CHAPTER 22

The Female Reproductive System

The female reproductive system consists of the paired ovaries and oviducts (or uterine tubes), the uterus, the vagina, and the external genitalia (Figure 22–1). This system produces the female gametes **(oocytes)**, provides the environment for fertilization, and holds the embryo during its complete development through the fetal stage until birth. As with male gonads, the ovaries produce steroidal sex hormones that control organs of the reproductive system and influence other organs. Beginning at **menarche**, when the first menses occurs, the reproductive system undergoes monthly changes in structure and function, which are controlled by neurohormonal mechanisms. **Menopause** is a variably timed period during which the cyclic changes become irregular and eventually disappear. In the postmenopausal period the reproductive organs slowly involute. Although the mammary glands do not belong to the genital system, they are included here because they undergo changes directly connected to the functional state of the reproductive organs.

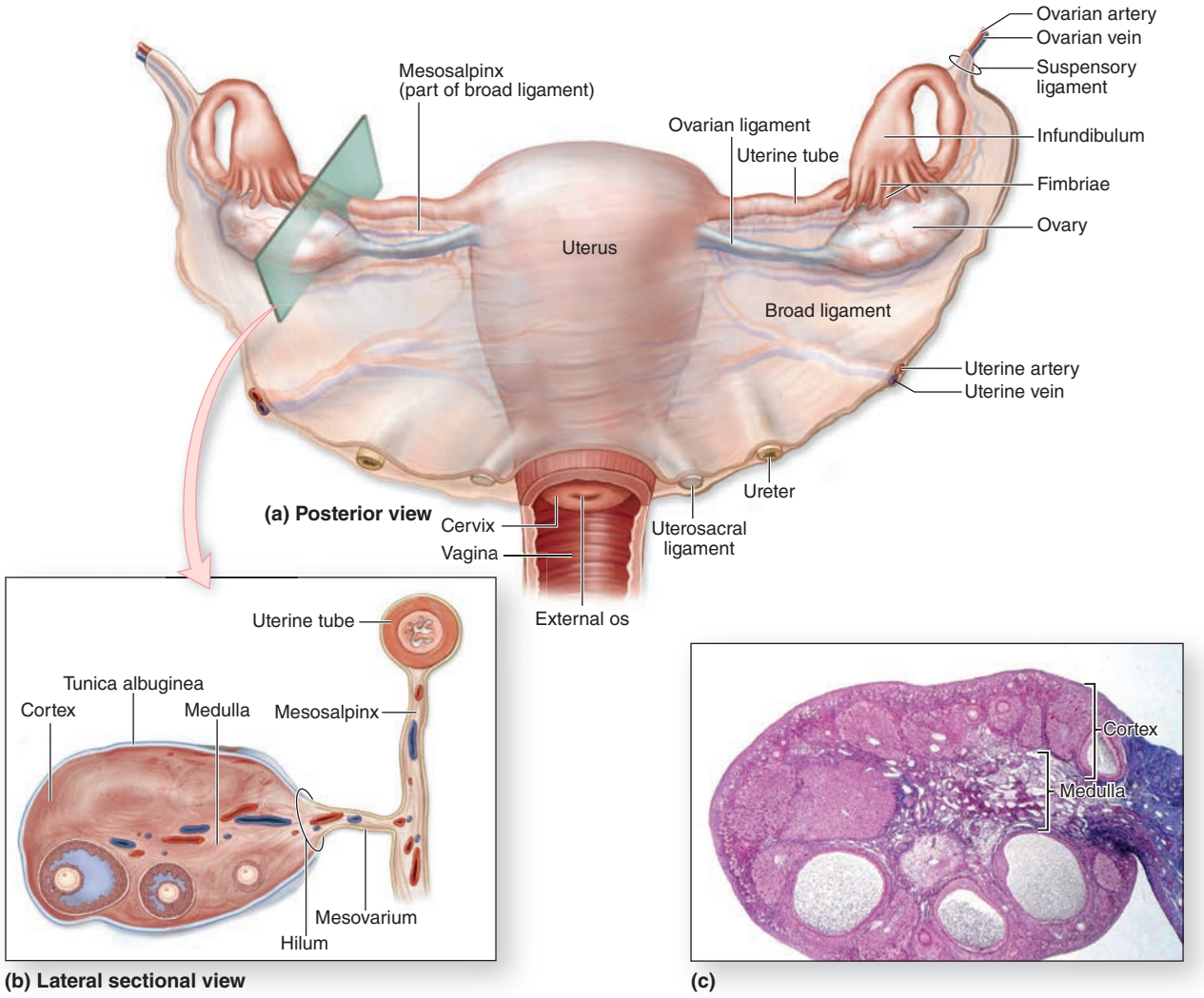
OVARIES

Ovaries are almond-shaped bodies approximately 3-cm long, 1.5-cm wide, and 1-cm thick. Each ovary is covered by a simple cuboidal epithelium, the **surface** (or germinal) **epithelium**, continuous with the mesothelium and overlying a layer of dense connective tissue capsule, the **tunica albuginea**, like that of the testis. Most of the ovary consists of the **cortex**, a region with a stroma of highly cellular connective tissue and many **ovarian follicles** varying greatly in size after menarche (Figure 22–1). The most internal part of the ovary, the **medulla**, contains loose connective tissue and blood vessels entering the organ through the hilum from mesenteries suspending the ovary (Figures 22–1 and 22–2). There is no distinct border between the ovarian cortex and the medulla.

Early Development of the Ovary

In the first month of embryonic life, a population of **primordial germ cells** migrates from the yolk sac to the gonadal primordia. As the ovaries develop these germ cells undergo synchronized mitotic divisions with incomplete cytokinesis, producing a few million interconnected **oogonia**. This mitotic activity ceases at 11-12 weeks gestation in humans and the clustered oogonia enter the long prophase of a first meiotic division (see Chapter 3). Most of these cells undergo apoptotic cell death, but others complete synapsis and genetic recombination and then arrest without progressing to later stages of meiosis. These cells in meiotic arrest are called **primary oocytes** (Gr. *oon*, egg + *kytos*, cell) and each becomes surrounded by flattened support cells called **follicular cells** to form a non-growing follicle. At birth there are about 680,000 such follicles, sometimes called the "ovarian reserve," of which about 460,000 remain at puberty, the others having been lost

FIGURE **22–1** **The female reproductive system and overview of ovary.**



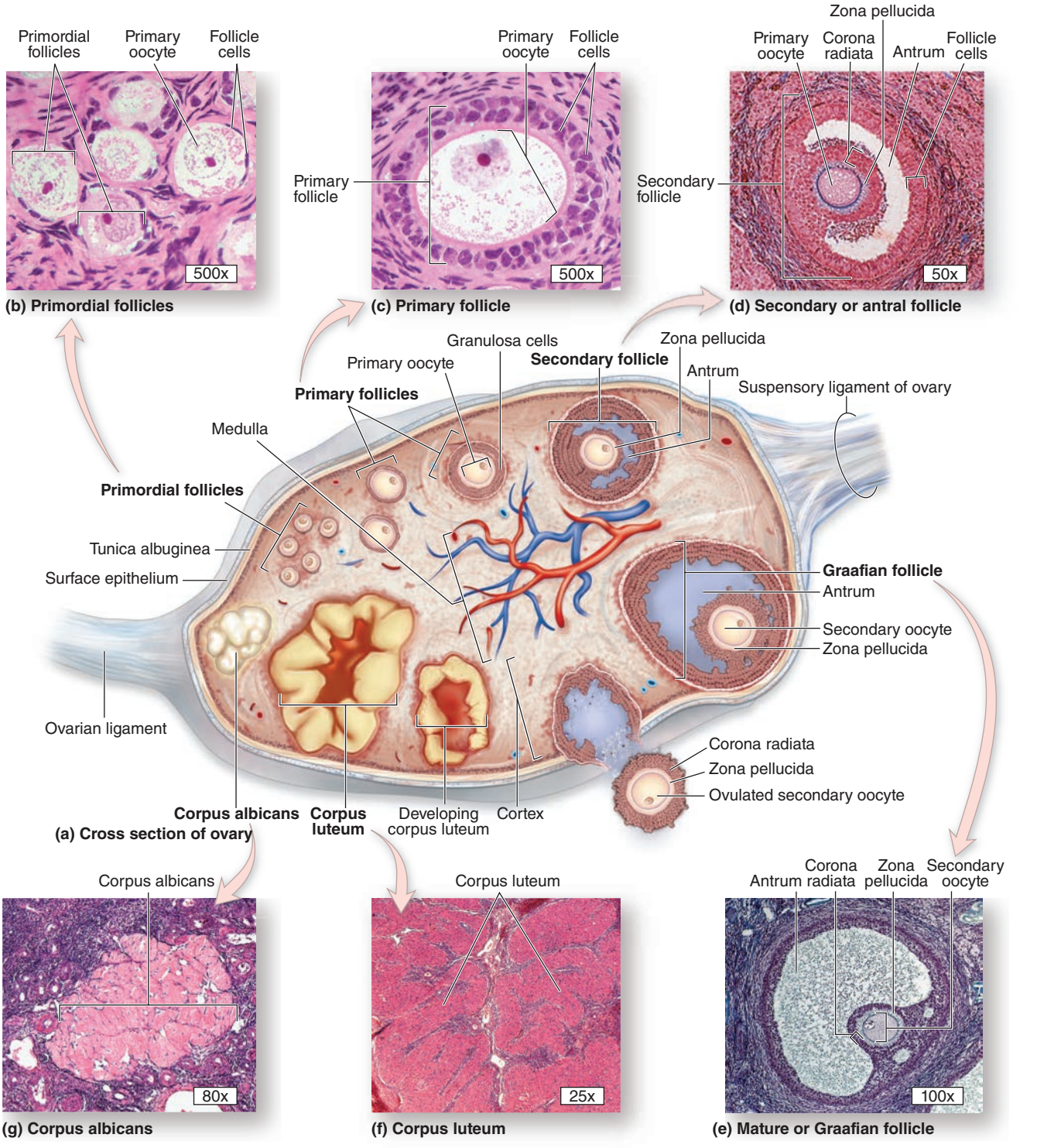
(a) The diagram shows the internal organs of the female reproductive system, which includes as the principal organs: the **ovaries**, **uterine tubes**, **uterus**, and **vagina**. **(b)** A lateral sectional view of an ovary shows the ovary and the relationship of its main supporting mesenteries, the mesovarium, and the mesosalpinx of the broad ligament. **(c)** A sectioned ovary, indicating the medulla and cortex, with follicles of several different sizes in the cortex. (X15; H&E)

through the degenerative process called **atresia**, which only ends with menopause. Because generally only one oocyte resuming meiosis undergoes ovulation during each menstrual cycle and the reproductive life of a woman is about 30-35 years, only about 450 oocytes are liberated from ovaries by ovulation. All others degenerate through atresia.

Ovarian Follicles

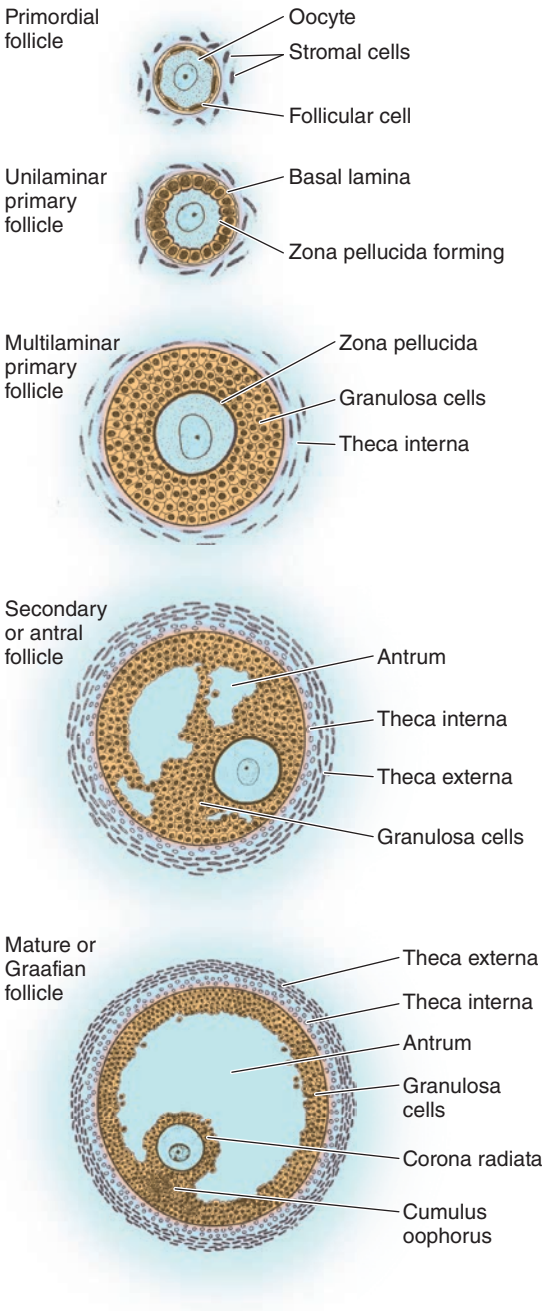
An ovarian follicle consists of an oocyte surrounded by one or more layers of epithelial cells within a basal lamina. The follicles that are formed during fetal life—**primordial follicles**—consist of a primary oocyte enveloped by a single layer of the flattened follicular cells (Figures 22–2b, 22–3, and 22–4). These follicles occur in the superficial ovarian cortex. The oocyte in the primordial follicle is spherical and about 25 µm in diameter, with a large nucleus containing chromosomes in the first meiotic prophase. The organelles tend to be concentrated near the nucleus and include numerous mitochondria, several Golgi complexes, and extensive RER. The basal lamina surrounding the follicular cells marks a clear boundary between the follicle and the vascularized stroma and acts as a blood-follicle barrier.

