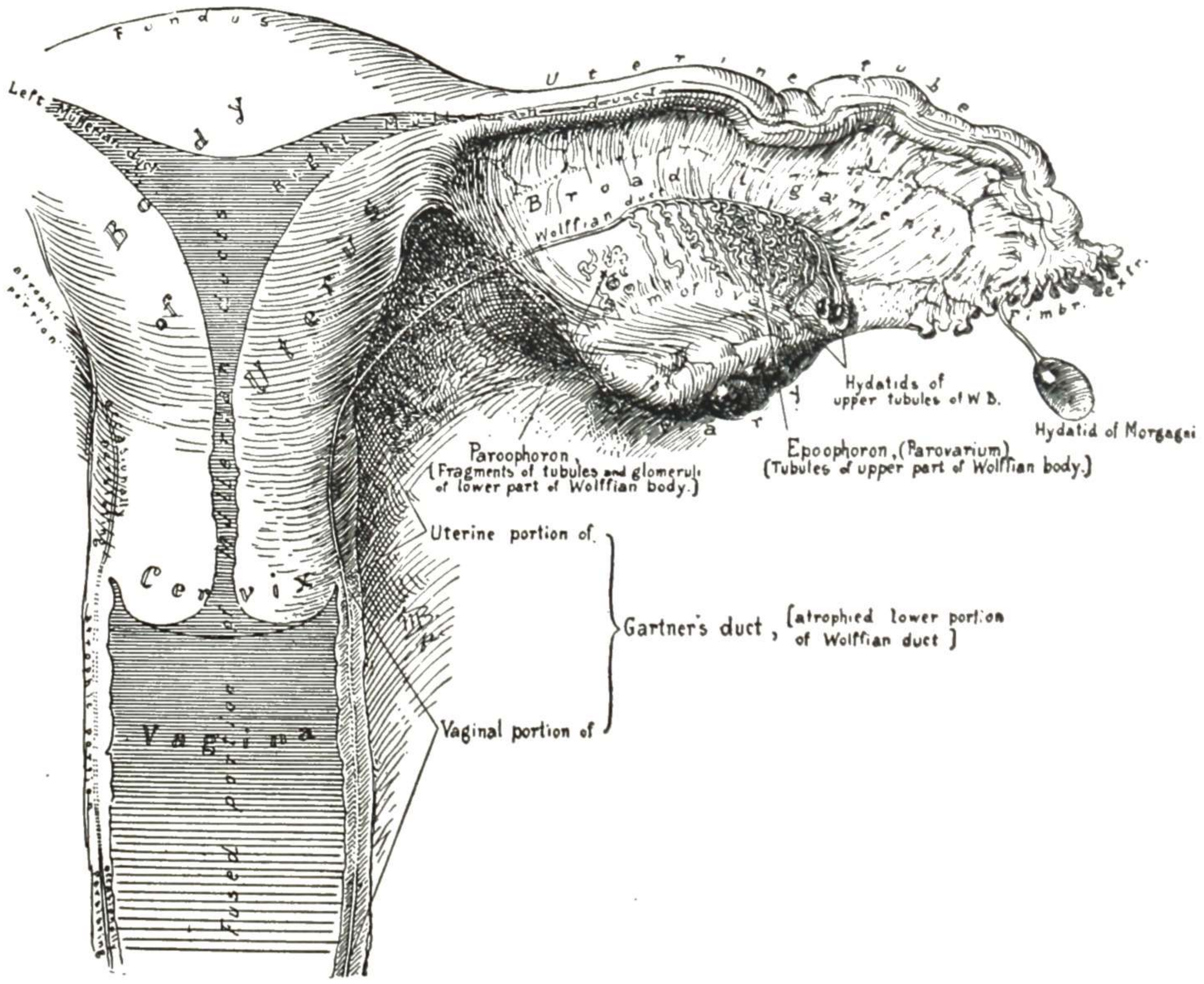


Fig. 49.—Adult genital organs showing parovarium, Gärtner's duct and various other structures. (Kelly, after Cullen—*Operative Gynecology*, D. Appleton-Century Company.)

The tubules of the parovarium and paroophoron are embedded in the delicate connective tissue between the layers of the broad ligament and have no connection with any of the surrounding organs.

The structure has no function, and it is of interest chiefly because it gives rise to certain tumors of the broad ligament.

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. 50). 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. 51).

The uterus has a small central **cavity** (Figs. 50 to 52) 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.

The **size** of the uterus is, of course, different in the different periods of life (Figs. 53 to 55). **At birth** it is a trifle over one inch long and the cervix

comprises two-thirds of the organ (Fig 53). It is important to keep in mind 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. A rather common condition and a very troublesome one (see dysmenorrhea) is a sharp anteflexion of the cervix, the corpus uteri being in practically normal position, but the cervix being flexed sharply for-

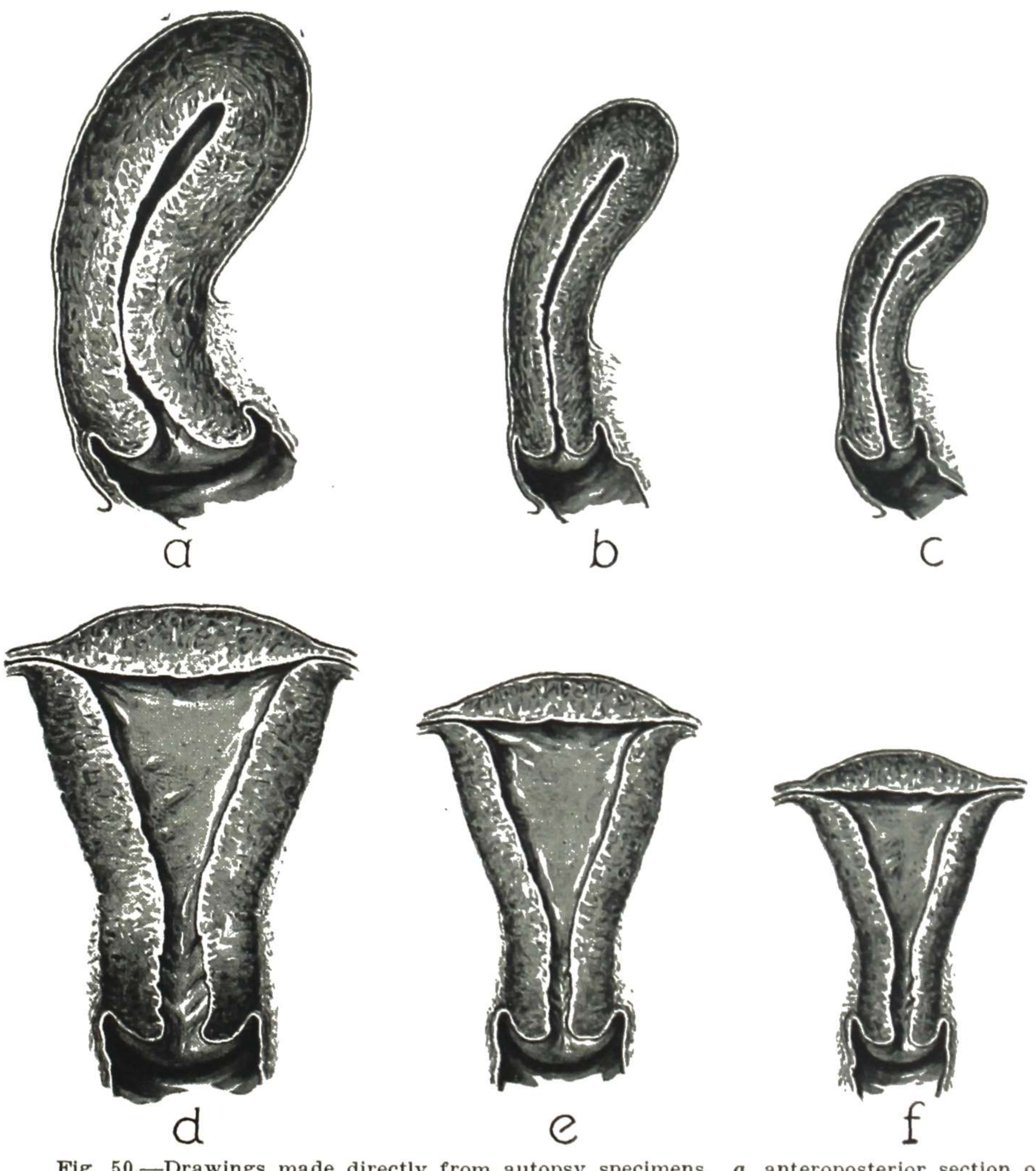


Fig. 50.—Drawings made directly from autopsy specimens. *a*, anteroposterior section of uterus from an individual, aged twenty-three years; *b*, aged fifty years; *c*, aged seventy years; *d, e, f*, transverse sections of the same uteri: *d*, aged twenty-three years; *e*, aged fifty years; *f*, aged seventy years.

ward and directed along the vaginal canal toward the opening. 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."

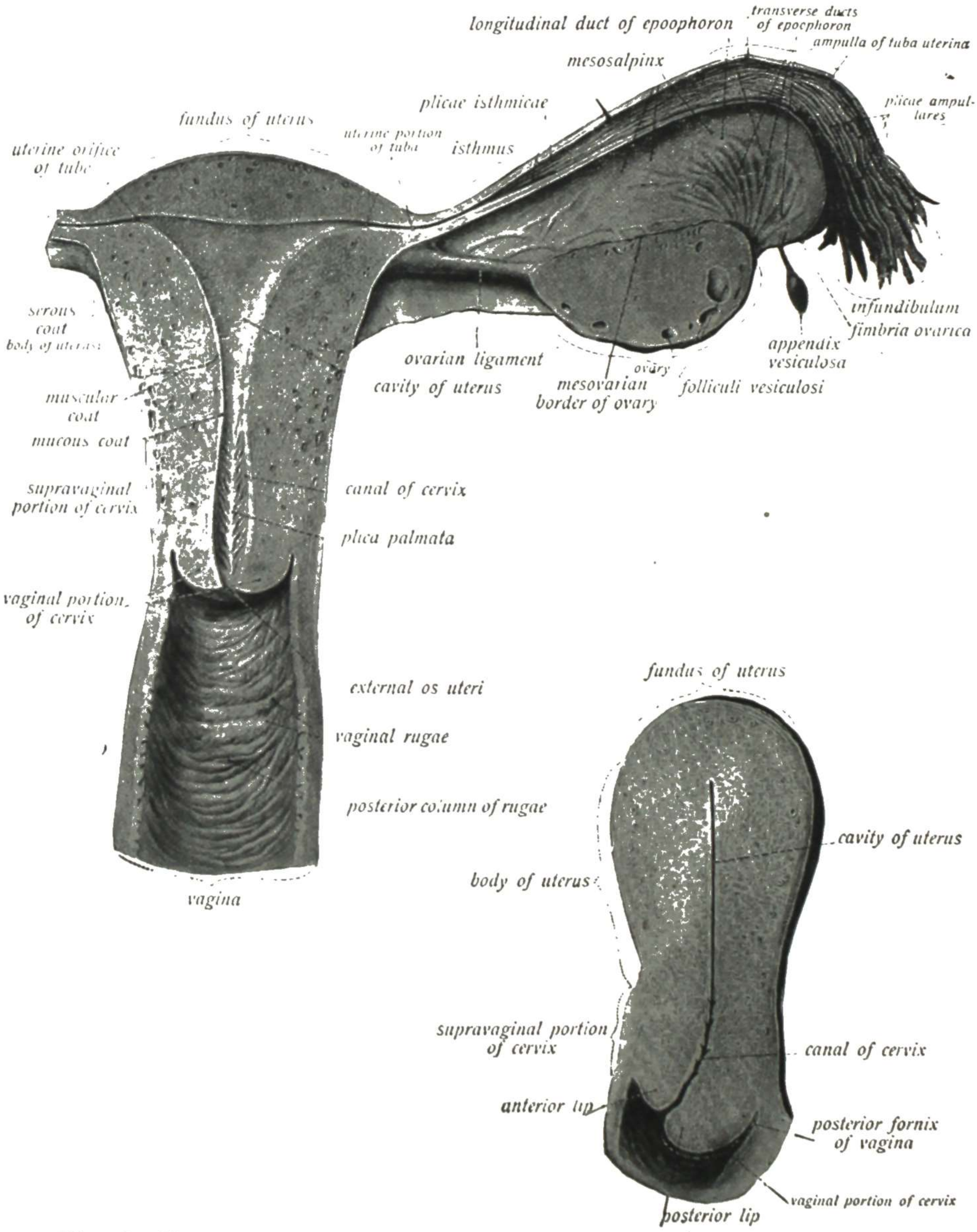


Fig. 51.—The uterus and the right fallopian tube and the right ovary, laid open. View from behind. In the right lower corner, an anteroposterior section of the uterus is shown. (Sobotta and McMurrich—*Human Anatomy*, G. E. Stechert & Company.)

The principal significance of this condition, when found in examination, is the indication that the uterus is underdeveloped—not only in the relation of the cervix to the corpus, which is of minor importance, but in its nervous and nutritional stability, which may have much to do with pain and endometrial functioning and hence must be considered in dysmenorrhea and in

sterility. Occasionally there is an associated narrowing of the canal, interfering with easy escape of menstrual blood and clots and increasing the uterine hypersensitiveness and contractility.

As to the approximate measurements, the **adult virgin** uterus is three inches long (cavity two and one-half inches) and the cervix forms one-third of the organ. The transverse measurement at the widest part is one and a half to two inches, and the average thickness is one inch. It weighs from an ounce and a half to two ounces. After **childbirth** the uterus is always a little larger

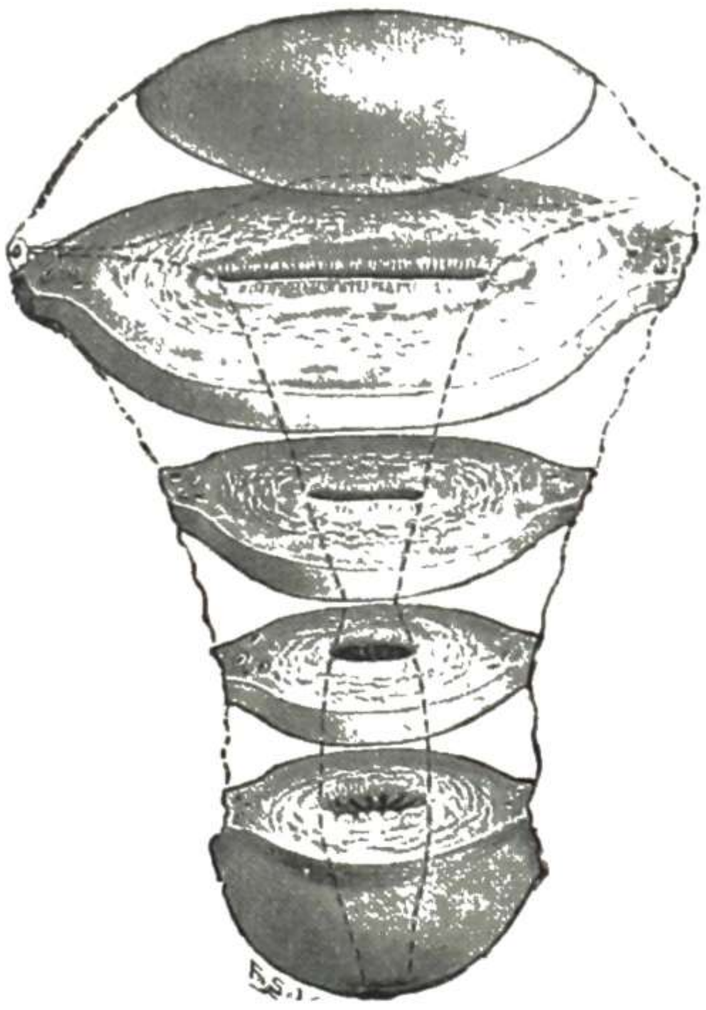


Fig. 52.

Fig. 53.

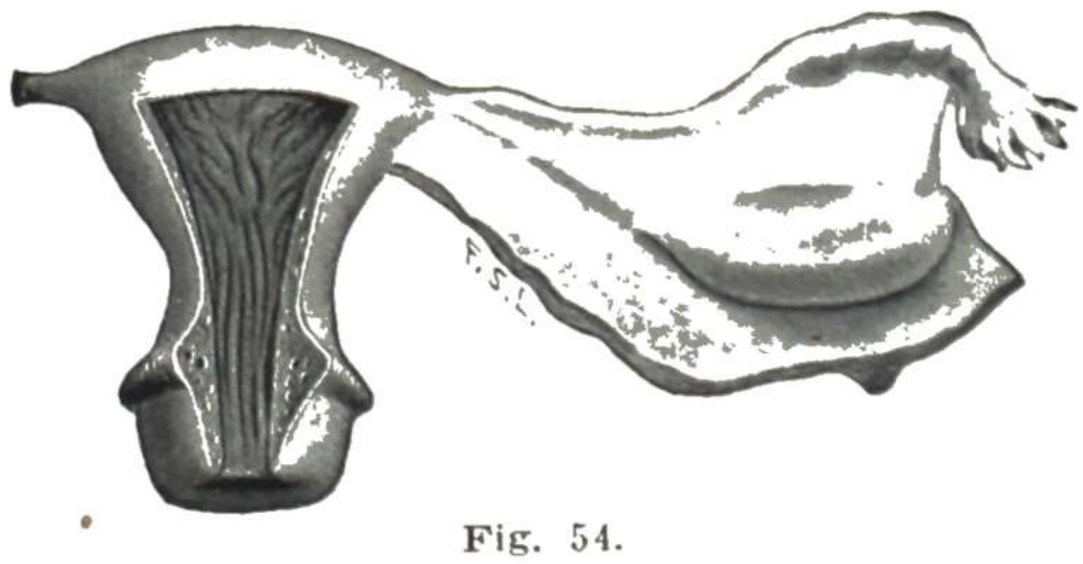


Fig. 54.

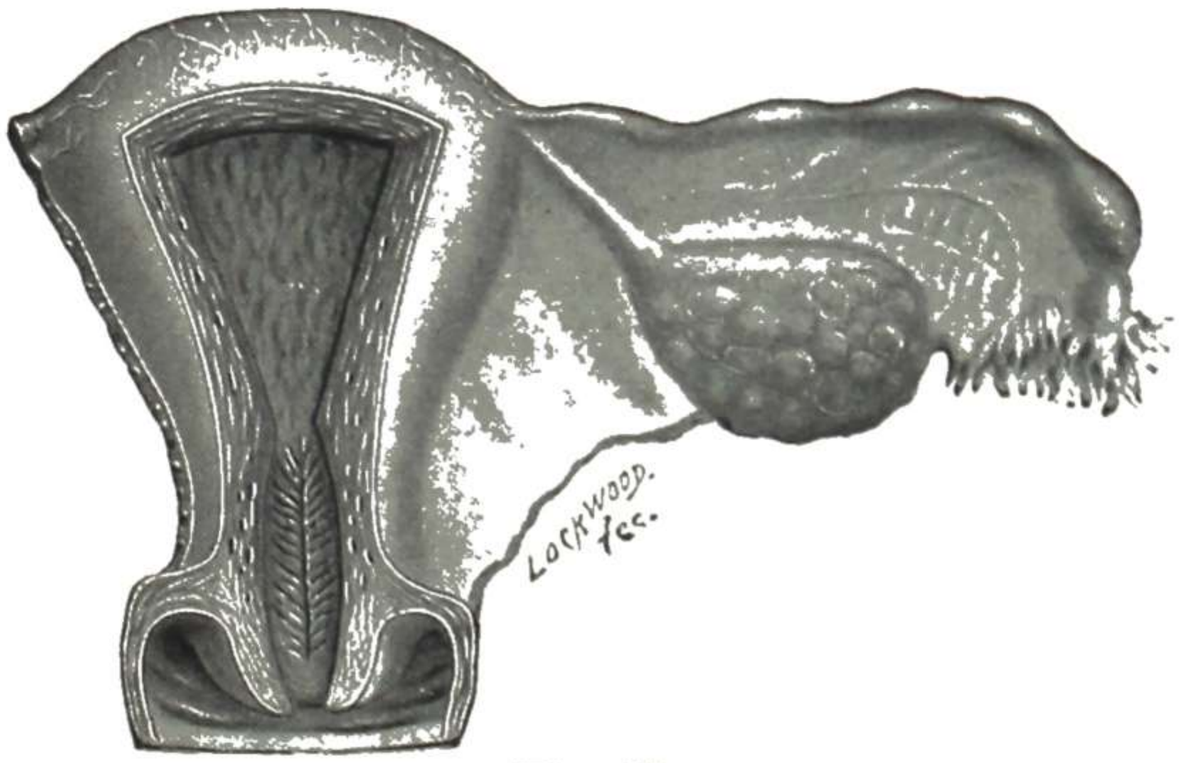


Fig. 55.

Fig. 52.—Reconstruction of the uterus, showing the shape of the cavity. (Williams—*Obstetrics*, D. Appleton-Century Company.)

Fig. 53.—Uterus and appendages of a young child. (Williams—*Obstetrics.*)

Fig. 54.—Uterus and tube and ovary of a fourteen-year-old girl. (Williams—*Obstetrics.*)

Fig. 55.—Uterus and tube and ovary of a twenty-year-old multipara. (Williams—*Obstetrics.*)

than the virgin uterus. The parous uterus is of course the kind most frequently requiring examination. The cavity measures from two and one-half to three inches. After the **menopause** there is marked atrophy of all the genital organs, including the uterus (Fig. 56). 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 (Figs. 50, 57).

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. **Muscular Layer.**—This is the real wall of the uterus. It is from 11 to 15 mm. thick and is composed of involuntary muscular tissue. Under the microscope, the principal elements are seen to be the long muscle cells. They are fusiform in shape and are arranged in parallel rows. These rows of muscle cells are arranged in bundles that extend in various directions.

The muscular wall of the uterus is divided somewhat into **strata.** In the unimpregnated uterus, the different strata are not clearly defined, but, speaking in a general way, it may be said that the muscular bundles are arranged in three strata—a thin outer longitudinal stratum, a thick middle stratum of interlocking bundles extending largely in a circular direction, and a thin inner stratum with fibers extending in various directions.

The **connective tissue** of the muscular layer comprises most of the connective tissue of the utreus. 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.

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 tissue being absent (Figs. 57, 58). 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 (Fig. 57). 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 leucocyte and having a round or oval nucleus that stains lightly (Fig. 59). 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. 54). They are packed closely together, with nothing separating them except a few cell processes and a small amount of serous or

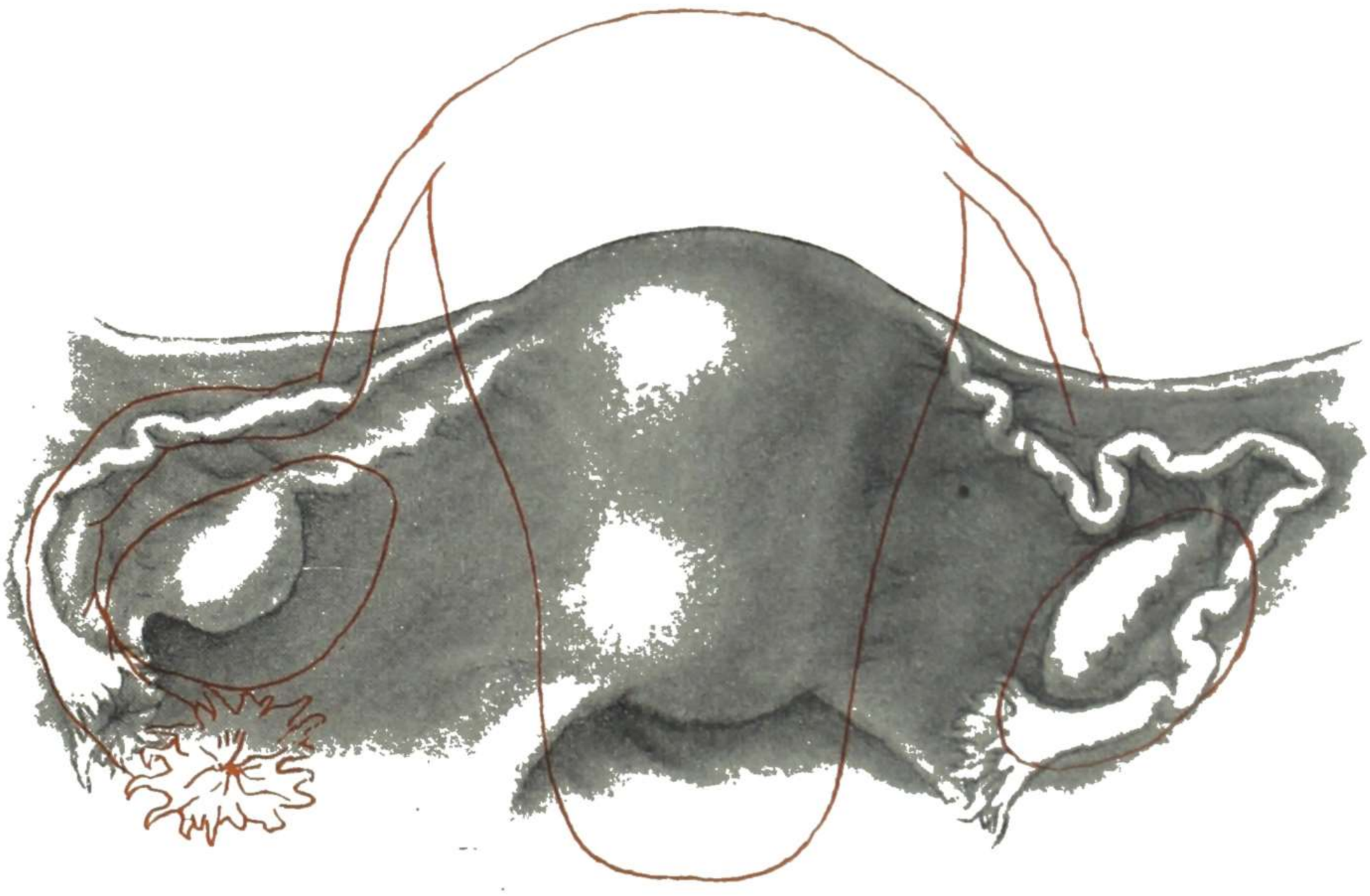


Fig. 56.—Drawing directly from an autopsy specimen of the ovaries, tubes, and uterus at seventy years of age. The shrinkage from age is very marked, but is so uniform that the relative size of the organs is maintained. The tubes have diminished more in thickness than in length.