FIGURE 22–2 Follicle development and changes within the ovary.



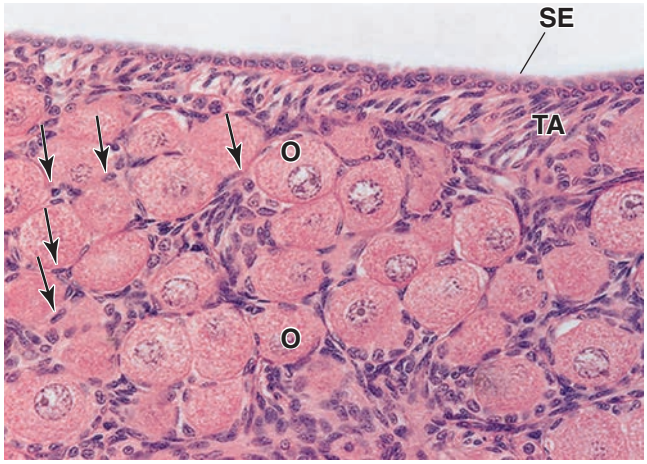
The ovary produces both oocytes and sex hormones. A diagram of a sectioned ovary **(a)** shows the **different stages of follicle maturation**, **ovulation**, and **corpus luteum formation and degeneration**. All of the stages and structures shown in this diagram actually would appear at different times during the ovarian cycle and do not occur simultaneously. Follicles are arranged here for easy comparisons. The **primordial follicles** shown are greatly enlarged. The histologic sections identify primordial follicles **(b)**, a primary follicle **(c)**, a secondary or antral follicle **(d)**, and a large vesicular follicle **(e)**. After ovulation, the portion of the follicle left behind forms the corpus luteum **(f)**, which then degenerates into the corpus albicans **(g)**. (All H&E)

FIGURE 22–3 Stages of ovarian follicles, from primordial to mature.



Diagrams of sectioned ovarian follicles show the changing size and morphology of follicular/granulosa cells at each stage and the disposition of the surrounding thecal cells. However, the relative proportions of the follicles are not maintained in the series of drawings: mature follicles are much larger relative to the early follicles. Deep within each follicle is a single large, growing oocyte with a large nucleus and prominent nucleolus. Follicular or granulosa cells around the oocyte support that cell's rapid growth.

FIGURE 22–4 Primordial follicles.



The cortical region of an ovary is surrounded by the surface epithelium (**SE**), a mesothelium with usually cuboidal cells. This layer is sometimes called the germinal epithelium because of an early erroneous view that it was the source of oogonia precursor cells. Underlying the epithelium is a connective tissue layer, the tunica albuginea (**TA**). Groups of primordial follicles, each formed by an oocyte (**O**) surrounded by a layer of flat epithelial follicular cells (**arrows**), are present in the ovarian connective tissue (stroma). (X200; H&E)

Follicular Growth & Development

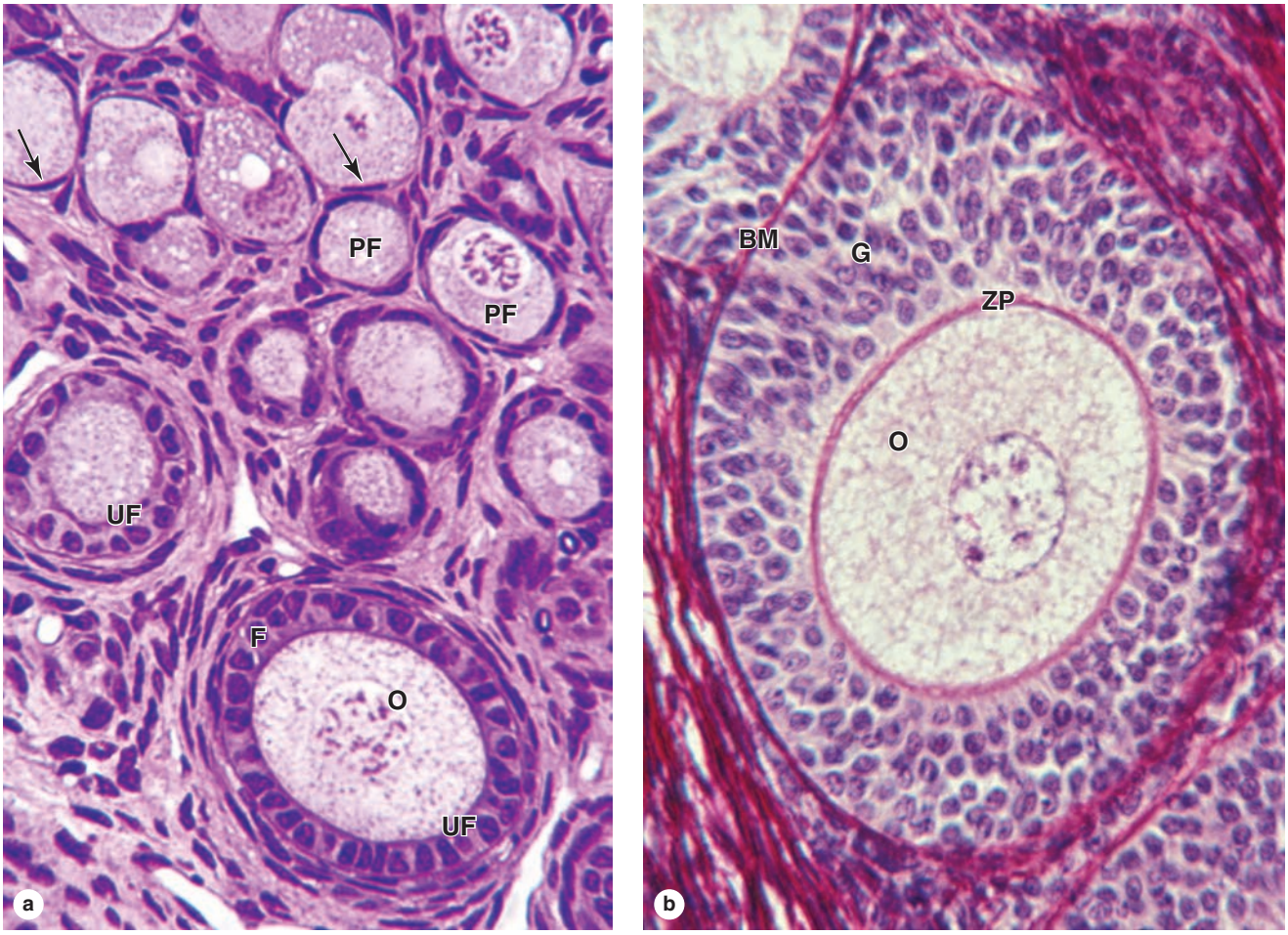
Beginning in puberty with the release of follicle-stimulating hormone (FSH) from the pituitary, a small group of primordial follicles each month begins a process of follicular growth. This involves growth of the oocyte, proliferation and changes in the follicular cells, as well as proliferation and differentiation of the stromal fibroblasts around each follicle. Selection of the primordial follicles that undergo growth and recruitment early in each cycle and of the dominant follicle destined to ovulate that month both involve complex hormonal balances and subtle differences among follicles in FSH receptor numbers, aromatase activity, estrogen synthesis, and other variables.

Prompted by FSH, an oocyte grows most rapidly during the first part of follicular development, reaching a diameter of about 120 μm. Oocyte differentiation includes the following:

- Growth of the cell and nuclear enlargement.
- Mitochondria becoming more numerous and uniformly distributed.
- RER becoming much more extensive and Golgi complexes enlarging and moving peripherally.
- Formation of specialized secretory granules called **cortical granules** containing various proteases. These lie just inside the oocyte's plasma membrane and undergo exocytosis early in fertilization.

Follicular cells undergo mitosis and form a simple cuboidal epithelium around the growing oocyte. The follicle is now

FIGURE **22–5** **Primary follicles: unilaminar and multilaminar.**



(a) A micrograph of ovarian cortex shows several primordial follicles (**PF**) and their flattened follicle cells (**arrows**), and two unilaminar primary follicles (**UF**) in which the follicle cells (**F**) form a single cuboidal layer around the large primary oocyte (**O**). (X200; PT)

(b) This micrograph taken at the same magnification shows a larger multilayered primary follicle. Follicle cells are now active granulosa cells (**G**) and have proliferated to form several layers. Between them and the oocyte (**O**) is the 5- to 10-µm-thick zona pellucida (**ZP**), a glycoprotein layer produced by the oocyte that is required for sperm binding and fertilization. The primary oocyte is now a very large cell. With this stain, the basement membrane (**BM**) separating the follicle from the surrounding stroma can also be seen. (X200; PSH)

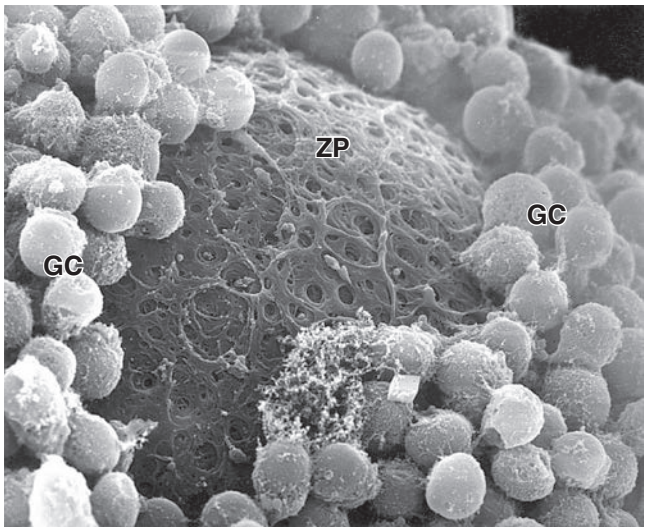
called a **unilaminar primary follicle** (Figures 22–3 and 22–5a). The follicular cells continue to proliferate, forming a stratified follicular epithelium, the **granulosa**, in which the cells communicate through gap junctions. Follicular cells are now termed **granulosa cells** and the follicle is a **multilaminar primary follicle** (Figures 22–3 and 22–5b) still avascular and surrounded by a basement membrane.

Between the oocyte and the first layer of granulosa cells of the growing primary follicle, extracellular material accumulates as the **zona pellucida**, 5-10-µm thick and containing four glycoproteins secreted by the oocyte (Figures 22–5b and 22–6). The zona pellucida components ZP3 and ZP4 are important sperm receptors, binding specific proteins on the sperm surface and inducing acrosomal activation. Filopodia of granulosa cells and microvilli of the oocyte penetrate the zona pellucida, allowing communication between these cells via gap junctions.

›› MEDICAL APPLICATION

Growing primary follicles can become involved in **polycystic ovary syndrome** (**PCOS**) that is characterized by enlarged ovaries with numerous cysts and an anovulatory state (with no follicles completing maturation successfully). The clinical presentation of this disorder is variable and the etiology is unclear, although increased androgen production by the ovaries or adrenals is likely involved. PCOS is a common cause of **infertility** in women.

FIGURE 22–6 Ultrastructure of primary follicle and zona pellucida.



An SEM of a fractured primary follicle shows the oocyte surrounded by granulosa cells (**GC**) of the corona radiata. Between the very large oocyte surface and the granulosa cells is a layer of extracellular material, the zona pellucida (**ZP**), which contains four related glycoproteins that bind sperm and form an irregular meshwork. (X3000)

Stromal cells immediately outside each growing primary follicle differentiate to form the vascularized **follicular theca** (Gr. *theca*, outer covering), which subsequently differentiates further as two distinct tissues around the follicle (see Figures 22–3, 22–7, and 22–8):

- A well-vascularized endocrine tissue, the **theca interna**, with typical steroid-producing cells secreting androstenedione. This precursor molecule diffuses into the follicle through the basement membrane, and in the granulosa cells the enzyme aromatase converts it to estradiol, an FSH-dependent function. This estrogen returns to the thecae and stroma around the follicle, enters capillaries, and is distributed throughout the body, inducing the changes characteristic of puberty.
- A more fibrous **theca externa** with fibroblasts and smooth muscle merges gradually with the surrounding stroma.

As the primary follicles grow, they move deeper in the ovarian cortex. Within such follicles small spaces appear between the granulosa layers as the cells secrete **follicular fluid** (or **liquor folliculi**). This fluid accumulates, the spaces enlarge and gradually coalesce, and the granulosa cells reorganize themselves around a larger cavity called the **antrum** (Figures 22–3 and 22–7a), producing follicles now called **secondary** or **antral follicles**. Follicular fluid contains the large GAG hyaluronic acid, growth factors, plasminogen, fibrinogen, the anticoagulant heparan sulfate proteoglycan, and high concentrations of steroids (progesterone, androstenedione, and estrogens) with binding proteins.

As the antrum develops, the granulosa cells around the oocyte form a small hillock, the **cumulus oophorus**, which protrudes into the antrum (Figures 22–3 and 22–7b). The tightly adhering granulosa cells immediately surrounding the zona pellucida make up the **corona radiata** and accompany the oocyte when it leaves the ovary at ovulation.

The single large antrum of a **mature** or **Graafian follicle** (named after the 17th-century reproductive biologist Regnier De Graaf) rapidly accumulates more follicular fluid and expands to a diameter of 2 cm. A mature follicle forms a bulge at the ovary surface visible with ultrasound imaging. The granulosa layer becomes thinner at this stage because its cells do not multiply in proportion to the growth of the antrum. A mature follicle has thick thecal layers and normally develops from a primordial follicle over a period of about 90 days.

Follicular Atresia

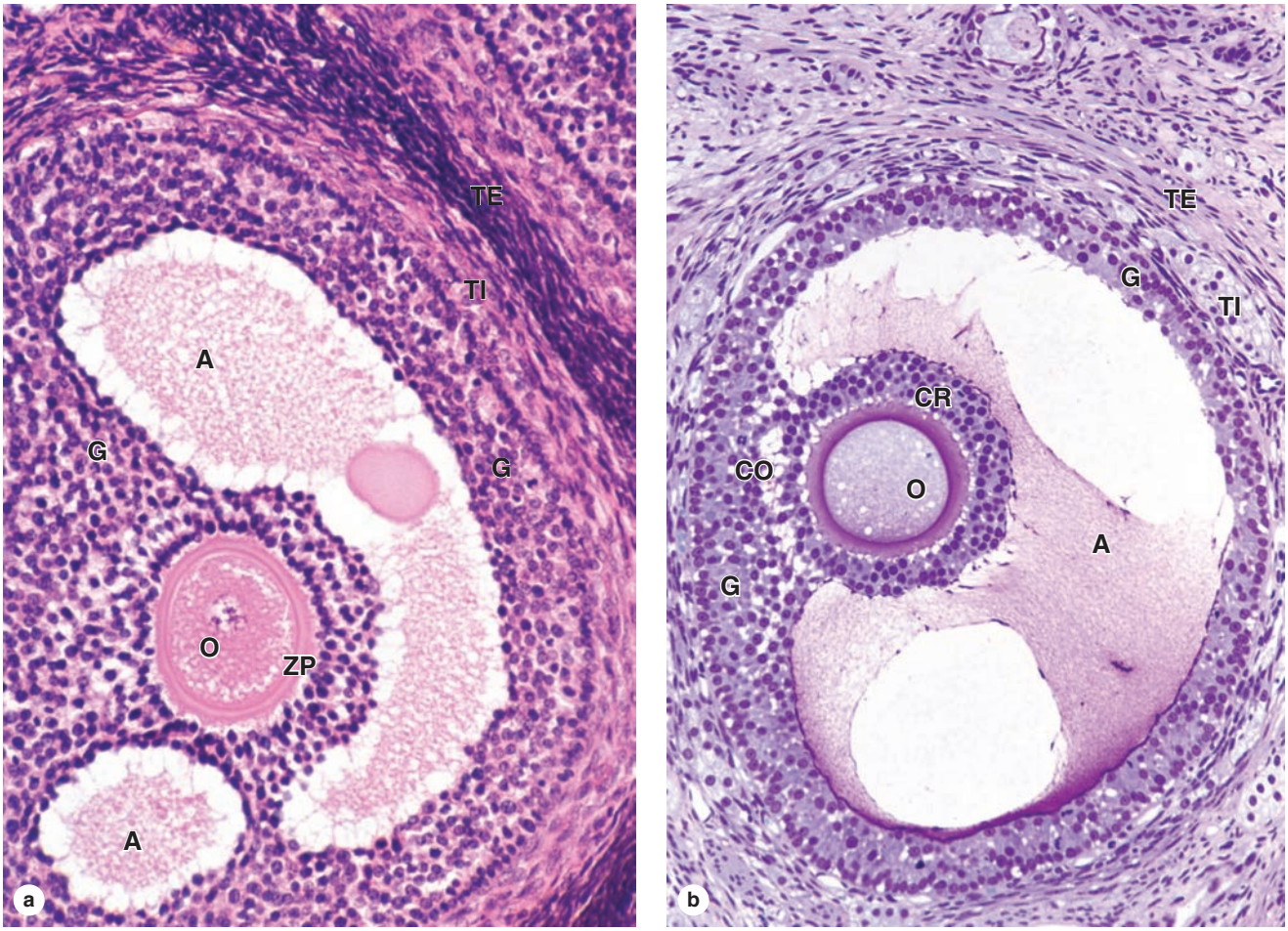
Most ovarian follicles undergo the degenerative process called **atresia**, in which follicular cells and oocytes undergo apoptosis and removal by phagocytic cells. Follicles at any stage of development, including nearly mature follicles, may become atretic (Figure 22–9). Atresia involves detachment of the apoptotic granulosa cells, autolysis of the oocyte, and collapse of the zona pellucida. Macrophages invade the degenerating follicle and phagocytose the apoptotic material and other debris. Typically during a woman's fourth decade, menopause begins when atresia and ovulation have reduced the ovarian reserve to fewer than about 1000 follicles.

During a typical menstrual cycle, one follicle becomes dominant and develops farther than the others. The **dominant follicle** usually reaches the most developed stage of follicular growth and undergoes ovulation, while the other primary and antral follicles undergo atresia. Although their oocytes are never directly used, the large growing follicles each month produce much estrogen before becoming atretic. As described later, this estrogen stimulates preparation of the reproductive tract to transport and sustain the embryo if the oocyte from the dominant follicle is fertilized.

›› MEDICAL APPLICATION

Late primary or antral follicles can produce **follicular cysts**, which are thin-walled, fluid-filled structures with both granulosa and thecal endocrine cells. Follicular cysts are common and usually benign, but can produce high estrogen levels and lead to menstrual irregularities. If cyst formation disrupts blood vessels, blood enters the fluid, often rapidly, and produces a **hemorrhagic cyst**.

FIGURE **22–7** **Antral follicle and mature follicle.**



(a) An antral follicle shows the large, fluid-filled antral cavities or vesicles (**A**) forming within the granulosa layer as the cells produce follicular fluid. The oocyte (**O**) is surrounded by the zona pellucida (**ZP**) and granulosa cells (**G**), which also line the wall of the follicle. Fibroblastic cells immediately outside the growing follicles have developed as a steroid-secreting theca interna (**TI**) and a covering theca externa (**TE**). (X100; H&E)

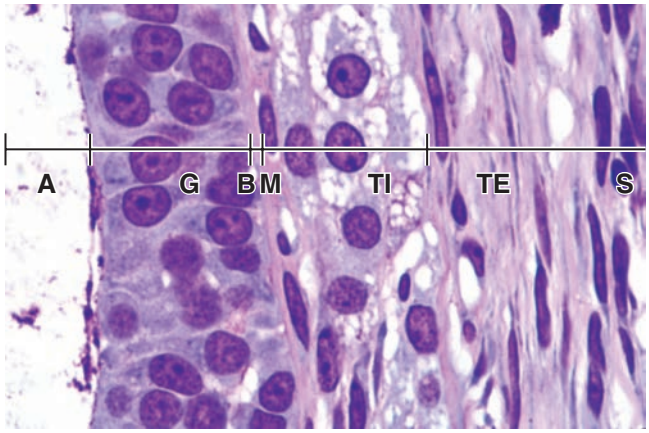
(b) A slightly more developed preovulatory follicle shows a very large single antrum (**A**) filled with follicular fluid in which the proteins formed a thin film during fixation. The oocyte (**O**) now projects into this fluid-filled cavity, still surrounded by tightly adherent granulosa cells, which now make up the corona radiata (**CR**). The corona radiata and oocyte are attached to the side of the follicle within a larger mass of granulosa cells called the **cumulus oophorus** (**CO**), which is continuous with the cells of the granulosa layer (**G**). Thecae interna (**TI**) and externa (**TE**) surround the whole follicle. (X100; PT)

Ovulation & Its Hormonal Regulation

Ovulation is the hormone-stimulated process by which the oocyte is released from the ovary. Ovulation normally occurs midway through the menstrual cycle, that is, around the 14th day of a typical 28-day cycle. In the hours before ovulation, the mature dominant follicle bulging against the tunica albuginea develops a whitish or translucent ischemic area, the **stigma**, in which tissue compaction has blocked blood flow. In humans usually only one oocyte is liberated during each cycle, but sometimes either no oocyte or two or more simultaneous oocytes may be expelled.

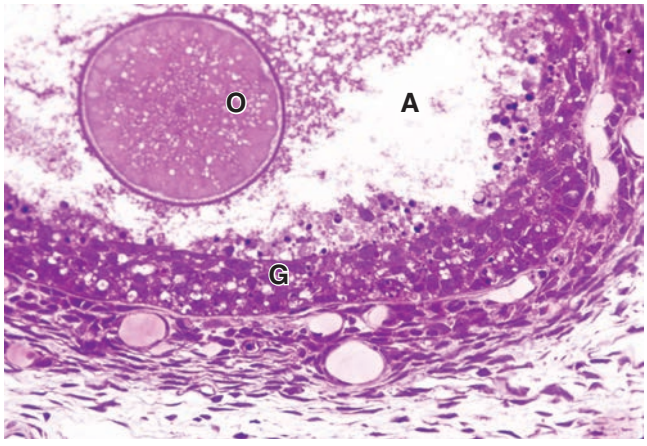
Just before ovulation the oocyte completes the first meiotic division, which it began and arrested in prophase during fetal life (Figure 22–10). The chromosomes are equally divided between the two daughter cells, but one of these retains almost all of the cytoplasm. That cell is now the **secondary oocyte** and the other becomes the **first polar body**, a very small nonviable cell containing a nucleus and a minimal amount of cytoplasm. Immediately after expulsion of the first polar body, the nucleus of the oocyte begins the second meiotic division but arrests at metaphase and never completes meiosis unless fertilization occurs (Figure 22–10).

FIGURE 22–8 Wall of antral follicle.



At higher magnification, a small part of the wall of an antral follicle shows the cell layers of the granulosa (**G**) next to the antrum (**A**), in which proteins have aggregated on cells in contact with the follicular fluid. The theca interna (**TI**) surrounds the follicle, its cells appearing vacuolated and lightly stained because of their cytoplasmic lipid droplets, a characteristic of steroid-producing cells. The overlying theca externa (**TE**) contains fibroblasts and smooth muscle cells and merges with the stroma (**S**). A basement membrane (**BM**) separates the theca interna from the granulosa, blocking vascularization of the latter. (X400; PT)

FIGURE 22–9 Atresia.



Atresia or degeneration of a follicle can begin at any stage of follicular development and is shown here in a follicle that had already developed a large antrum. Atresia is characterized by apoptosis of follicle or granulosa cells (**G**) and autolysis of the oocyte, with macrophages entering the degenerating structure to clean up debris. Many apoptotic bodies are seen loose in the antrum (**A**) here and the cells of the corona radiata have already disappeared, leaving the degenerative oocyte (**O**) free within the antrum. (X200; PT)

As mentioned before, follicular development depends on FSH from pituitary gonadotrophs, whose secretion is stimulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus. Figure 22–11 summarizes the main hormonal interactions that regulate follicular growth as well as the ovulation and formation of the corpus luteum. Note that negative feedback of estrogen and progesterone on the hypothalamus and anterior pituitary is reinforced by a polypeptide hormone, **inhibin**, also produced by granulosa and luteal cells. In the days preceding ovulation, the dominant follicle secretes higher levels of estrogen that stimulate more rapid pulsatile release of GnRH from the hypothalamus.