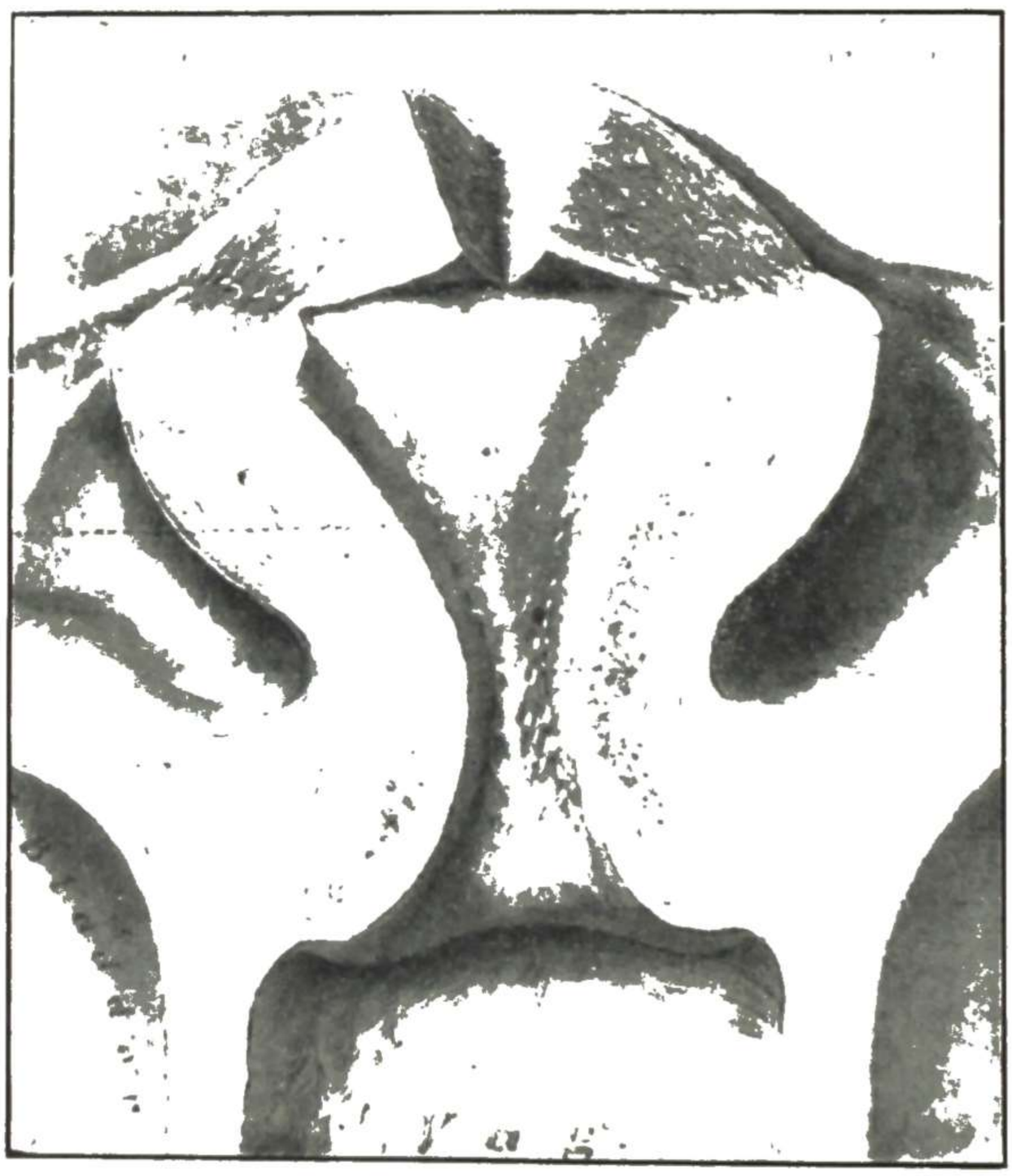
The marked senile shrinkage is indicated by the superimposed twenty-three-year-old organs, in red outline.

mucoid intercellular substance. The tissue thus formed is known as **cytogenic tissue.** When a specimen of it is stained, the microscopic field seems to be almost entirely occupied by rounded or oval reticular nuclei (Fig 59). The cell protoplasm stains so lightly and is so small in amount that it is scarcely noticeable. The stroma probably represents embryonic connective tissue. In the resting endometrium the stromal cells are closely packed and stain very deeply. Under certain conditions, however, they 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.

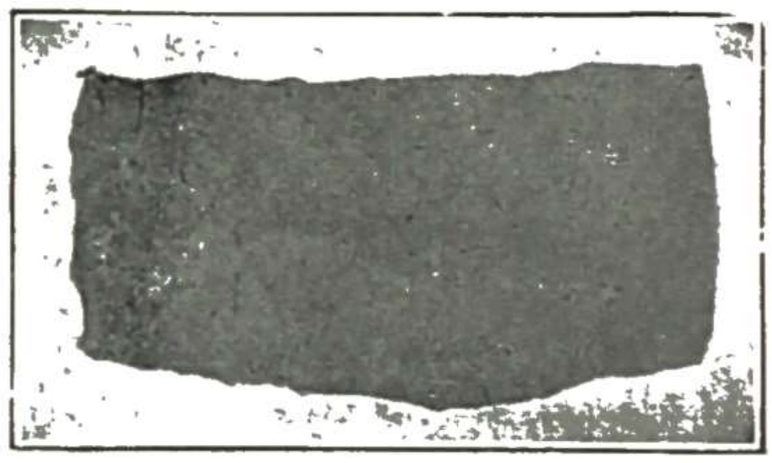
The stroma is rich in capillaries which become much increased in size and number in the premenstrual stage. They arise in the basal layer and course upward, forming right-angled loops near the surface.

Embedded in the stroma are the **uterine glands** (Figs. 58, 59). 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.



A.



B.

Fig. 57.—*A*, A normal uterus divided from in front, showing the smoothness of the endometrium and also its relative thickness. (Cullen —*Cancer of the Uterus*, W. B. Saunders.)

B, Photograph of normal uterine wall magnified approximately two times, showing the relative thickness of the endometrium (at left end) and of the myometrium. Gyn. Lab.

Peculiarities of the Cervix Uteri

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

a. The greater part of the cervix has no peritoneal covering (Fig. 60).

b. The muscular layer of the cervix has a much larger proportion of connective tissue and hence is much firmer.

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

d. The mucous membrane lining the cervix (cervical mucosa) is disposed in prominent folds (Figs. 50, 51). These folds extend more or less obliquely outward from two ridges, one situated near the center of the posterior lip and the other near the center of the anterior lip.

e. The glands of the cervix approach the racemose variety. They consist of branching ducts with dilated ends (Figs. 61, 62). The glands are lined with columnar epithelial cells which are even taller than those on the surface. The nucleus of each cell lies at the base. These cells secrete mucus which does not

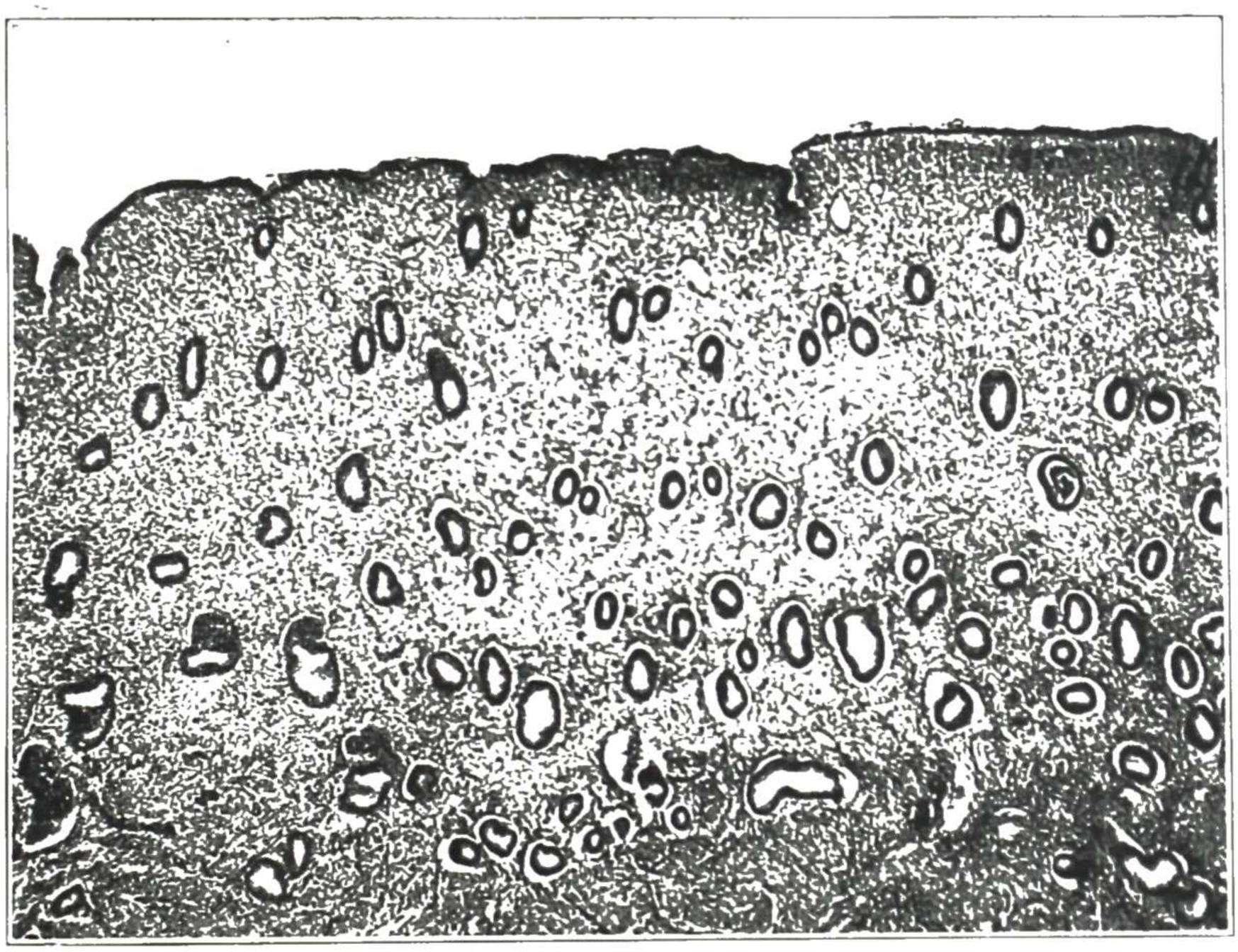


Fig. 58.—Normal endometrium, midgrowth stage. The stroma is quite compact and the glands are seen as simple tubular glands. They are not so simple, however, as appears on one cross-section. Modeling of the glands from serial sections demonstrates their frequent branching. Gyn. Lab.