The increased level of GnRH causes a surge of luteinizing hormone (LH) release from the pituitary gland that rapidly triggers a sequence of major events in and around the dominant follicle:

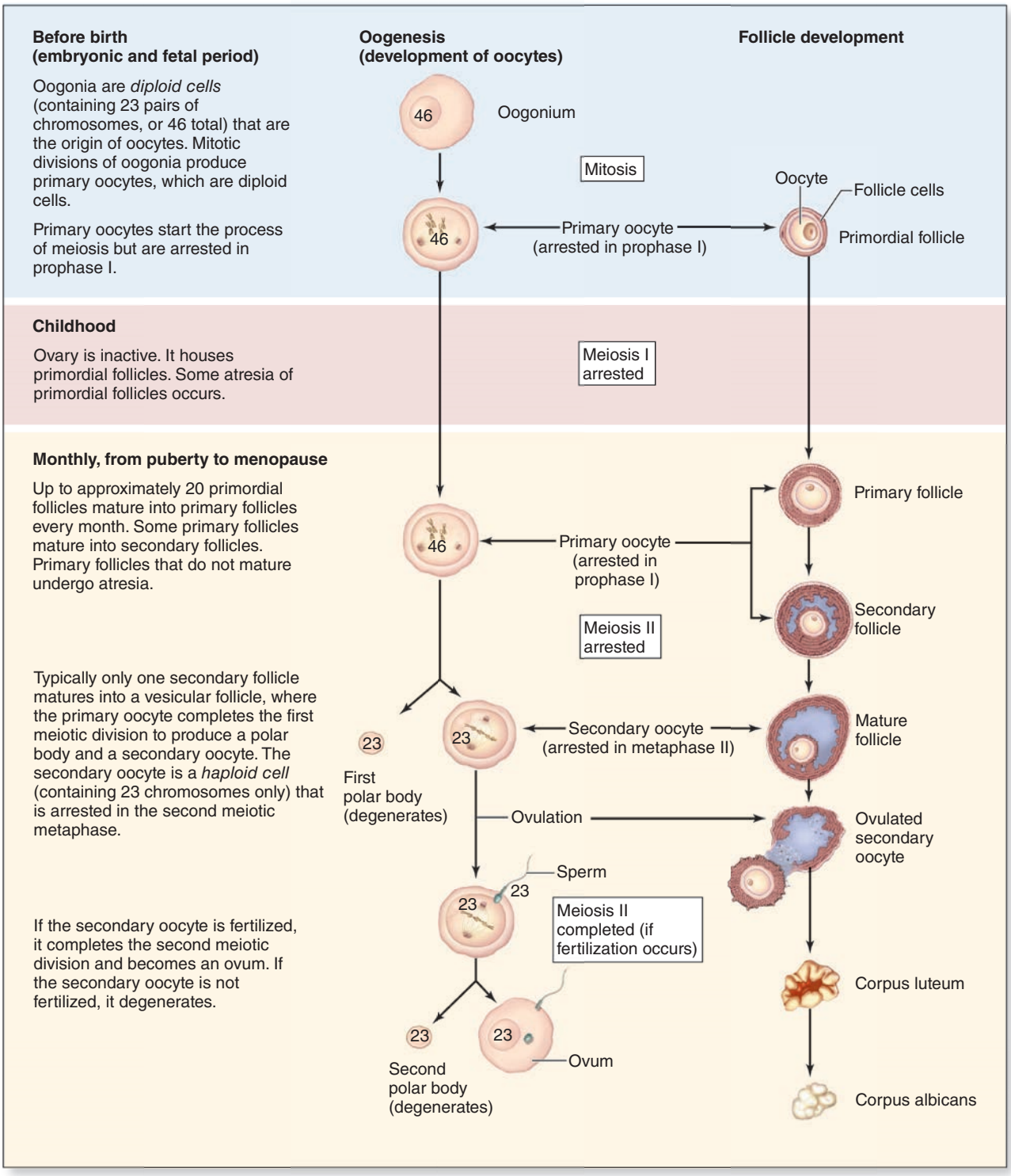
- **Meiosis I is completed** by the primary oocyte, yielding a secondary oocyte and the first polar body that degenerates (Figure 22–10).
- Granulosa cells are stimulated to produce more follicular fluid containing **prostaglandins**, proteoglycans, and proteases that remove the surrounding blood-follicle barrier. The granulosa cells in the cumulus oophorus-oocyte complex mainly release **hyaluronan**, which increases the fluid viscosity and swells to greatly increase the extracellular volume within this complex, loosening its outer cells, and dissociating it from the follicle wall.
- Ballooning at the stigma, the **ovarian wall weakens** as activated plasminogen (plasmin) from broken capillaries degrades collagen in the tunica albuginea and surface epithelium.
- **Smooth muscle contractions** begin in the theca externa, triggered by prostaglandins diffusing from follicular fluid.

The increasing pressure with the follicle and weakening of the wall lead to rupture of the ovarian surface at the stigma. The oocyte and its surrounding corona radiata, along with follicular fluid, are expelled by the local smooth muscle contractions. The ovulated secondary oocyte adheres loosely to the ovary surface in the viscous follicular fluid and, as described later, is drawn into the opening of the uterine tube where fertilization may occur. If not fertilized within about 24 hours, the secondary oocyte begins to degenerate. Cells of the ovulated follicle that remain in the ovary redifferentiate under the influence of LH and give rise to the corpus luteum (Figure 22–11).

Corpus Luteum

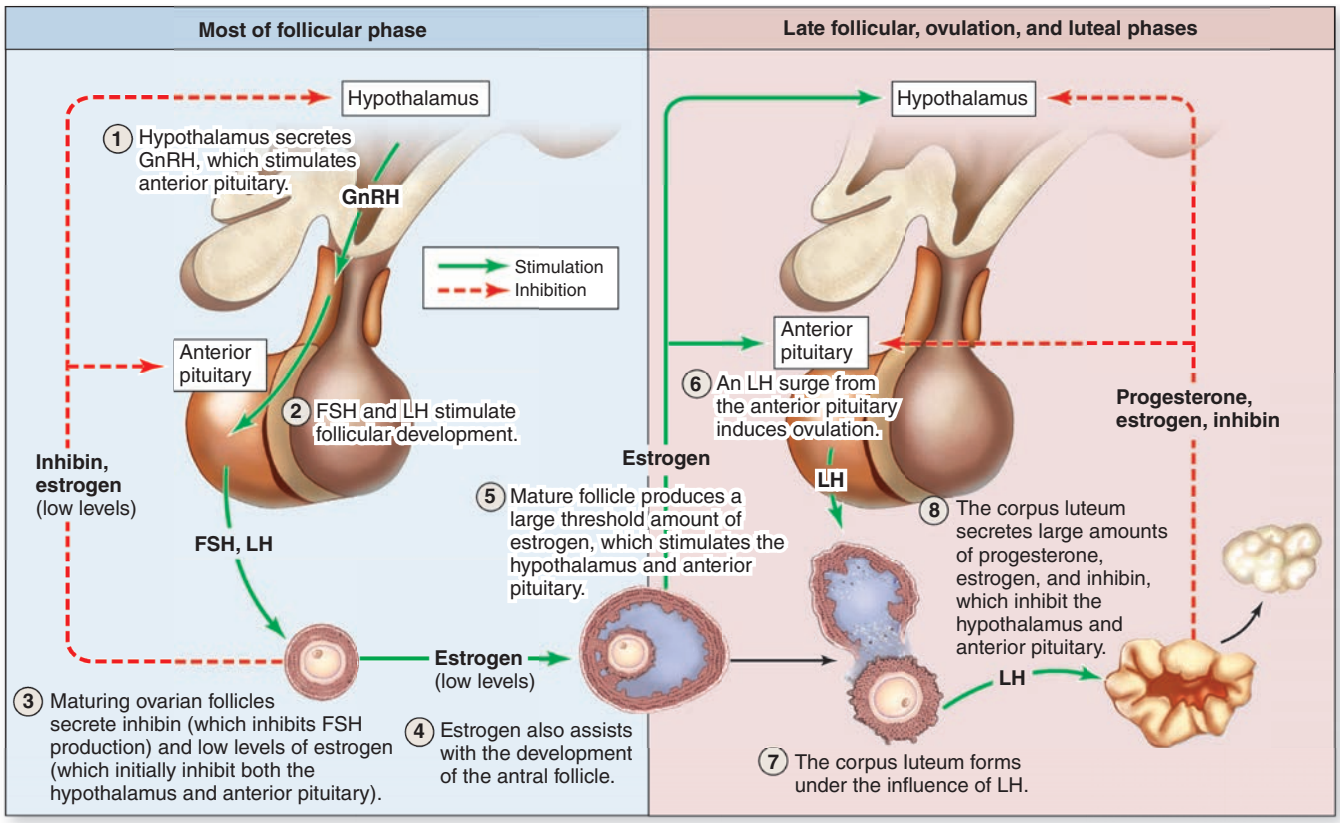
After ovulation, the granulosa cells and theca interna of the ovulated follicle reorganize to form a larger temporary endocrine gland, the **corpus luteum** (L., yellowish body), in the ovarian cortex. Ovulation is followed immediately by the collapse and folding of the granulosa and thecal layers of the follicle's wall, and blood from disrupted capillaries typically accumulates as a clot in the former antrum (Figure 22–12). The granulosa is now invaded by capillaries. Cells of both the granulosa and theca interna change histologically and

FIGURE 22–10 Oogenesis.



Oogenesis begins in the female fetus, with primary oocytes arresting at prophase I in primordial follicles, which remain inactive during childhood. At puberty, a population of primordial follicles begins to develop each month. Typically one per month produces a female gamete (a secondary oocyte).

FIGURE 22–11 Hormonal regulation of ovarian function.



The **ovarian cycle** of follicular growth, followed by ovulation and luteal formation, is initiated when the hypothalamus secretes GnRH. This stimulates the anterior pituitary to secrete FSH and LH, in the cycle depicted here.

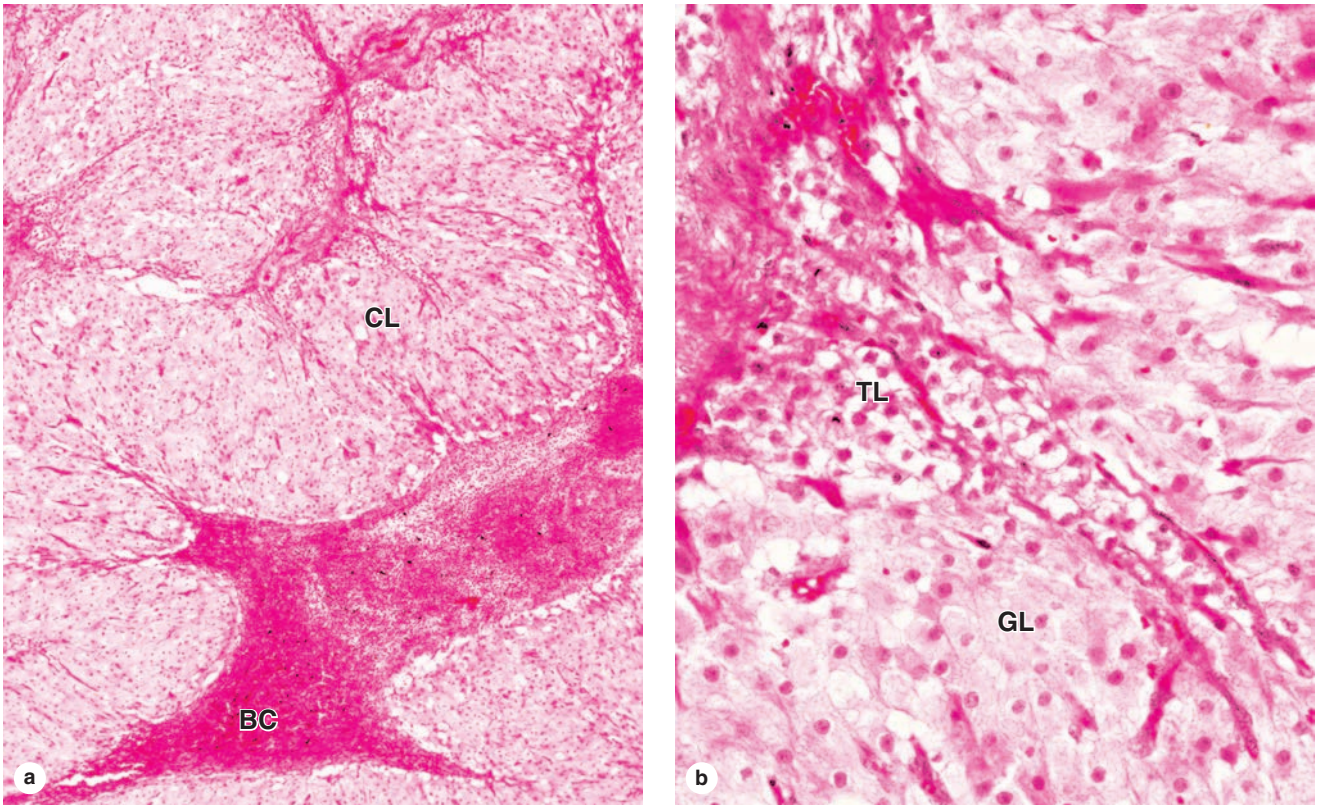
functionally under the influence of LH, becoming specialized for more extensive production of progesterone in addition to estrogens.

Granulosa cells increase greatly in size (20-35 μm in diameter), without dividing, and eventually comprise about 80% of the corpus luteum. They are now called **granulosa lutein cells** (Figure 22–12) and have lost many features of protein-secreting cells to expand their role in aromatase conversion of androstenedione into estradiol. The former theca interna forms the rest of the corpus luteum, as **theca lutein cells** (Figure 22–12). These cells are half the size of the granulosa lutein cells and are typically aggregated in the folds of the wall of the corpus luteum, which, like all endocrine glands, becomes well vascularized. Luteinizing hormone causes these cells to produce large amounts of progesterone as well as androstenedione.

The short-term fate of the corpus luteum depends on whether a pregnancy occurs. The ovulatory LH surge causes the corpus luteum to secrete progesterone for 10-12 days. Without further LH stimulation and in the absence of pregnancy, both major cell types of the corpus luteum cease steroid production and undergo apoptosis, with regression of the tissue. A consequence of the decreased secretion of progesterone is menstruation, the shedding of part of the uterine mucosa. Estrogen produced by the active corpus luteum inhibits FSH release from the pituitary. However, after the corpus luteum degenerates, the blood steroid concentration decreases and FSH secretion increases again, stimulating the growth of another group of follicles and beginning the next menstrual cycle. The corpus luteum that persists for part of only one menstrual cycle is called a **corpus luteum of menstruation**. Remnants from its regression are phagocytosed by macrophages, after which fibroblasts invade the area and produce a scar of dense connective tissue called a **corpus albicans** (L., white body) (Figure 22–13).

If pregnancy occurs, the uterine mucosa must not be allowed to undergo menstruation because the embryo would be lost. To prevent the drop in circulating progesterone, trophoblast cells of the implanted embryo produce a glycoprotein hormone called **human chorionic gonadotropin (hCG)** with targets and activity similar to that of LH. Human chorionic gonadotropin maintains and promotes further growth of the corpus luteum, stimulating secretion of progesterone to maintain the uterine mucosa. This **corpus luteum of pregnancy** becomes very large and is maintained by hCG for

FIGURE **22–12** **Corpus luteum.**



The corpus luteum is a large endocrine structure formed from the remains of the large dominant follicle after it undergoes ovulation. **(a)** A low-power micrograph shows the corpus luteum (**CL**), characterized by folds of the former granulosa, which collapses as the theca externa contracts at ovulation. The former antrum often contains a blood clot (**BC**) from vessels in the thecal layers disrupted during ovulation. Cells of the granulosa and theca interna become reorganized under the influence of pituitary LH and their names are changed. (X15; H&E)

(b) Granulosa lutein cells (**GL**), seen at higher magnification here, undergo significant hypertrophy, producing most of the corpus luteum's increased size, and begin producing progesterone. The theca lutein cells (**TL**) increase only slightly in size, are somewhat darker-staining than the granulosa lutein cells, and continue to produce estrogens. Theca lutein cells, derived from the theca interna, are typically located within the folds that comprise the bulk of this tissue. (X100; H&E)

4-5 months, by which time the placenta itself produces progesterone (and estrogens) at levels adequate to maintain the uterine mucosa. It then degenerates and is replaced by a large corpus albicans.

UTERINE TUBES

The paired **uterine tubes**, or **oviducts**, supported by ligaments and mesenteries, which allow considerable mobility, each measure about 10-12 cm in length (Figure 22–14). Each opens into the peritoneal cavity near the ovary, with regions in the following sequence:

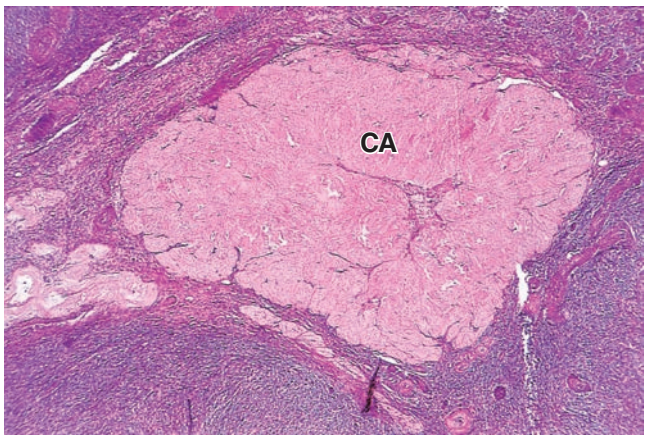
- The **infundibulum**, a funnel-shaped opening fringed with fingerlike extensions called **fimbriae** (L., fringes) next to the ovary;
- The **ampulla**, the longest and expanded region where fertilization normally occurs;
- The **isthmus**, a more narrow portion nearer the uterus; and
- The **uterine** or **intramural part**, which passes through the wall of the uterus and opens into the interior of this organ.

The wall of the oviduct consists of a folded mucosa, a thick, well-defined muscularis with interwoven circular (or spiral) and longitudinal layers of smooth muscle (Figure 22–15a), and a thin serosa covered by visceral peritoneum with mesothelium.

The numerous branching, longitudinal folds of the mucosa are most prominent in the ampulla, which in cross section resembles a labyrinth (Figure 22–14b). These mucosal folds become smaller in the regions closer to the uterus and are absent in the intramural portion of the tube.

Along its entire length, the mucosa is lined by simple columnar epithelium on a lamina propria of loose connective

FIGURE 22–13 Corpus albicans.



A corpus albicans (**CA**) is the scar of connective tissue that forms at the site of a corpus luteum after its involution. It contains mostly collagen, with few fibroblasts or other cells, and gradually becomes very small and lost in the ovarian stroma. Involution of the corpus luteum does not involve atresia. (X60; H&E)

tissue (Figure 22–15b). The epithelium contains two interspersed, functionally important cell types:

- **Ciliated cells** in which ciliary movements sweep fluid toward the uterus.
- **Secretory peg cells**, nonciliated and often darker staining, often with an apical bulge into the lumen, which secrete glycoproteins of a nutritive mucus film that covers the epithelium.

Triggered primarily by estrogens, the cilia elongate and both cell types undergo hypertrophy during the follicular growth phase of the ovarian cycle and undergo atrophy with loss of cilia during the late luteal phase.

At the time of ovulation, mucosal hypertrophy and increased local blood flow have enlarged and moved the uterine tubes. The fringed infundibulum lies very close to the ovary and the fimbriae partially surround that organ. This favors the transport of the ovulated secondary oocyte into the tube. Promoted by sweeping muscular contractions of the fimbriae and ciliary activity, the oocyte enters the infundibulum and moves to the ampulla. The secretion covering the mucosa has nutritive and protective functions for both the oocyte and the sperm, including **capacitation factors** that activate sperm and make those cells able to fertilize an oocyte.

MAJOR EVENTS OF FERTILIZATION

Fertilization, the union of the female and male gametes, normally occurs in the ampulla of a uterine tube, a site usually reached by only a few hundred of the millions of ejaculated sperm. Only sperm that have undergone capacitation in the female reproductive tract are capable of fertilization, a process with the following major steps:

- Upon contact with cells of the corona radiata, sperm undergo the **acrosomal reaction** in which **hyaluronidase** is released by exocytosis at multiple locations around the sperm head. This allows sperm to move more easily to the zona pellucida.
- Specific proteins on the sperm surface bind the receptors ZP3 and ZP4, activating the protease **acrosin** on the acrosomal membrane to degrade the zona pellucida locally.
- The first sperm penetrating the zona pellucida fuses with the oocyte plasmalemma and triggers Ca^{2+} release from vesicles, which induces exocytosis of proteases from the cortical granules. This **cortical reaction** quickly spreads like a wave across the entire surface of the oocyte, with the proteases converting the zona pellucida to the impenetrable **perivitelline barrier** that constitutes a permanent block to polyspermy.
- The nucleus of the secondary oocyte immediately completes meiosis II, producing a second polar body and the **female pronucleus** of the haploid **ovum**. The haploid nucleus of the single penetrating sperm head undergoes decondensation, becoming the **male pronucleus**. Fusion of the two pronuclei yields the new diploid cell, the **zygote** (Gr. *zygotos*, yoked together).

Cell division occurs while the embryo is transported by contractions of the oviduct muscularis and ciliary movements to the uterus, which takes about 5 days. This transport occurs normally in women with immotile ciliary syndrome, indicating a more important role for muscle contractions in moving the embryo.

MEDICAL APPLICATION

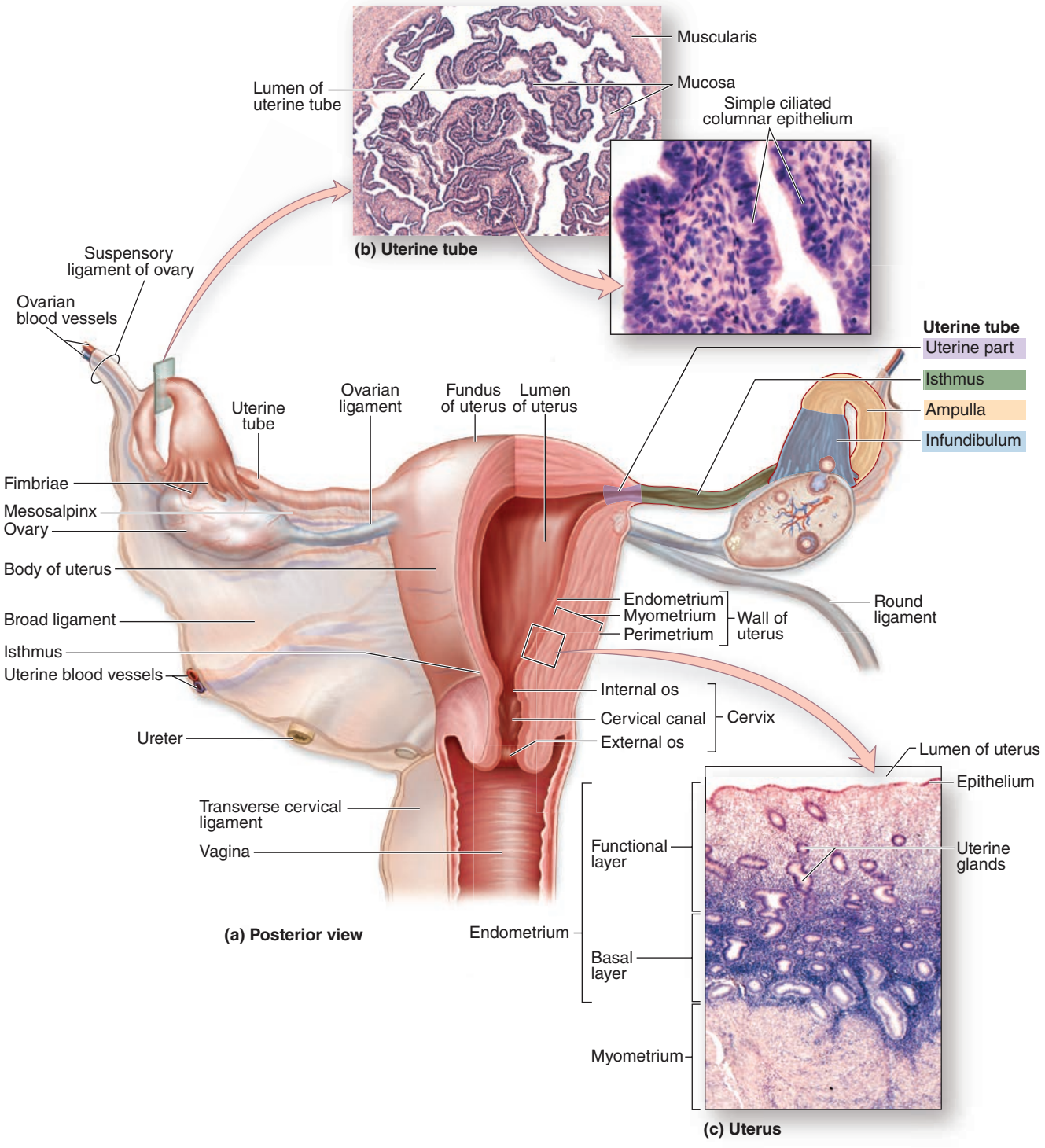
Tubal ligation is a common surgical type of contraception. The uterine tube mucosa can become inflamed if infectious agents ascend from the lower genital tract, producing a condition named **salpingitis** after another name for these tubes, the **salpinges**. Mucosal damage or adhesions caused by chronic salpingitis can lead to **infertility** or an **ectopic** (**tubal**) **pregnancy** if there is blockage of oocyte or embryo transport to the uterus.