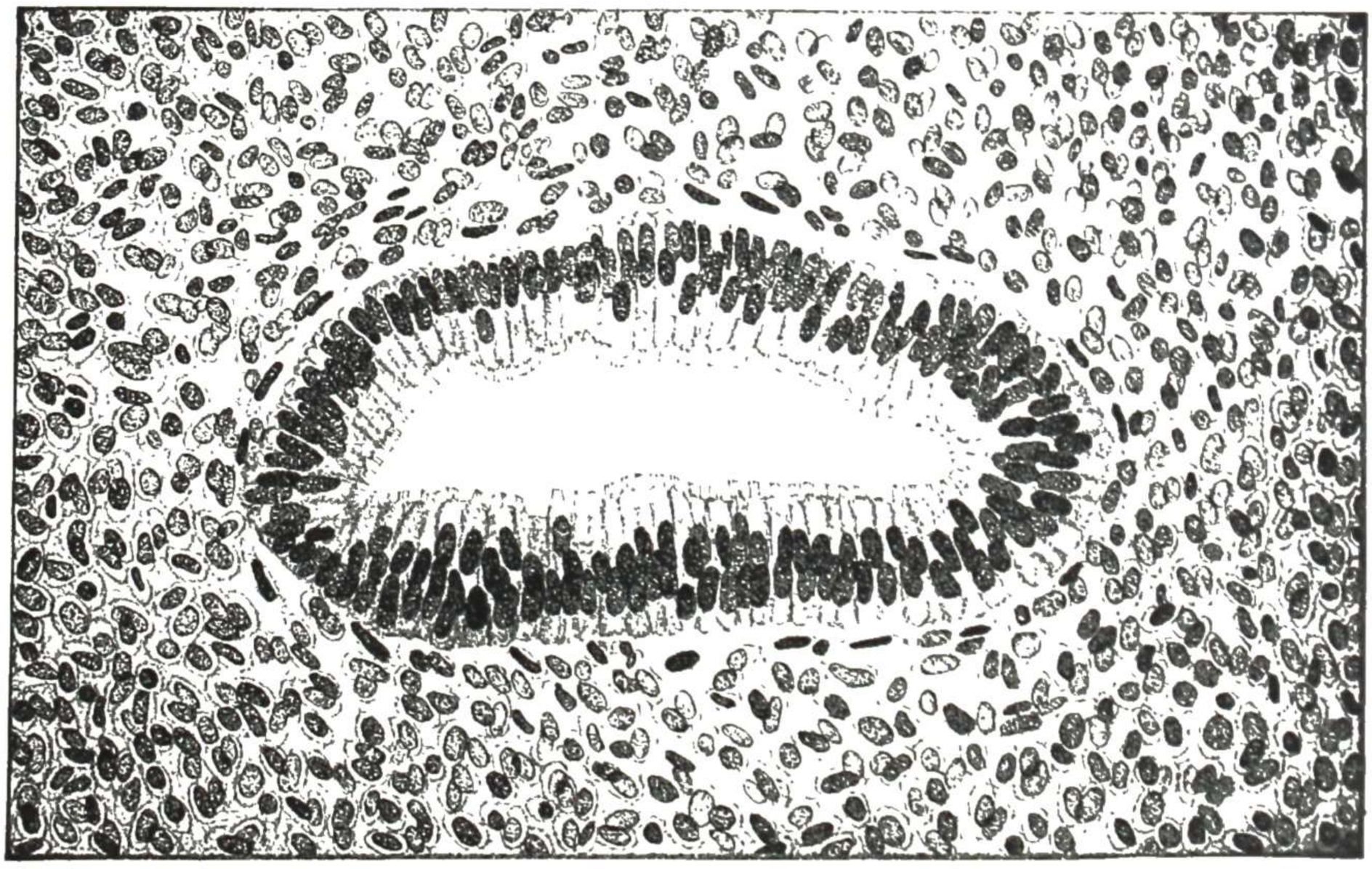


Fig. 59.—A microscopic section of the endometrium, showing the stroma cells and also a cross-section of a gland. The structures are magnified 420 times. (Williams—*Obstetrics.*)

stain appreciably in ordinary preparations (hematoxylin and eosin); consequently that portion of the cell lying next to the lumen, which part of the cell is usually filled with mucus, appears clear (Fig. 62).

The glands of the cervix secrete a clear, viscid, tenacious mucus that fills the cervical canal and serves to close it and prevent invasion of the uterine cavity. The ducts of these glands sometimes become obstructed, causing retention cysts. These are sometimes called "ovulae Nabothi." There may be many of them, in which case the cervix is said to be in a state of "cystic degeneration."

f. The layer of cytogenic tissue with characteristic stroma cells is comparatively thin in the cervix.

g. The cervical mucosa does not undergo the marked menstrual changes of the endometrium. There are, however, some cyclic changes in the cervical epithelium, as shown in Fig. 1 (colored Frontispiece) and described later under Physiology of the Uterus. During pregnancy there is marked proliferation of the mucosa. It also undergoes atrophy of senility, but the change is not so marked as in the endometrium.

h. The vaginal portion of the cervix is covered with squamous epithelium. As can be seen from the photomicrograph (Fig. 63), the squamous epithelium covering the cervix is divided into three layers: the basal layer, the intra-epithelial horny layer, and the functional or superficial layer.

The portion of the uterus just above the cervix is called the "isthmus." It is an indefinitely outlined area, the mucosa of which shades from the endometrial to the cervical type, in structure and function. The mucosa of this area takes little part in the menstrual cyclic changes. This is well shown in Fig. 86, which is from a uterus removed just before menstruation. Though ordinarily little noticed, this area of the uterine wall becomes more distinct and of greater significance in obstetrics. Martius has emphasized the importance of the isthmus of the uterus.

Ligaments of the Uterus

The uterus is held in its position by the pelvic floor and by certain ligaments (Fig. 64). They are the broad ligaments, the round ligaments, the sacro-uterine ligaments and the vesico-uterine ligament.

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

The **sacro-uterine ligaments** are folds of peritoneum extending from the uterus around the rectum to the sacrum (Fig. 64). They contain also fibrous tissue and muscular fibers, hence they are stronger.

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. 64). 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.

The **broad ligament** of each side extends from the lateral portion of the uterus to the pelvic wall (Fig. 64). The attachment to the uterus extends all along the side of the organ from the cervix to the fundus, and there is a correspondingly wide attachment to the pelvic wall. This gives a broad band of tissue (hence the name "broad" ligament) extending from the lateral margins of the uterus to the pelvic wall and holding the uterus in its appointed position in the center of the pelvic cavity (Fig. 64). Each broad ligament is composed of two layers of peritoneum (Fig 65), and between them are a number of important structures. This disposition of the peritoneum and consequent formation of the broad ligaments is represented very well by a thin cloth laid over the pelvis and then tucked down snugly around the pelvic organs. The peritoneum covering the anterior surface of the uterus, when continued laterally, forms the anterior layer of the broad ligament, and that covering the posterior surface of the uterus, continued laterally, forms the posterior layer of the broad ligament. Between these two layers of peritoneum is a considerable amount of connective tissue, especially at the lower part

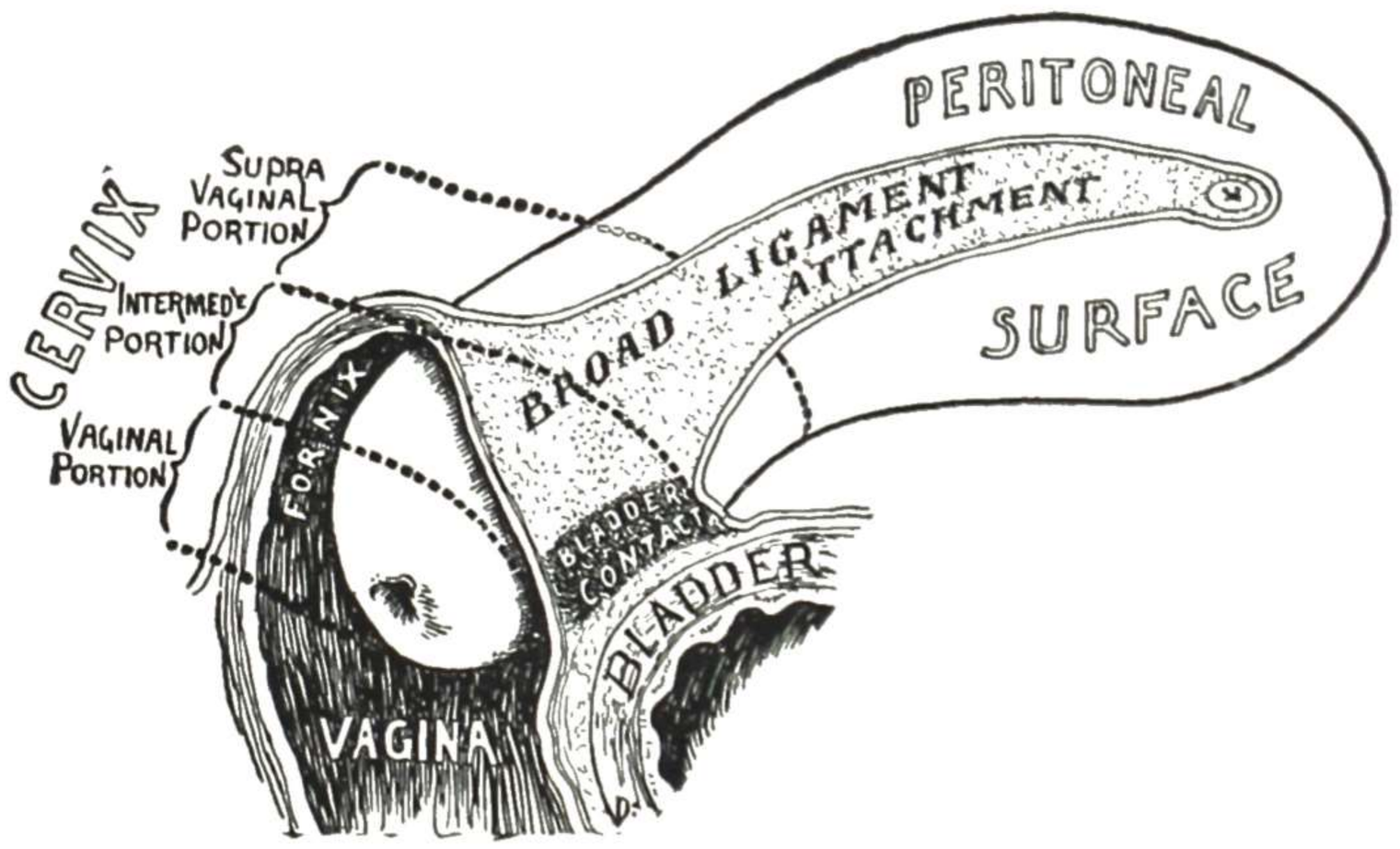


Fig. 60.—Showing the relations of the uterus to the vagina and bladder and peritoneum. (Dickinson—*American Textbook of Obstetrics.*)

(Fig. 65). This connective tissue area around the uterus is known as the "parametrium," and inflammation there is spoken of as "parametritis." Between the peritoneal layers of the broad ligament are the following important structures: fallopian tube, parovarium, ovarian vessels (Fig. 66) round ligament, uterine vessels (Fig. 66), and ureter. The ureter, in its course to the bladder, lies in the lower part of the broad ligament near the cervix and just under the uterine artery, as shown in Fig. 66.

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. 66) 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. 66.

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 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."

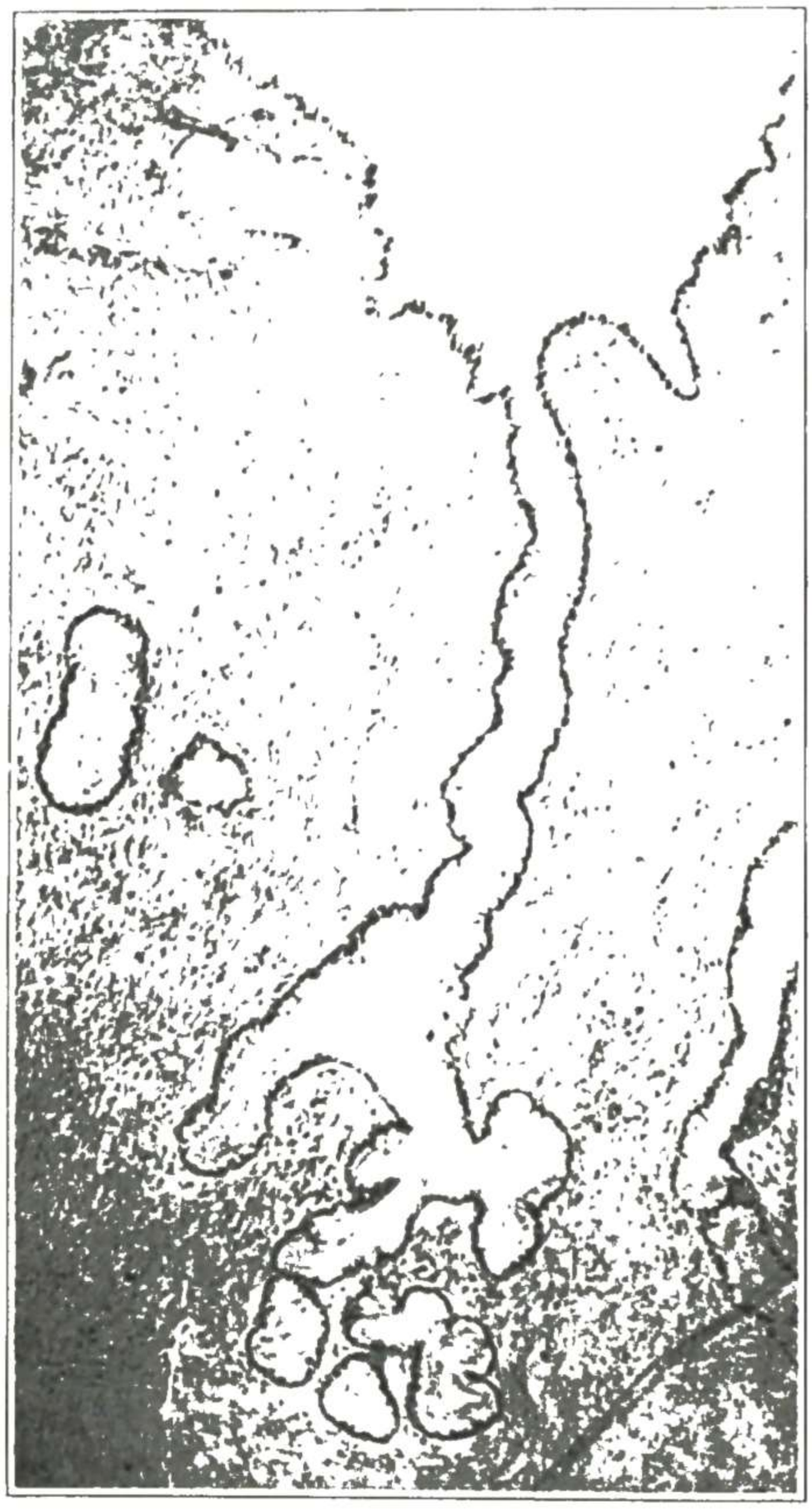


Fig. 61.

Fig. 62.

Fig. 61.—A typical cervical gland is seen in center of picture, with its long neck connecting it with the cervical canal. Gyn. Lab.

Fig. 62.—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 **ovarian artery** of each side supplies the tube, and ovary, and upper part of the uterus as shown in Fig. 66. They 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.

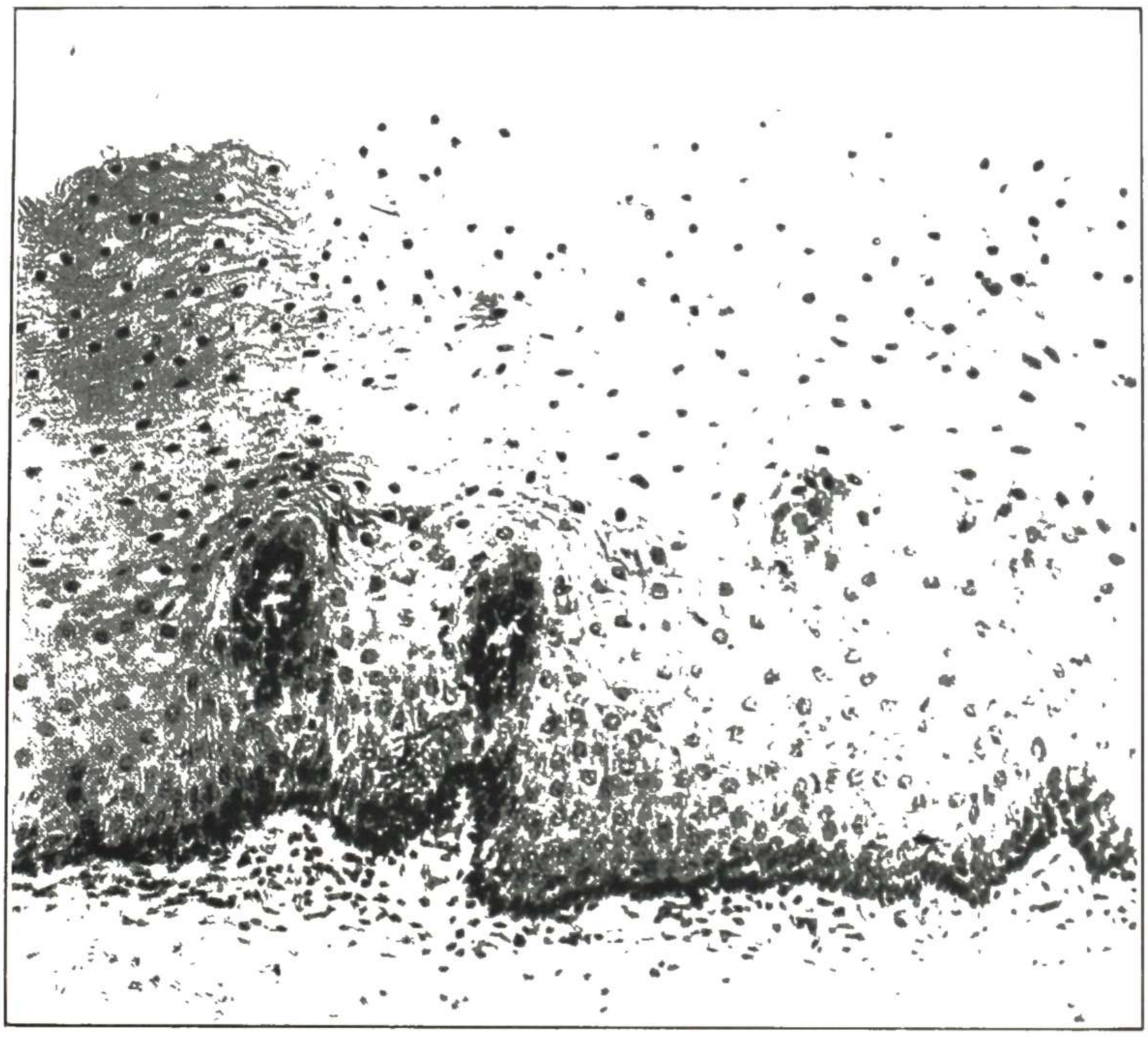


Fig. 63.—Epithelial covering of cervix uteri. Note the three layers: the superficial layer of flat epithelial cells with small nuclei and indistinct cell margins, the middle layer of cuboidal cells, with larger nuclei and fairly distinct cell outline, and the basal layer of high cuboidal cells with basal nuclei. This latter layer takes a much darker stain than do the other two. Gyn. Lab.

Lymphatics

The distribution of the uterine lymphatics to the various gland groups is shown in Fig. 67. 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.

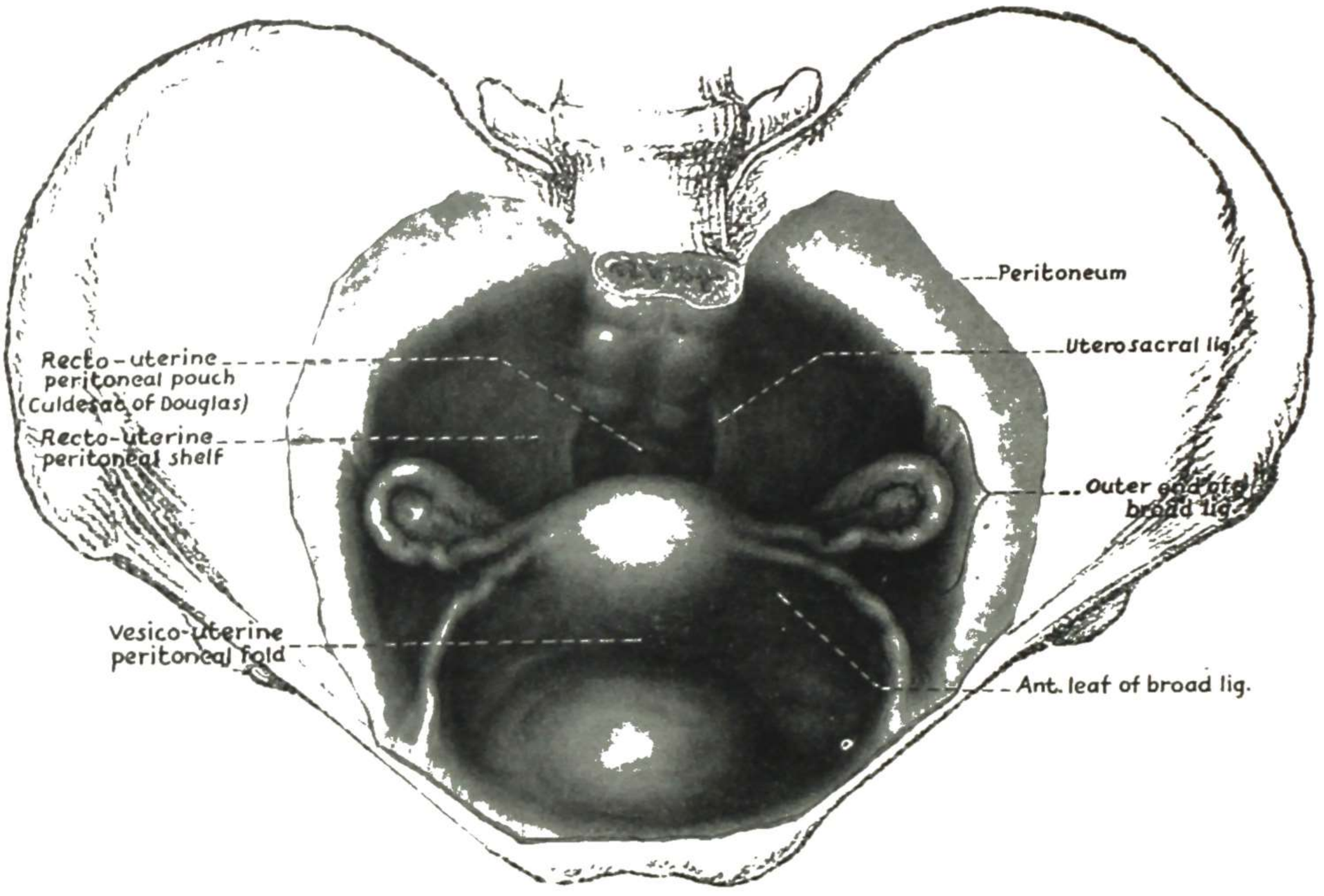


Fig. 64.—Showing the distribution of the peritoneum within the pelvis, and the various ligaments and pouches thus formed. It is as though a thin cloth were laid over the pelvis and then tucked in around all the organs and their wall connections.

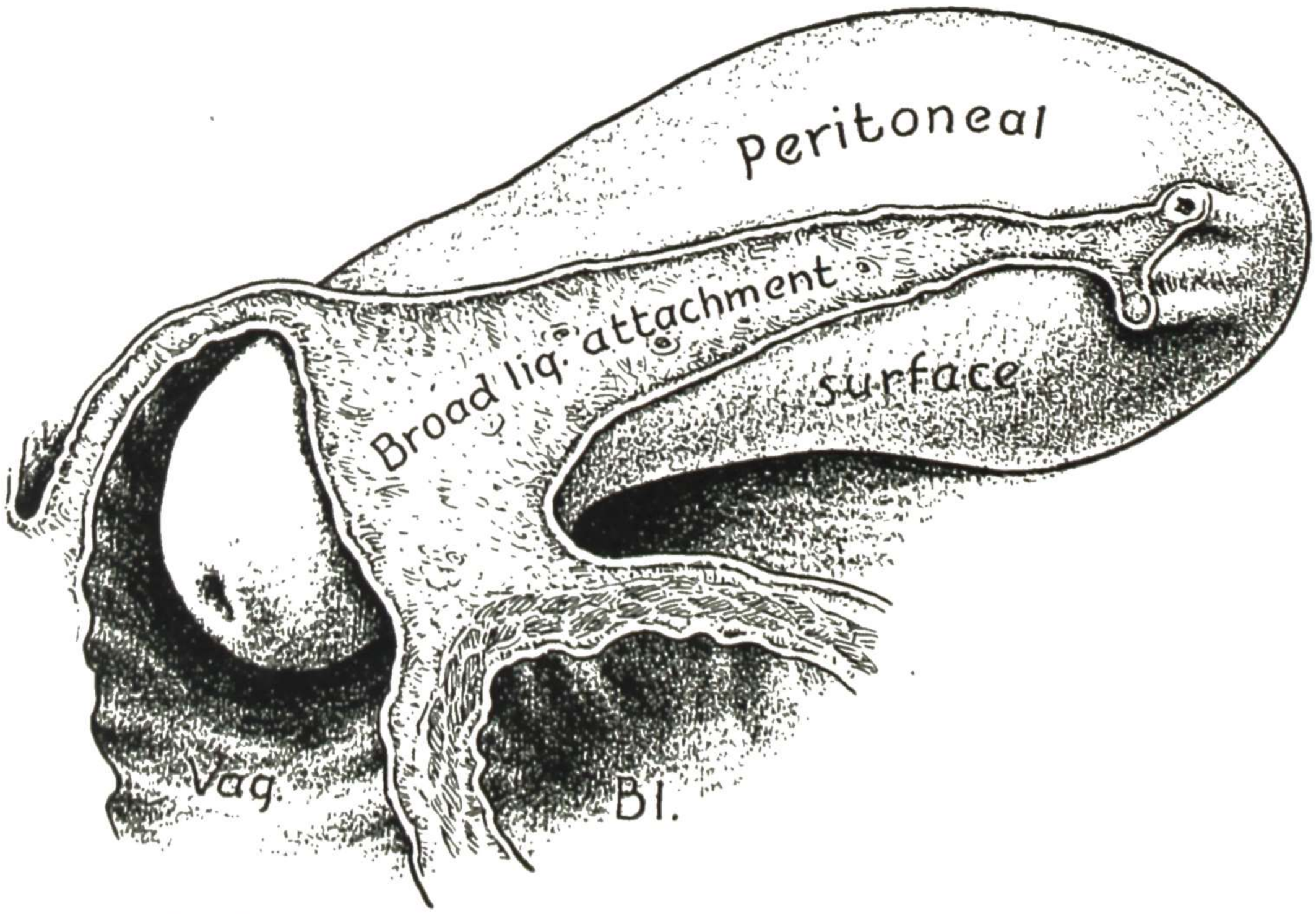


Fig. 65.—This diagrammatic anteroposterior section to the right of the median line shows the broad-ligament attachment to the uterus, and also the relations of the peritoneum anterior and posterior to the uterus. (Modified from Dickinson—*American Textbook of Obstetrics.*)