In tubal pregnancies, the lamina propria may react like the uterine endometrium and form decidual cells. But because of its small diameter and inability to expand, the tube cannot contain the growing embryo and will rupture, causing potentially fatal hemorrhage.

UTERUS

As shown in Figure 22–14, the uterus is a pear-shaped organ with thick, muscular walls. Its largest part, the **body**, is entered by the left and right uterine tubes and the curved, superior

FIGURE 22–14 Uterine tubes and uterus.

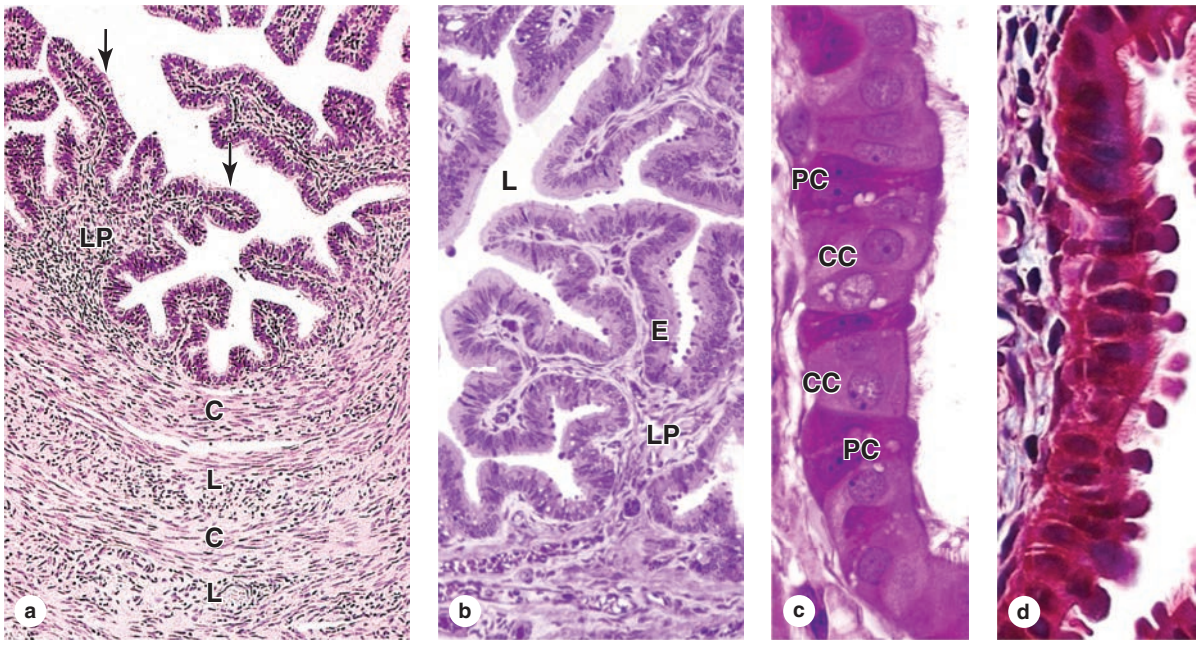


The uterine tubes or oviducts are paired ducts that catch the ovulated secondary oocyte, nourish both the oocyte and sperm, provide the microenvironment for fertilization, and transport the embryo undergoing cleavage to the uterus. **(a)** The diagram shows the relationship between the uterine tubes and the uterus in an intact posterior view (left) and in a cutaway view (right).

(b) Shown here is a cross section of uterine tube with a high magnification of the mucosa. (X35 and 400; H&E)

(c) Shown here is the uterine wall with the myometrium and the two layers of the endometrium. (X45; H&E)

FIGURE 22–15 Mucosa of the uterine tube wall.



(a) A cross section of the uterine tube at the ampulla shows the interwoven circular (**C**) and longitudinal (**L**) layers of smooth muscle in the muscularis and in the complex of folded mucosa, the lamina propria (**LP**) underlying a simple columnar epithelium (arrows). (X140; H&E)

(b) The oviduct mucosa, with folds projecting into the lumen (**L**), has simple columnar epithelium (**E**) on the lamina propria (**LP**). (X200; PT)

(**c, d**) Higher magnification of the epithelium shows two cell types: ciliated cells (**CC**) interspersed with the secretory peg cells (**PC**), which produce the nutritive fluid covering the epithelium. These cells' histologic and functional features vary during the ovarian cycle due to hormonal fluctuations. In **(d)** the peg cells shown are at their most developed and most active state in the period shortly after ovulation when an embryo might be present. (c: X400, PT; d: X400, Mallory trichrome)

area between the tubes is called the **fundus**. The uterus narrows in the **isthmus** and ends in a lower cylindrical structure, the **cervix**. The lumen of the cervix, the **cervical canal**, has constricted openings at each end: the **internal os** (L. *os*, mouth) opens to the main uterine lumen and the **external os** to the vagina (Figure 22–14).

Supported by the set of ligaments and mesenteries also associated with the ovaries and uterine tubes (Figure 22–1), the uterine wall has three major layers (Figure 22–14):

- An outer connective tissue layer, the **perimetrium**, continuous with the ligaments, which is adventitial in some areas, but largely a serosa covered by mesothelium;
- A thick tunic of highly vascularized smooth muscle, the **myometrium** (Figure 22–16); and
- A mucosa, the **endometrium**, lined by simple columnar epithelium.

These three layers are continuous with their counterparts in the uterine tubes. The thickness and structure of the endometrium is influenced cyclically by the shifting levels of ovarian hormones even more than the mucosa of the uterine tubes (Figure 22–17).

Myometrium

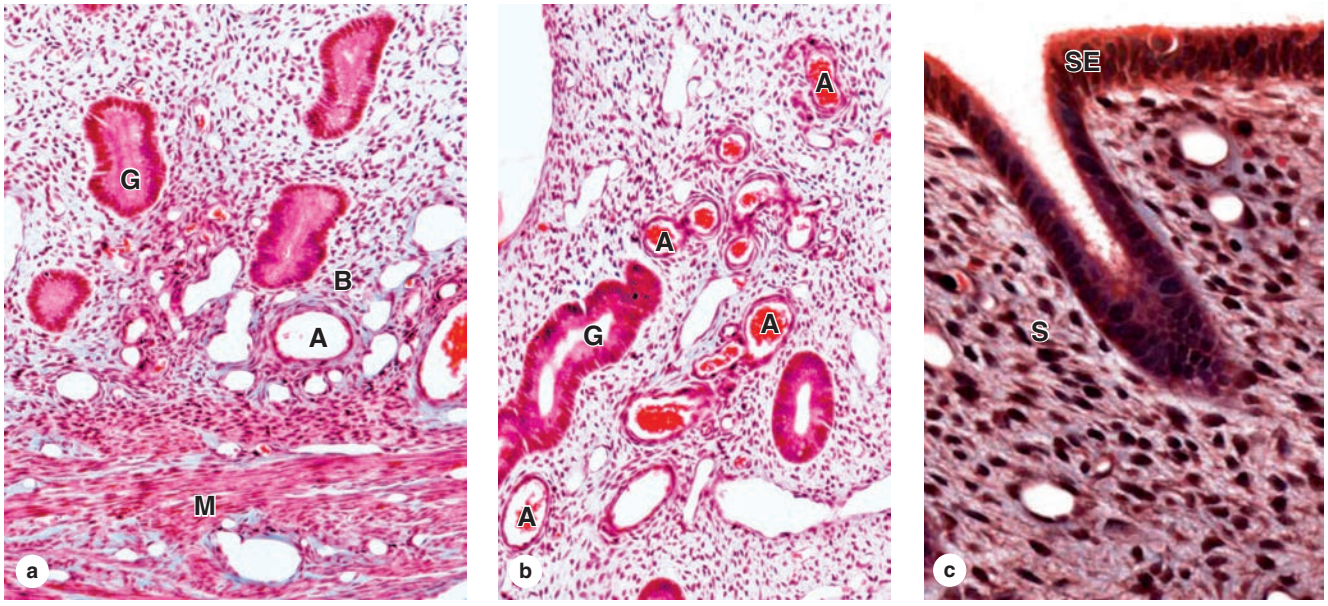
The **myometrium** (Gr. *myo*, muscle + *metra*, uterus), the thickest tunic of the uterus, shows bundles of smooth muscle fibers separated by connective tissue containing venous plexuses and lymphatics (Figure 22–16). The smooth muscle forms interwoven layers, with fibers of the inner and outer layers disposed generally parallel to the long axis of the organ.

During pregnancy, the myometrium goes through a period of extensive growth involving both **hyperplasia** (increasing the number of smooth muscle cells), cell hypertrophy, and increased collagen production by the muscle cells, which strengthens the uterine wall. This well-developed uterine myometrium contracts very forcefully during **parturition** to expel the infant from the uterus. After pregnancy, uterine smooth muscle cells shrink and many undergo apoptosis, with removal of unneeded collagen, and the uterus returns almost to its prepregnancy size.

Endometrium

The lamina propria or stroma of the **endometrium** contains primarily nonbundled type III collagen fibers with abundant

FIGURE **22–16** **Uterus.**



(a) The basal layer (**B**) of the endometrium, bordering the myometrium (**M**), contains the basal ends of the uterine glands (**G**) and many small arteries (**A**) embedded in a distinctive connective tissue stroma with many fibroblasts, ground substance, and primarily fine type III collagen, but no adipocytes. (X100; Mallory trichrome)

(b) Superficial to the basal layer of the endometrium is its functional layer, the part that changes histologically and functionally depending on estrogen levels. This micrograph shows only the functional layer and includes parts of the long uterine glands (**G**) as well as one spiral artery (**A**). (X100; Mallory trichrome)

(c) The surface epithelium (**SE**) lining the endometrium is simple columnar, with many cells having cilia. The underlying stroma (**S**) has an extensive microvasculature, much ground substance, and fibroblastic cells with large, active nuclei. (X400; Mallory trichrome)

fibroblasts and ground substance. Its simple columnar epithelial lining has both ciliated and secretory cells, and the latter line the numerous tubular **uterine glands**, which penetrate the full thickness of the endometrium (Figures 22–16 and 22–18).

The endometrium has two concentric zones:

- The **basal layer** adjacent to the myometrium has a more highly cellular lamina propria and contains the deep basal ends of the uterine glands (Figure 22–16a).
- The superficial **functional layer** has a spongier lamina propria, richer in ground substance, and includes most of the length of the glands, as well as the surface epithelium (Figure 22–16b,c).

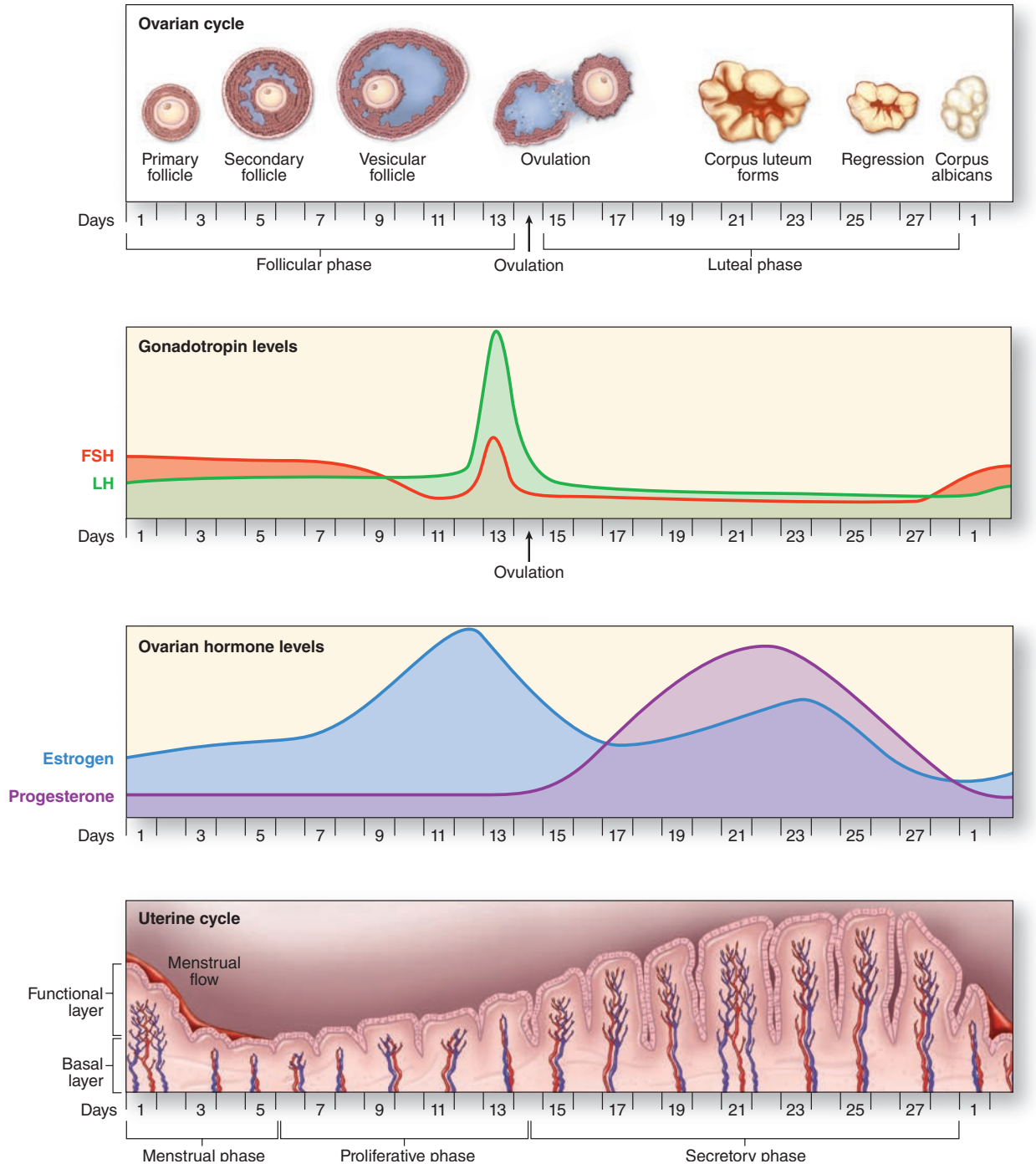
The functional layer undergoes profound changes during the menstrual cycles, but the basal layer remains relatively unchanged (Figure 22–17).