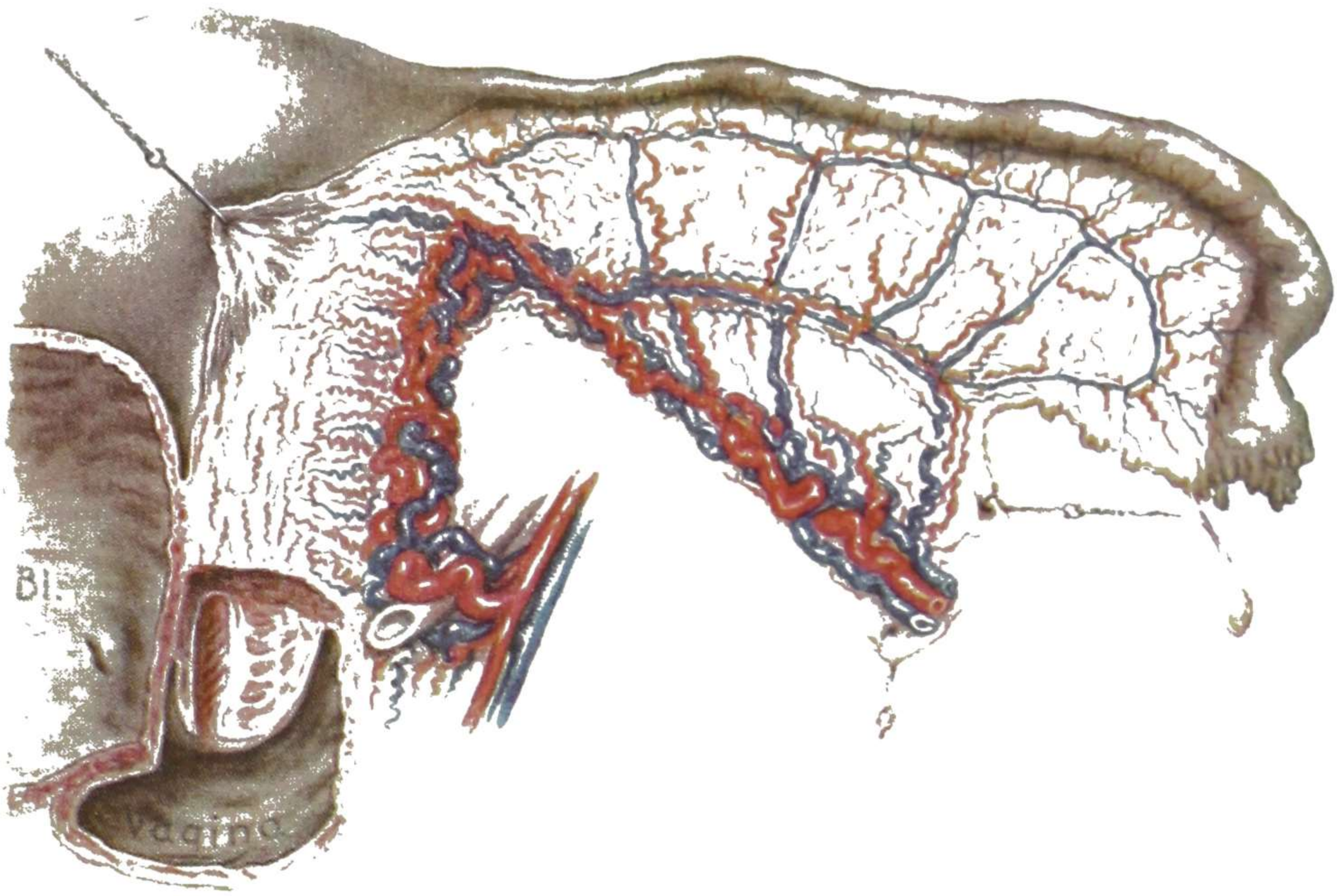


FIG. 66.—THE BLOOD SUPPLY OF THE UTERUS, TUBE, AND OVARY.

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. 67. THE DISTRIBUTION OF THE LYMPHATICS OF THE UTERUS TO THE VARIOUS GROUPS OF GLANDS. (After Doederlein and Kroenig—*Operative Gynaekologie.*)

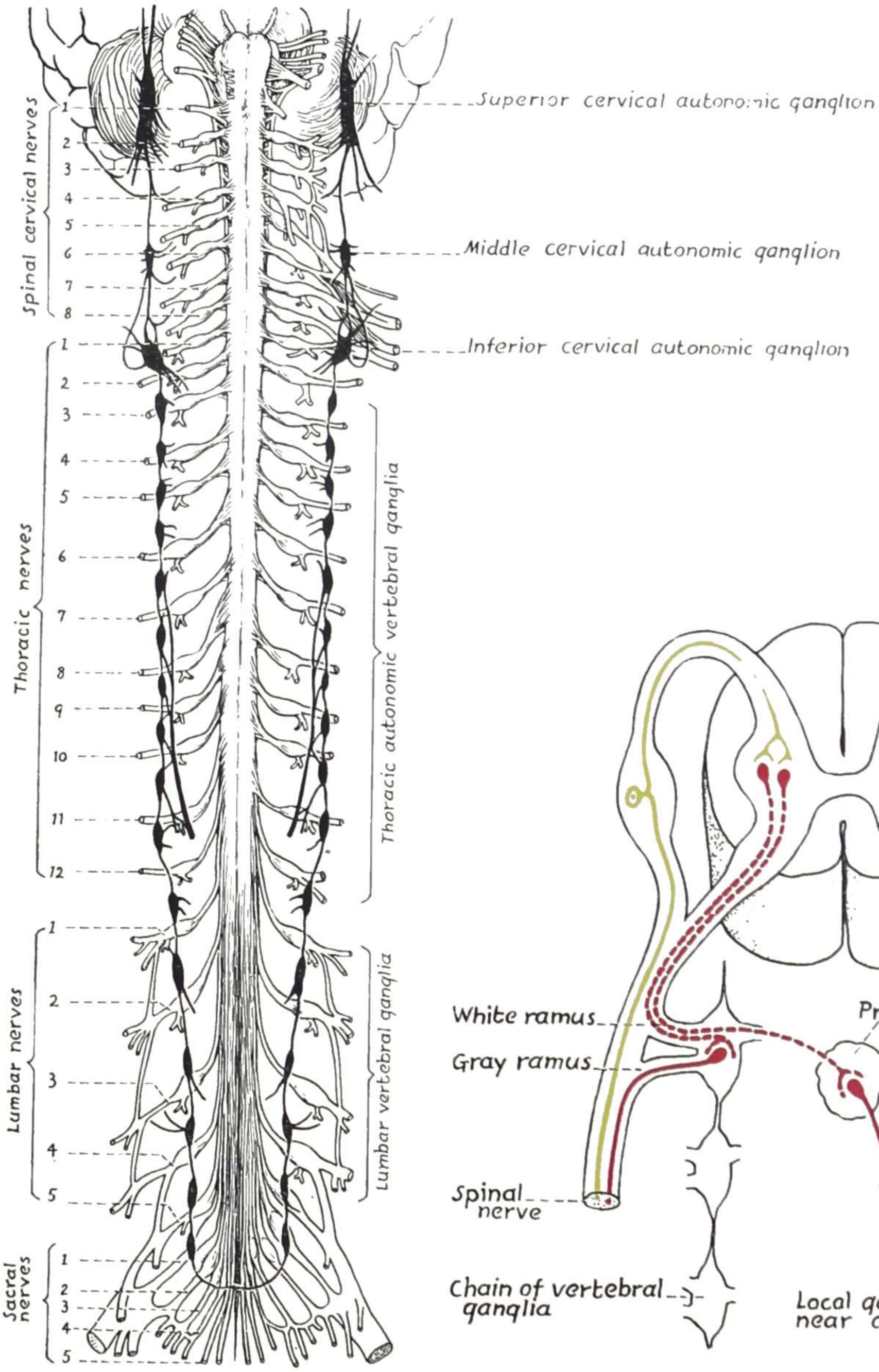


Fig. 68.

Fig. 69.

Fig. 68.—The nerve supply of the pelvic organs. The vertebral ganglia of the autonomic nervous system. (Modified from Jackson-Morris—*Human Anatomy.*)

Fig. 69.—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 and Wilkins.)

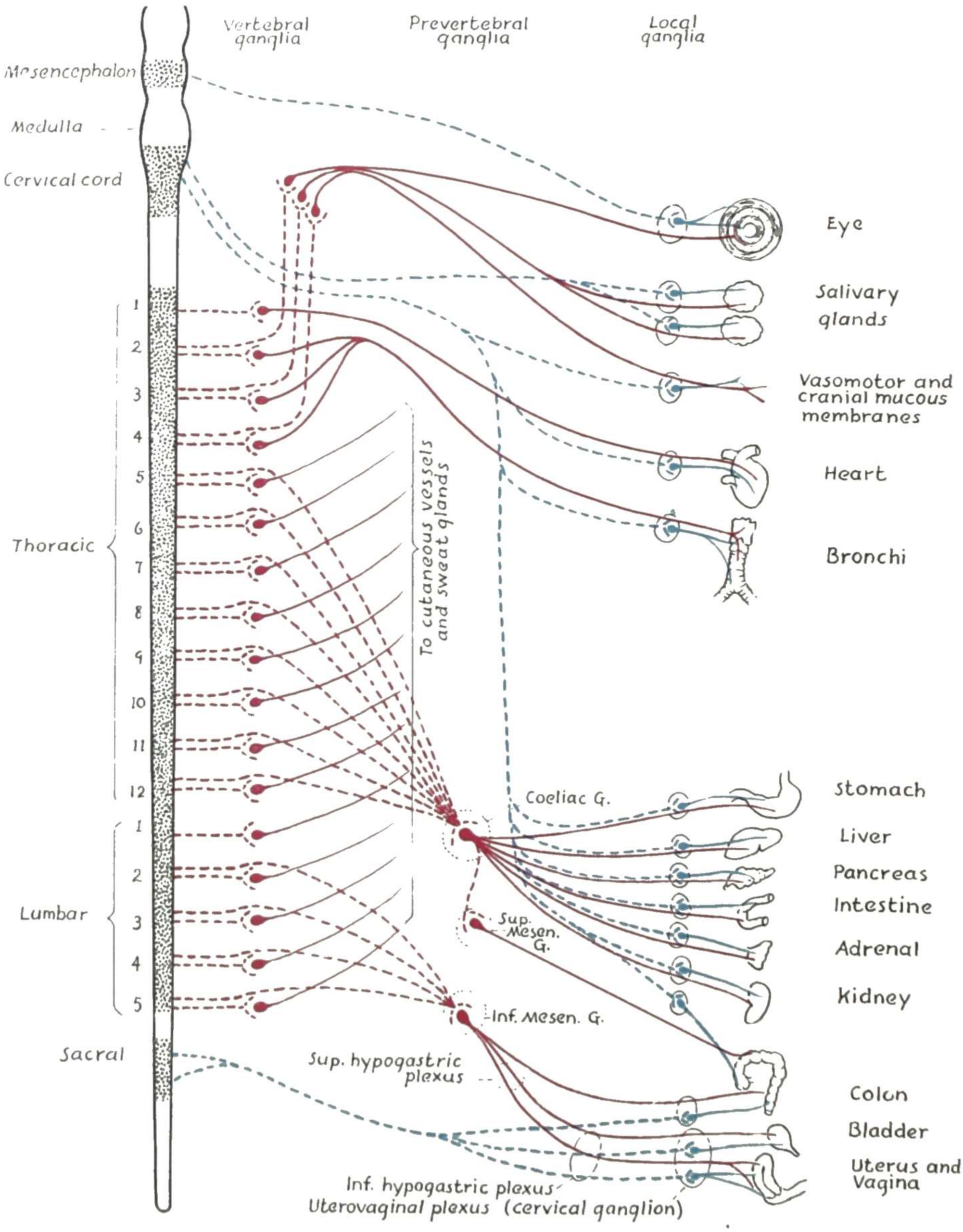


FIG. 70.—THE NERVE SUPPLY OF THE PELVIC ORGANS.

Diagrammatic representation of the autonomic nervous system, with the sympathetic nerves in red and the parasympathetic nerves in blue. The preganglionic fibers of each are dotted lines and the postganglionic fibers are solid lines. (Modified from Kuntz, after Meyer and Gottlieb, in *The Autonomic Nervous System*, Lea and Febiger.)

Considerable pride has been expressed, and justly so, in the perfection of modern plumbing in this country. The efficiency secured and the study and ingenuity displayed in overcoming the difficulties of installation and maintenance in modern homes and about the working parts of complicated machines are worthy of attention. 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 of 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 mucosa 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.

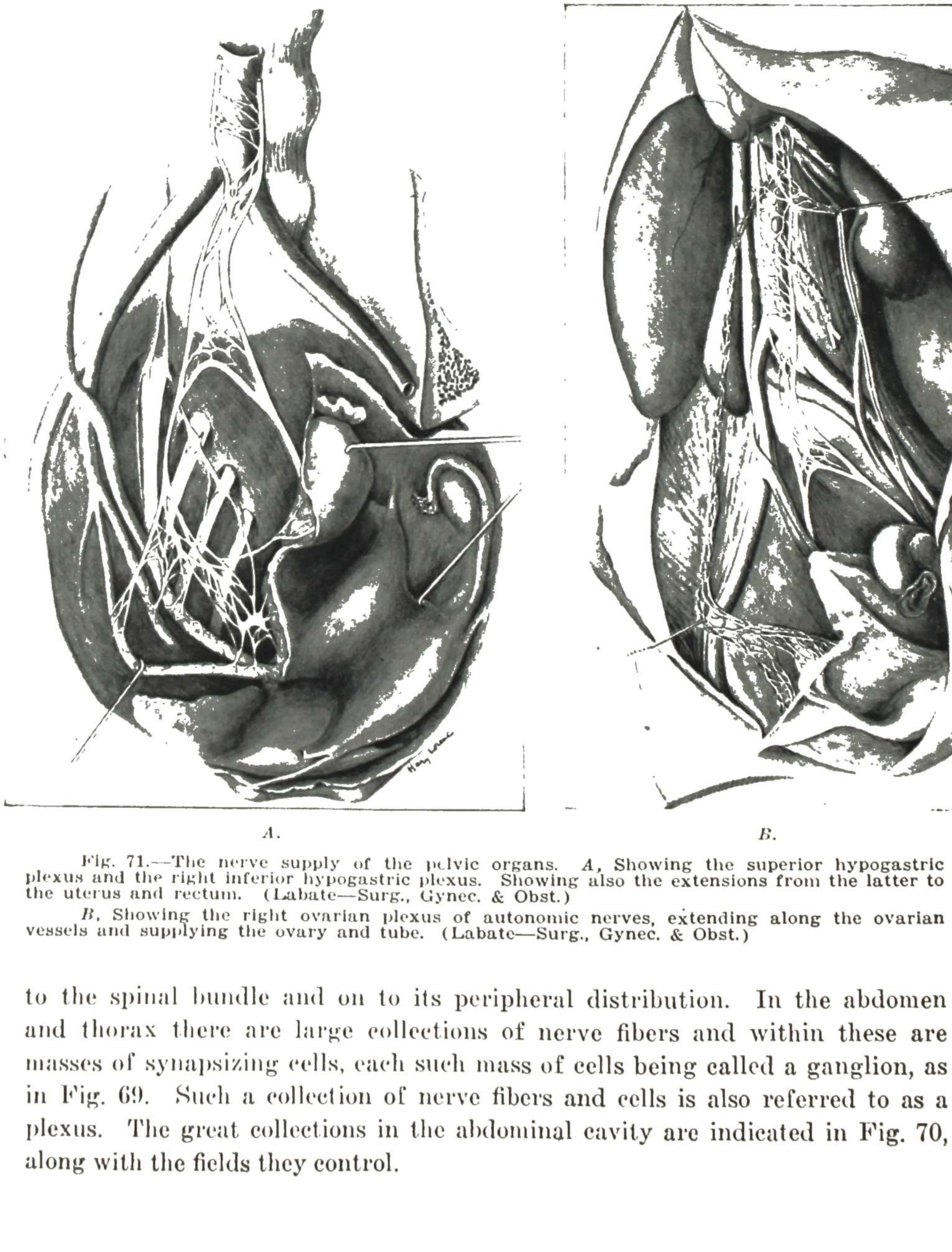
The lymphatic vessels of the uterus fall naturally into two groups—those of the cervix and those of the corpus. Those of the cervix uteri join with those of the upper part of the vagina and empty into the sacral and hypogastric and superior iliac glands. The lymphatics from the corpus uteri join with 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.

Nerves

The nerves of the pelvic organs, like those of other internal organs, are derived from the autonomic nervous system. Fig. 68 shows the large autonomic trunk ganglia (vertebral ganglia) which lie along each side of the spine back of the abdominal viscera. Fig. 69 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. 69 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



A. *B.*

Fig. 71.—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. (Labate—Surg., Gynec. & Obst.)

B, Showing the right ovarian plexus of autonomic nerves, extending along the ovarian vessels and supplying the ovary and tube. (Labate—Surg., Gynec. & Obst.)

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. 69. 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. 70, along with the fields they control.

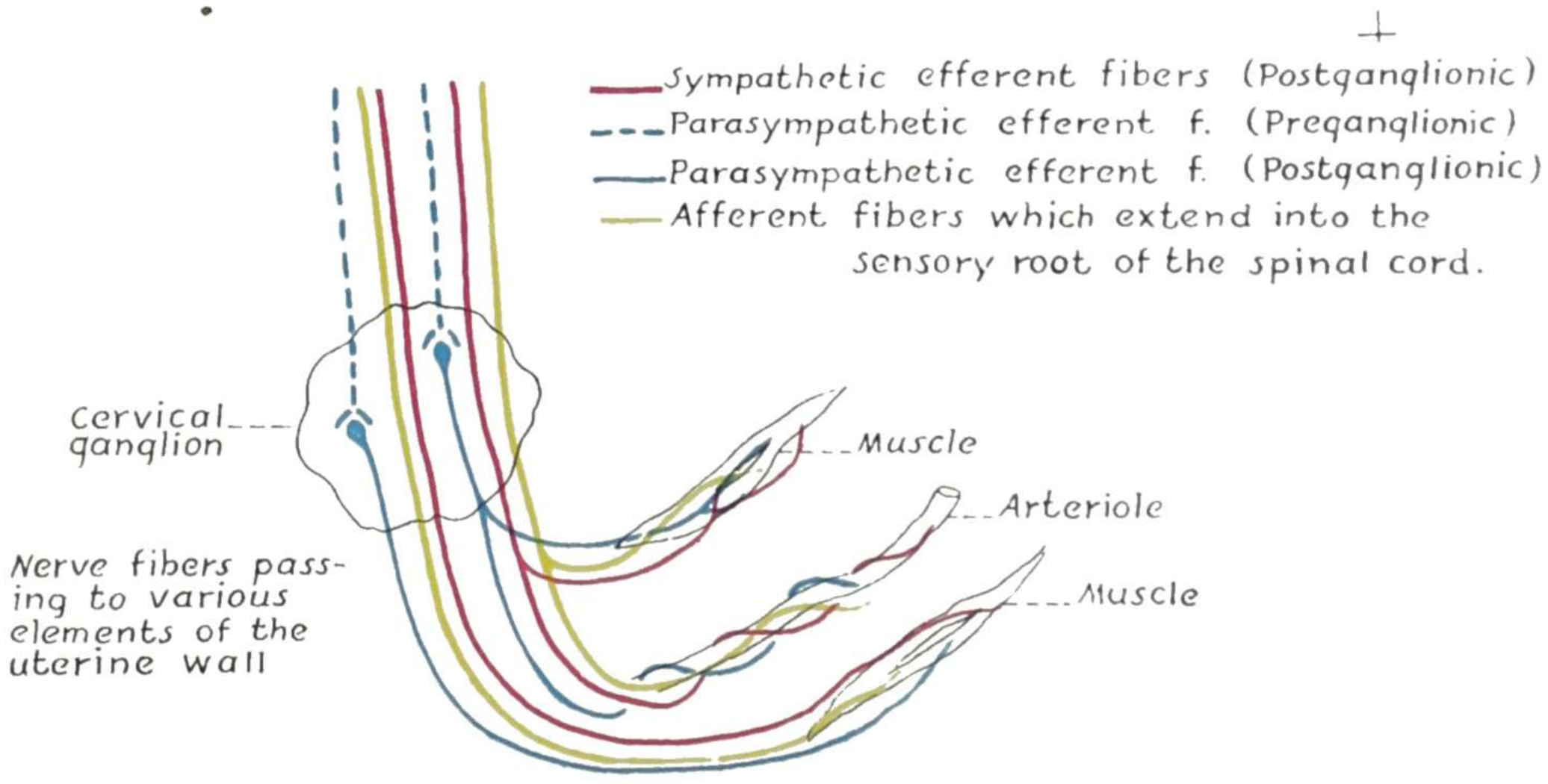


Fig. 72.—The nerve supply of the pelvic organs. Diagrammatic representation of the extensions of the autonomic and spinal nerves into the functioning areas of the uterus.

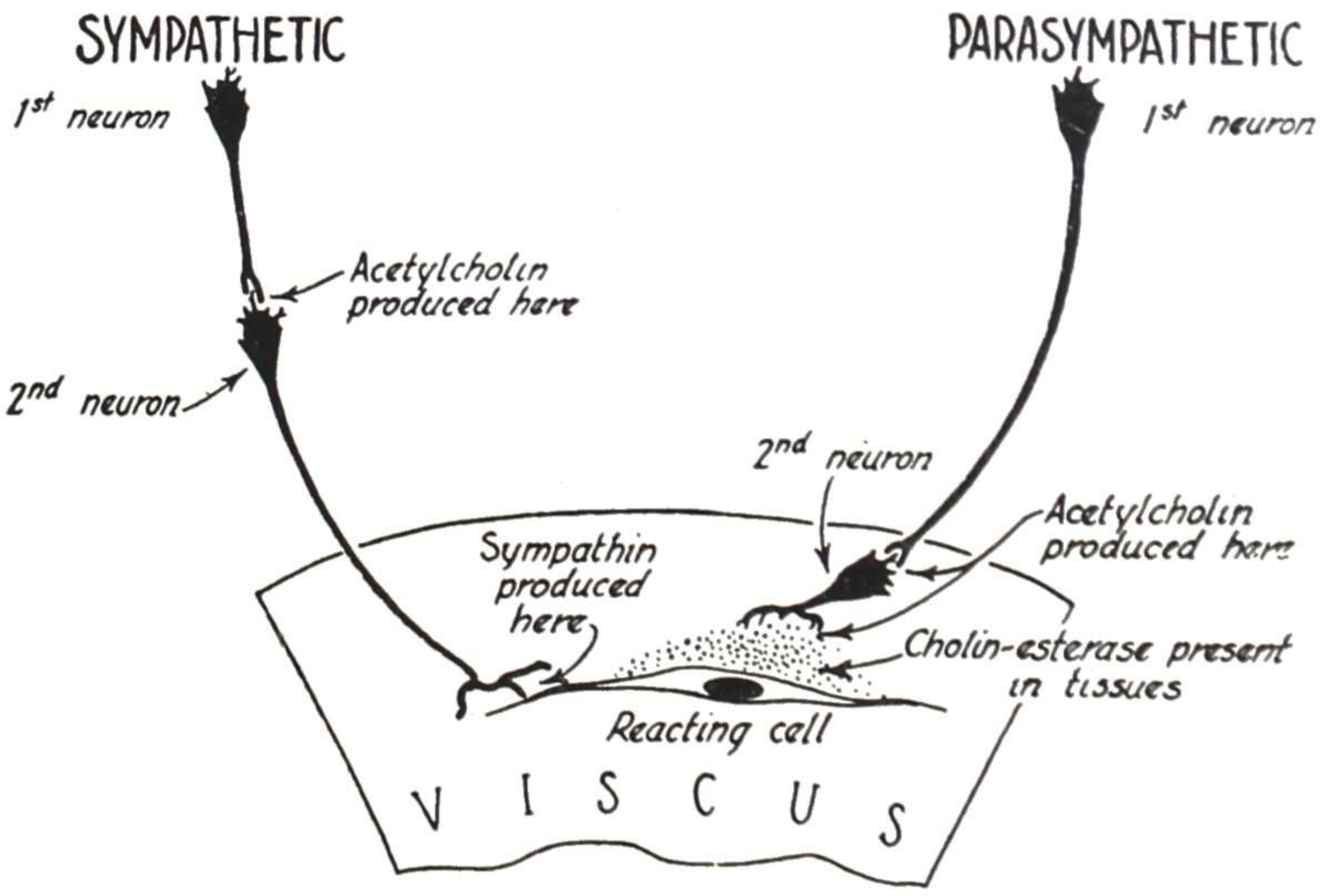


Fig. 73.—The nerve supply of the pelvic organs. The balance between sympathetic and parasympathetic nerves and esterase. (Myerson—*J. A. M. A.*)

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 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 postganglionic fibers takes place in a main autonomic ganglion (vertebral or prevertebral) while in the cervico-sacral 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 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. The distribution is shown diagrammatically in Fig. 70, the sympathetic nerves being indicated in red and the parasympathetic in blue. For each, the preganglionic fibers are indicated by broken line and the postganglionic fibers by solid line. The antagonistic actions of the two parts of the autonomic system are utilized in modern therapeutics, pharmacological experimentation having demonstrated that certain medicines stimulate the sympathetic nerves and others stimulate the parasympathetic.