The blood vessels supplying the endometrium have special significance in the periodic sloughing of the functional layer during menses. Arcuate arteries in the middle layers of the myometrium send two sets of smaller arteries into the endometrium (Figure 22–18): **straight arteries**, which supply only the basal layer, and long, progesterone-sensitive **spiral arteries**, which extend farther and bring blood throughout the functional layer. Spiral arteries branch with numerous arterioles supplying a rich, superficial capillary bed that includes many dilated, thin-walled **vascular lacunae** drained by venules.

Menstrual Cycle

Throughout the female reproductive system, estrogens and progesterone control growth and differentiation of epithelial cells and associated connective tissue. Even before birth, these cells are influenced by circulating maternal estrogen and progesterone that reach the fetus through the placenta. After menopause diminished synthesis of these hormones results in a general involution of tissues in the reproductive tract.

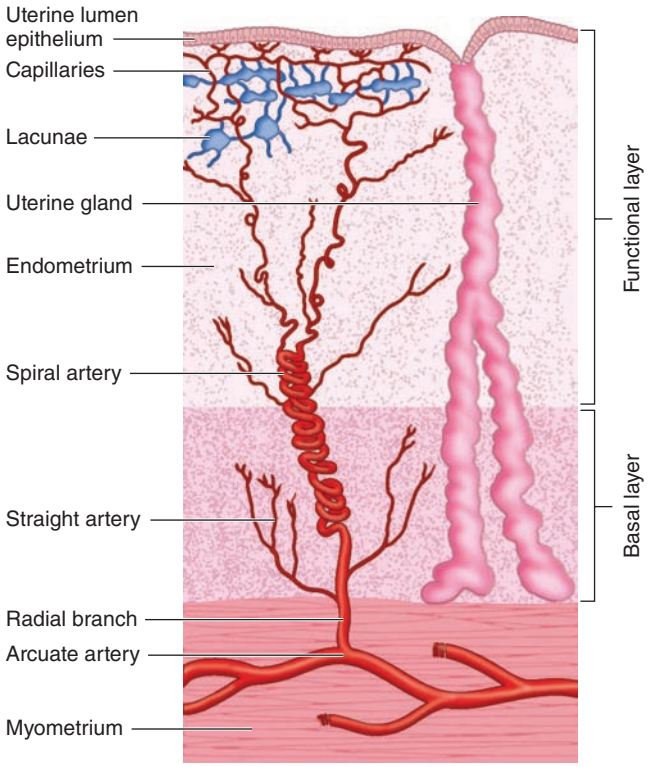
FIGURE 22–17 Correlation of ovarian and menstrual cycles with levels of their controlling hormones.



The cyclic development of **ovarian follicles** and the **corpus luteum**, controlled by the pituitary **gonadotropins** FSH and LH, lead to cyclic shifts in the levels of the major ovarian hormones: steroidal **estrogens and progesterone**. Estrogen stimulates the proliferative phase of the uterine cycle and its level peaks near the day of ovulation, which marks the midpoint of the ovarian cycle. After ovulation the corpus luteum forms and produces both progesterone and estrogens, which together promote growth and development of the endometrial **functional layer.**

Unless fertilization and implantation of an embryo occur, regression of the corpus luteum leads to declining levels of the steroid hormones and failure of the new endometrial tissue to be maintained. This tissue sloughs off as the menstrual flow, the first day of which is taken to mark day 1 of both the ovarian cycle and the uterine cycle. The basal layer of endometrium is not sensitive to the loss of progesterone and is retained during menstruation, serving to regenerate the functional layer during the ensuing proliferative phase.

FIGURE 22–18 Arterial supply to the endometrium.



The **basal and functional layers** of the endometrium are supplied by different sets of small arteries emerging from the uterine arcuate arteries in the myometrium: the **straight arteries** and **spiral arteries**, respectively. The spiral arteries are uniquely sensitive to progesterone, growing rapidly in a spiral fashion as the functional layer thickens under the influence of that luteal steroid and providing blood to a microvasculature, which includes many lacunae lined by thin endothelium. This blood supply brings oxygen and nutrients to cells of the functionalis and to an embryo implanting itself into that tissue. If no embryo is present to produce the gonadotropin replacing LH, the corpus luteum undergoes regression 8-10 days after ovulation. The rapid decline in the level of progesterone causes constriction of the spiral arteries and other changes, which quickly lead to local ischemia in the functional layer and its separation from the basal layer during menstruation.

›› MEDICAL APPLICATION

Viable endometrial cells frequently undergo menstrual reflux into or through the uterine tubes. In some women this can lead to **endometriosis**, a disorder with pelvic pain due to endometrial tissue growing on the ovaries, oviducts, or elsewhere. Under the influence of estrogen and progesterone, the ectopic tissue grows and degenerates monthly but cannot be removed effectively from the body. In addition to pain endometriosis can produce inflammation, ovarian cysts, adhesions, and scar tissue that can cause infertility.

From puberty until menopause at about age 45-50, pituitary gonadotropins produce cyclic changes in ovarian hormone levels, which cause the endometrium to undergo cyclic modifications during the menstrual cycle (Figures 22–17 and 22–19). The duration of the menstrual cycle may be variable but averages 28 days. Because menstrual cycles are a consequence of ovarian follicle changes related to oocyte production, a woman is fertile only during the years when she is having menstrual cycles.

Day 1 of the menstrual cycle is usually taken as the day when menstrual bleeding appears. The menstrual discharge consists of degenerating endometrium mixed with blood from its ruptured microvasculature. The **menstrual period** lasts 3-4 days on average. The next phase of the cycle, the **proliferative phase**, is of variable length, 8-10 days on average, and the **secretory phase** begins at ovulation and lasts about 14 days (Figure 22–17). The cyclic structural changes occur gradually and the activities characterizing these phases overlap to some extent.

Proliferative Phase

After the menstrual phase, the uterine mucosa is relatively thin (~0.5 mm). The beginning of the **proliferative phase**, also called the **follicular or estrogenic phase**, coincides with the rapid growth of a small group of ovarian follicles growing as vesicular follicles. With development of their thecae interna, these follicles actively secrete estrogen and increase its plasma concentrations (Figure 22–17).

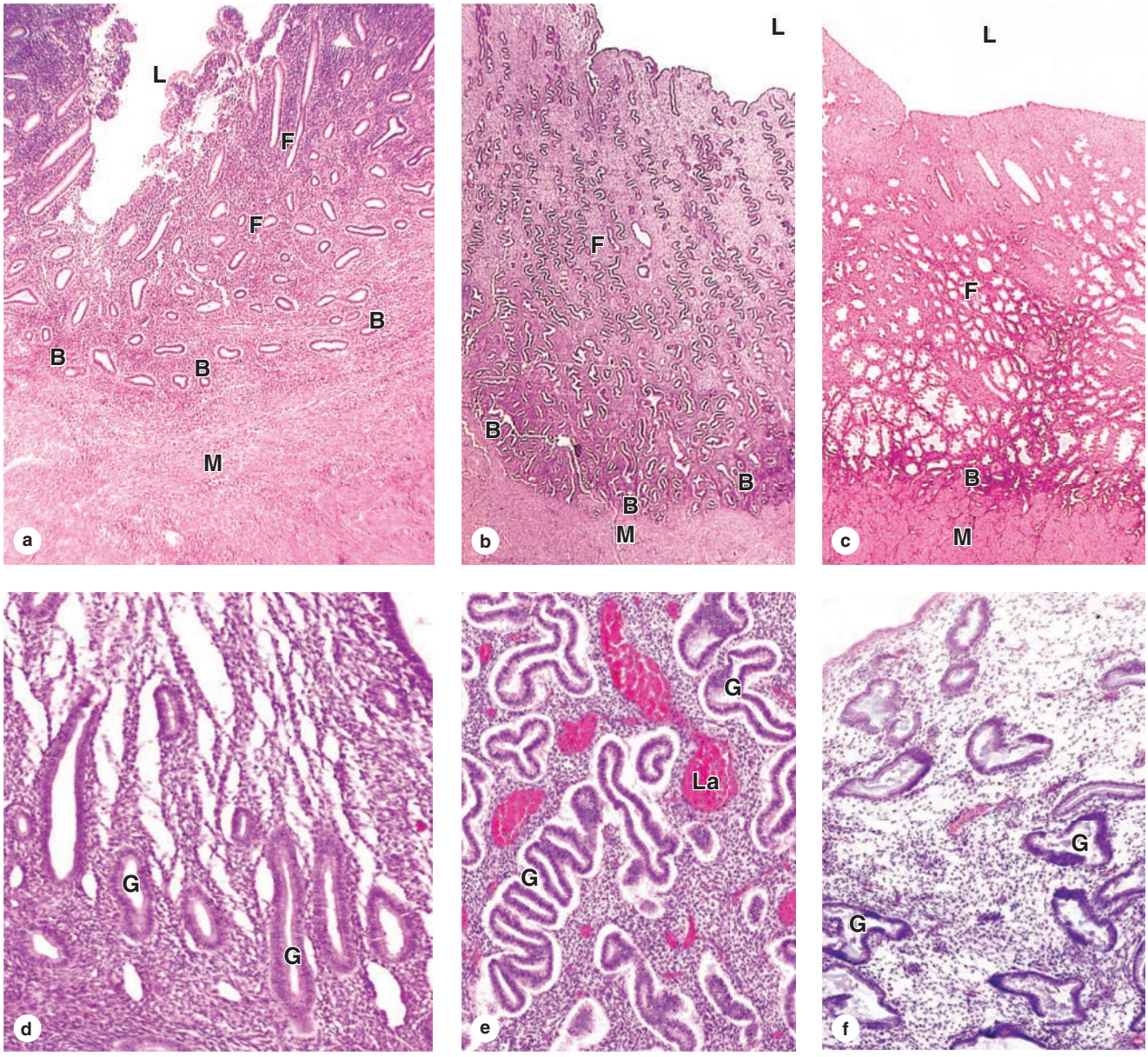
Estrogens act on the endometrium, inducing regeneration of the functional layer lost during menstruation. Cells in the basal ends of glands proliferate, migrate, and form the new epithelial covering over the surface exposed during menstruation. During the proliferative phase, the endometrial lining is a simple columnar surface epithelium and the uterine glands are relatively straight tubules with narrow, nearly empty lumens (Figure 22–19a,d). Mitotic figures can be found among both the epithelial cells and fibroblasts. Spiral arteries lengthen as the functional layer is reestablished and grows (Figure 22–16) and extensive microvasculature forms near the surface of the functional layer. At the end of the proliferative phase, the endometrium is 2-3 mm thick.

Secretory Phase

After ovulation, the **secretory** or **luteal phase** starts as a result of the progesterone secreted by the corpus luteum. Progesterone stimulates epithelial cells of the uterine glands that formed during the proliferative phase and these cells begin to secrete and accumulate glycogen, dilating the glandular lumens, and causing the glands to become coiled (Figure 22–19b,e). The superficial microvasculature now includes thin-walled, blood-filled lacunae (Figures 22–18 and 22–19e). The endometrium reaches its maximum thickness (5 mm) during the secretory phase as a result of the accumulation of secretions and edema in the stroma.

If fertilization occurred during the day after ovulation, the embryo has been transported to the uterus by about 5 days

FIGURE 22–19 Proliferative, secretory, and premenstrual phases in the uterus.