The nerves of the uterus are derived from the superior hypogastric plexus, extensions from which form the inferior hypogastric plexus of each side, as shown in Fig. 71, *A*. These collections of nerve cells and fibers, like the great nerve masses higher in the abdomen, contain spinal nerves as well as autonomic nerves, for as previously explained the sensory portion of the autonomic reflex arc is supplied by the spinal nerves. Also, there is free communication between the various autonomic ganglia and between the autonomic and the cerebrospinal systems. From the inferior hypogastric plexus of each side nerves extend to the various pelvic viscera. The extensions to the uterus and rectum are shown in Fig. 71, *A*. Smaller ganglia are found near some of the viscera. A ganglion lying near the cervix on each side is known as the Frankenhäuser ganglion. In local anesthesia for vaginal hysterectomy the injection is made along the side of the cervix to anesthetize the area of the

cervical ganglion, for associated with the motor autonomic nerves are the sensory spinal nerves. The nerve supply to the ovary comes from higher, as shown in Fig. 71, *B*.

The minute extensions of the nerves into the functioning elements of the uterus are indicated diagrammatically in Fig. 72. The importance of these minute extensions into the area of cellular function, where nerve impulses meet endocrine and other factors which condition response, is indicated in Fig. 73.

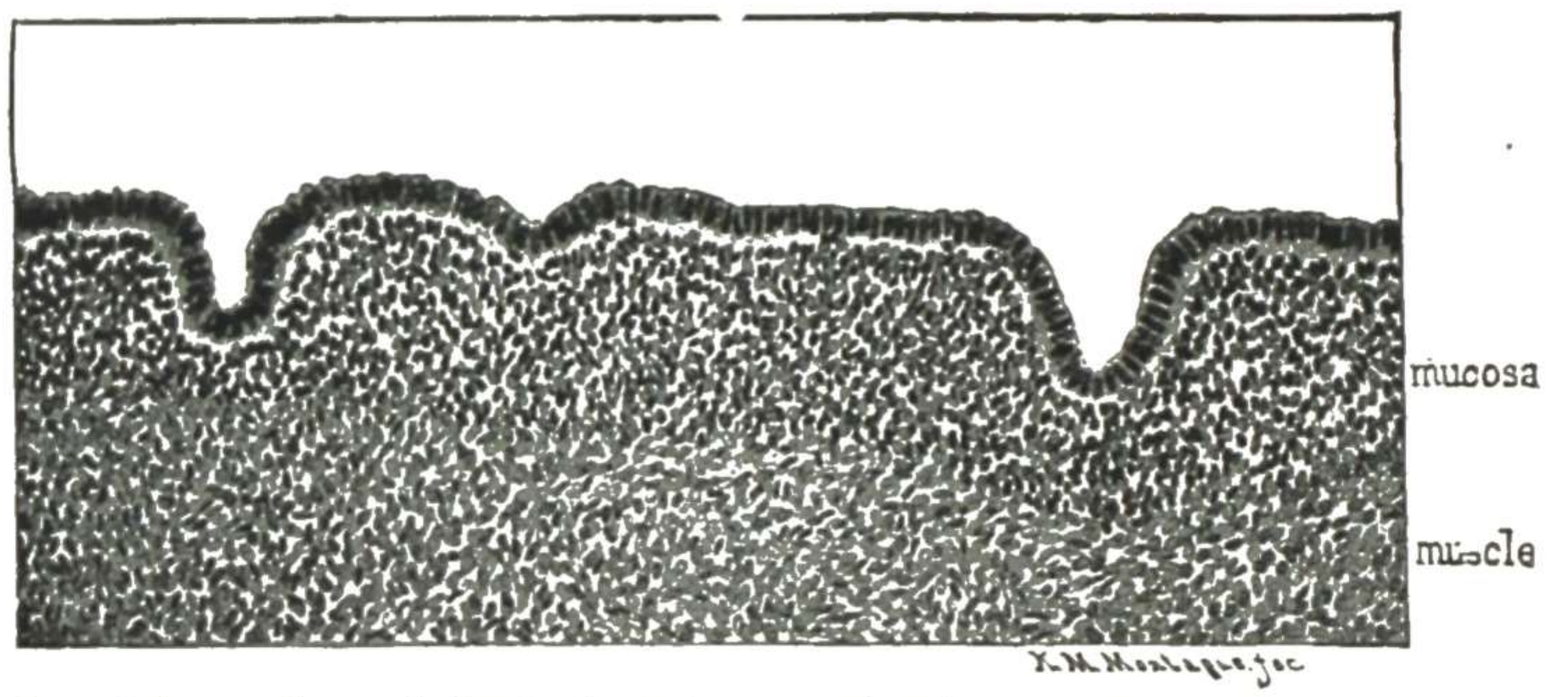
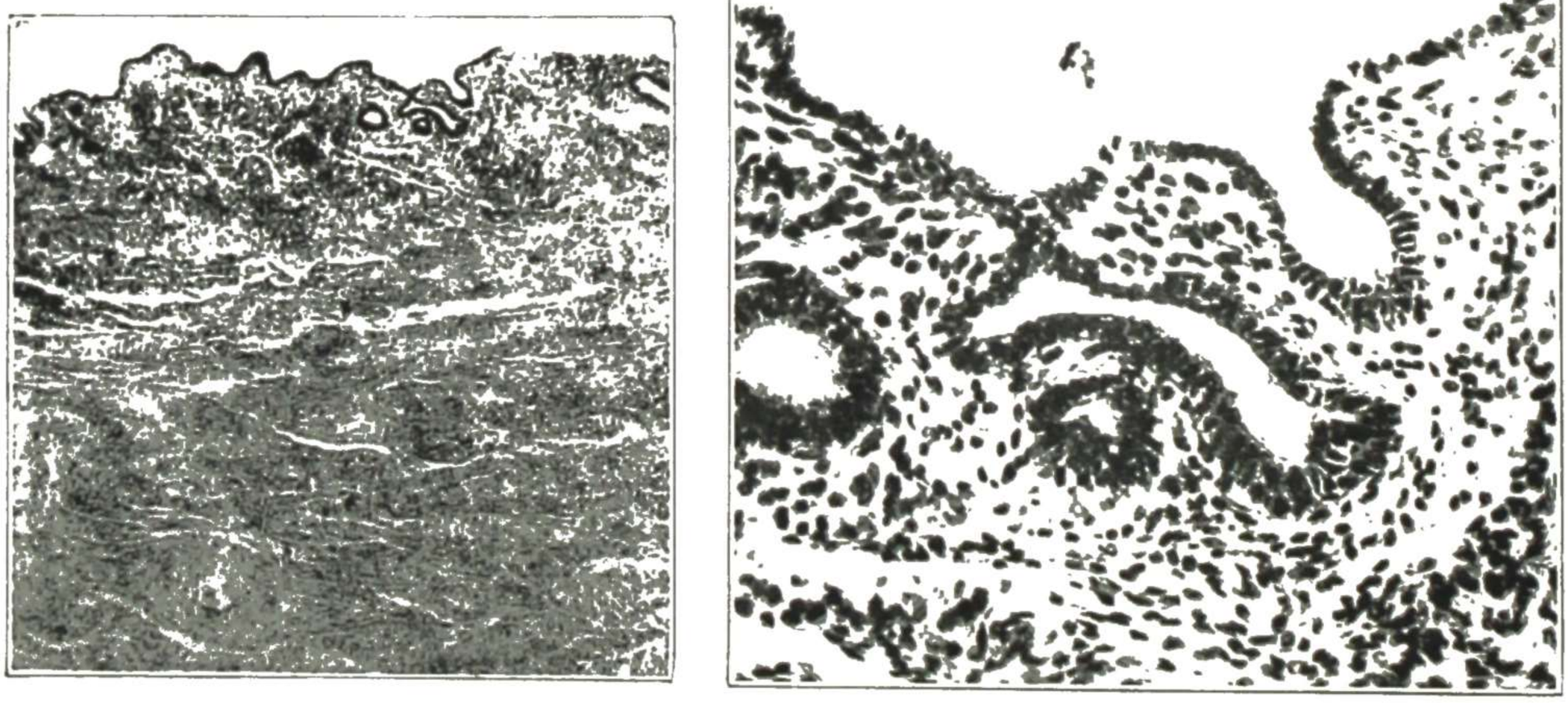


Fig. 74.—Endometrium of an infant, just born. (Williams—*Obstetrics*, D. Appleton-Century Company.)



A. *B.*

Fig. 75.—*A*, Microscopic section of uterine wall of child, aged eight years. Gyn. Lab. *B*, Higher power of the upper central portion of *A*. Gyn. Lab.

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 Figs. 74 and 75. As puberty is approached, more rapid development takes

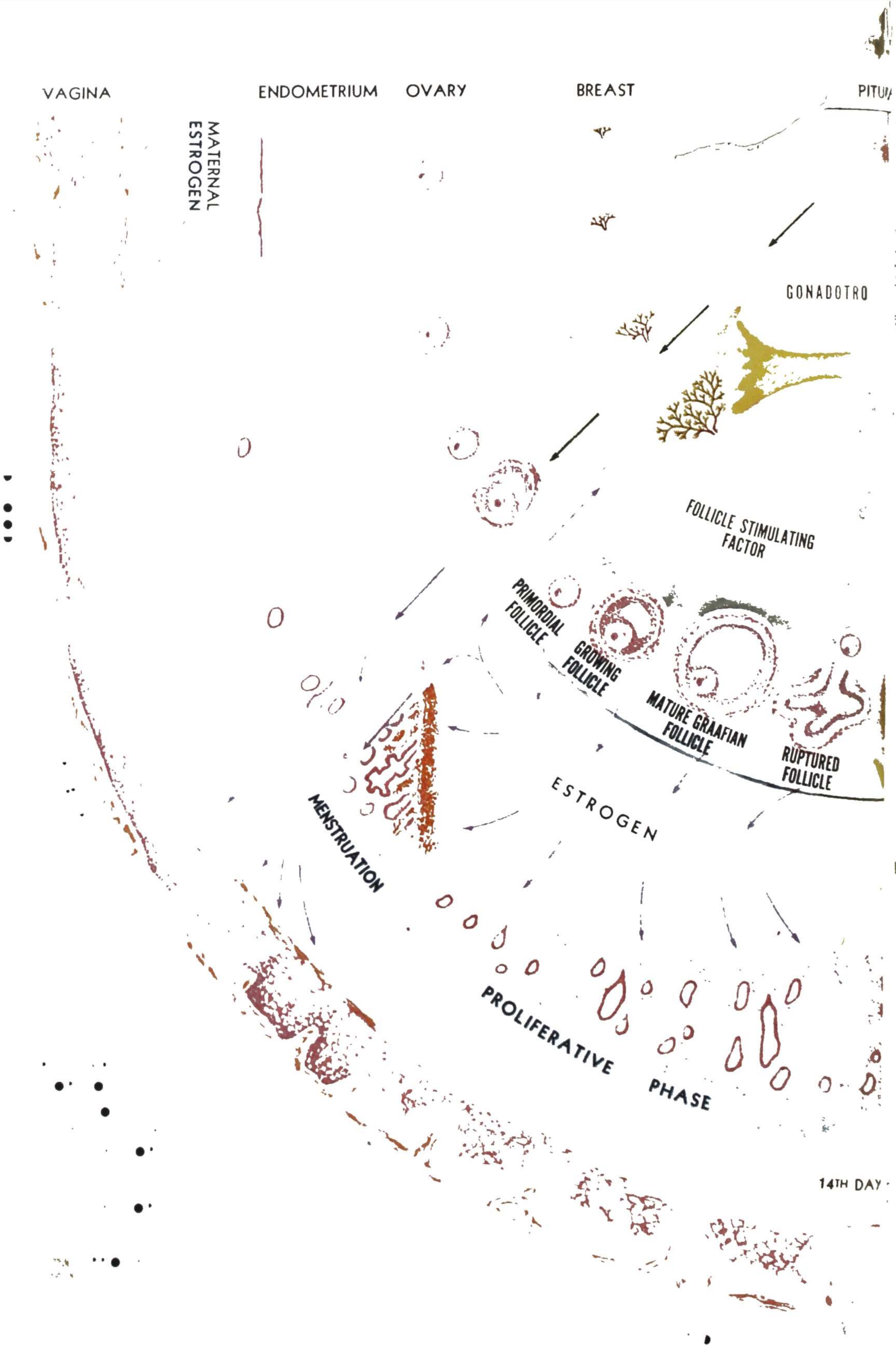


FIG. 76.—SCHEMATIC REPRESENTATION OF GENERALLY ACCEPTED HORMON