The major phases of the uterine cycle overlap but produce distinctly different and characteristic changes in the functional layer (**F**) closest to the lumen (**L**) with little effect on the basal layer (**B**) and myometrium (**M**). Characteristic features of each phase include the following. During most of the proliferative phase (**a, d**), the functional layer is still relatively thin, the stroma is more cellular, and the glands (**G**) are relatively straight, narrow, and empty.

In the secretory phase (**b, e**) the functional layer is less heavily cellular and perhaps four times thicker than the basal layer. The tubular glands have wider lumens containing secretory product and coil tightly up through the stroma, giving a zigzag or folded appearance histologically. Superficially in the functional layer, lacunae (**La**) are widespread and filled with blood.

The short premenstrual phase (**c, f**) begins with constriction of the spiral arteries, which produces hypoxia that causes swelling and dissolution of the glands (**G**). The stroma of the peripheral functionalis is more compact and near the basal layer typically appears more sponge-like during this time of blood stasis, apoptosis, and breakdown of the stromal matrix. (a: X20; b and c: X12; d, e, and f: X50. All H&E)

TABLE 22–1 Summary of events of the menstrual cycle.

	Stage of Cycle				
	Proliferative	Secretory or Luteal			Menstrual
Main actions of pituitary hormones	Follicle-stimulating hormone stimulates rapid growth of ovarian follicles	Peak of luteinizing hormone at the beginning of secretory stage, secreted after estrogen stimulation, induces ovulation and development of the corpus luteum			
Main events in the ovary	Growth of ovarian follicles; dominant follicle reaches preovulatory stage	Ovulation	Development of the corpus luteum	Degeneration of the corpus luteum	
Dominant ovarian hormone	Estrogens, produced by the growing follicles, act on vagina, tubes, and uterus	Progesterone, produced by the corpus luteum, acts mainly on the uterus		Progesterone production ceases	
Main events in the endometrium	Growth of the mucosa after menstruation	Further growth of the mucosa, coiling of glands, secretion			Shedding of part of the mucosa about 14 days after ovulation

later and now attaches to the uterine epithelium when the endometrial thickness and secretory activity are optimal for embryonic implantation and nutrition. The major nutrient source for the embryo before and during implantation is the uterine secretion. In addition to promoting this secretion, progesterone inhibits strong contractions of the myometrium that might interfere with embryo implantation.

Menstrual Phase

When fertilization of the oocyte and embryonic implantation do not occur, the corpus luteum regresses and circulating levels of progesterone and estrogens begin to decrease 8-10 days after ovulation, causing the onset of menstruation (Figure 22–17). The drop-off in progesterone produces (1) spasms of muscle contraction in the small spiral arteries of the functional layer, interrupting normal blood flow, and (2) increased synthesis by arterial cells of prostaglandins, which produce strong vasoconstriction and local hypoxia. Cells undergoing hypoxic injury release cytokines that increase vascular permeability and immigration of leukocytes. The leukocytes release collagenase and several other matrix metalloproteinases (MMPs) that degrade basement membranes and other ECM components (Figure 22–19c,f).

The basal layer of the endometrium, not dependent on the progesterone-sensitive spiral arteries, is relatively unaffected by these activities. However, major portions of the functional layer, including the surface epithelium, most of each gland, the stroma and blood-filled lacunae, detach from the endometrium and slough away as the menstrual flow or **menses**. Arterial constriction normally limits blood loss during menstruation, but some blood does emerge from the open ends of venules. The amount of endometrium and blood lost in menstruation varies among women and in the same woman at different times.

At the end of the menstrual phase, the endometrium is usually reduced to a thin layer and is ready to begin a new cycle as its cells begin dividing to reconstitute the mucosa. Table 22–1 summarizes the main events of the menstrual cycle.

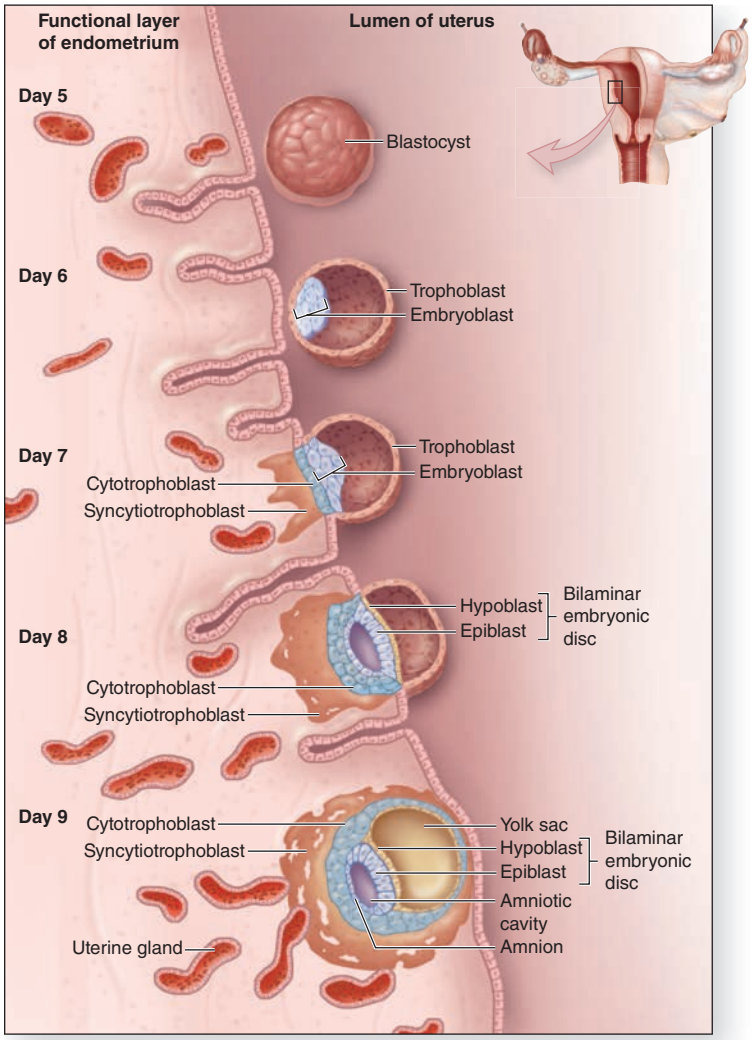
EMBRYONIC IMPLANTATION, DECIDUA, & THE PLACENTA

The zygote produced by fertilization undergoes mitotic cleavages as it is moved toward the uterus, with its cells called **blastomeres** (Gr. *blastos*, germ + *meros*, part) in a compact aggregate called the **morula** (L. *morum*, mulberry). No growth occurs during the period of cell cleavage, with blastomeres becoming smaller at each division, and the morula is about the same size as the oocyte at fertilization.

About 5 days after fertilization the embryo reaches the uterine cavity, by which time blastomeres have moved to form a central cavity in the morula and the embryo enters the **blastocyst** stage of development. The blastomeres then arrange themselves as a peripheral layer called the **trophoblast** around the cavity, while a few cells just inside this layer make up the **embryoblast** or **inner cell mass** (Figure 22–20). The blastocyst remains in the lumen of the uterus for about 2 days, immersed in the endometrial glands' secretion on the mucosa.

Implantation, or nidation, involves attachment of the blastocyst to the surface epithelial cells of the endometrium and its proteolytic penetration through this epithelium into the underlying stroma (Figure 22–20), a process lasting about 3 days. Cells of the trophoblast drive the events of implantation, during which time cells of the embryoblast rearrange around two new cavities, the **amnion** and the **yolk sac**. Where the cells lining these cavities make contact, the **bilaminar embryonic disc** develops with its **epiblast** layer continuous with the amnion and its **hypoblast** layer continuous with the yolk sac (Figure 22–20).

FIGURE 22–20 Embryo implantation.



The embryo enters the uterus as a blastocyst about 5 days after ovulation or fertilization, when the uterus is in the secretory phase and best prepared for implantation. To begin implantation, receptors on cells of the outer embryonic trophoblast bind glycoprotein ligands on the endometrial epithelium. The trophoblast forms an invasive, outer syncytial layer called the **syncytiotrophoblast**. Proteases are activated and/or released locally to digest stroma components, which allows the developing embryo to embed itself within the stroma. The newly implanted embryo absorbs nutrients and oxygen from the endometrial tissue and blood in the lacunae.

All parts of the embryo develop from this early embryonic disc. The yolk sac and amnion form extraembryonic structures, but only the latter persists throughout pregnancy. As shown in Figure 22–20, the trophoblast differentiates during implantation into the following:

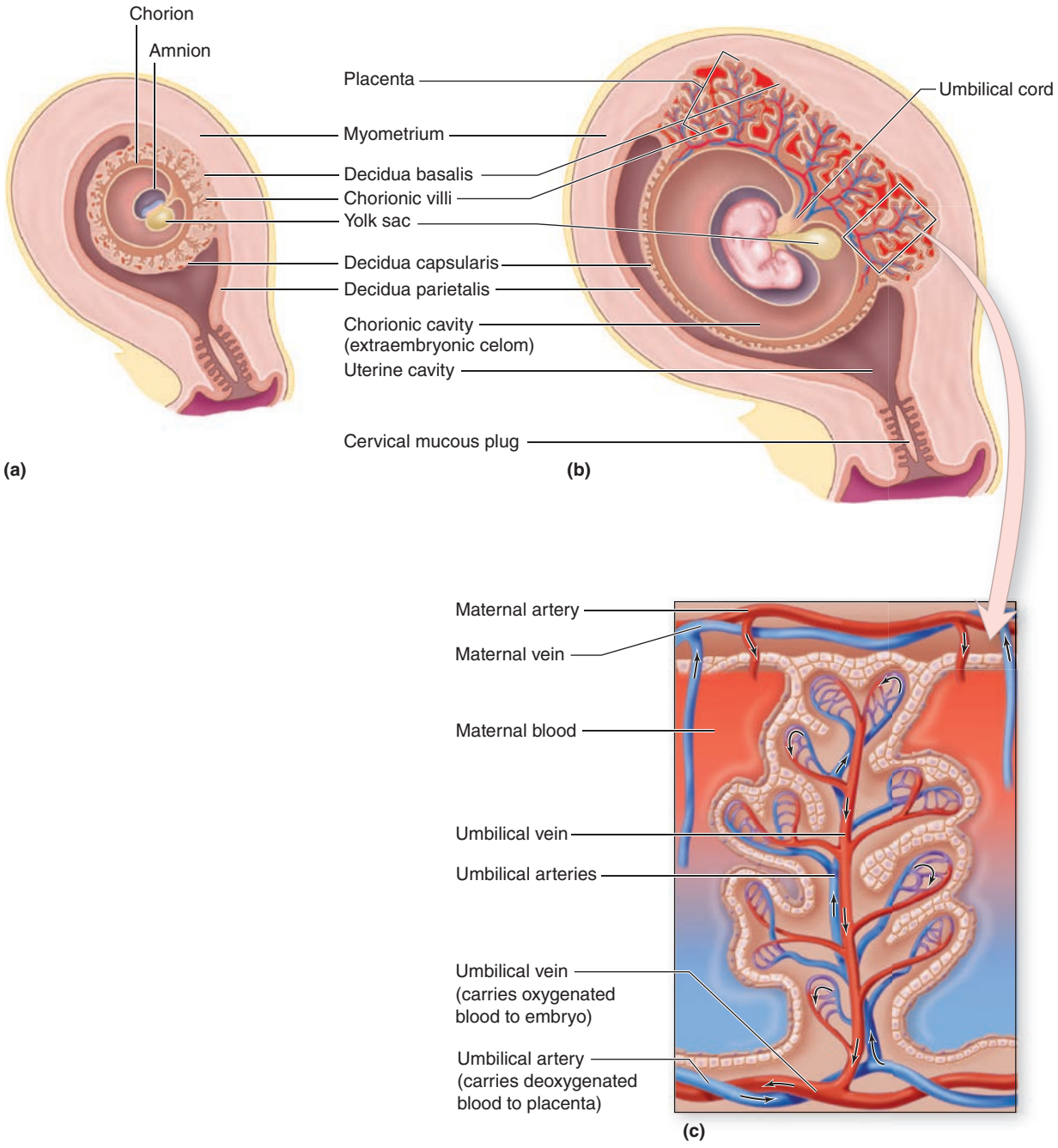
- The **cytotrophoblast**, a layer of mitotically active cells immediately around the amnion and yolk sac, and
- The **syncytiotrophoblast**, a more superficial, nonmitotic mass of multinucleated cytoplasm that invades the surrounding stroma.

By about the ninth day after ovulation, the embryo is totally implanted in the endometrium and derives nutrients primarily from blood there. Cytotrophoblast cells synthesize anti-inflammatory cytokines to prevent an adverse uterine reaction to the implanted embryo and these are supplemented later by various embryonic factors that produce local immune tolerance for the embryo throughout the pregnancy.

The endometrial stroma undergoes histologic changes in the period following implantation. Fibroblasts become enlarged, polygonal, more active in protein synthesis, and are now called **decidual cells**. The whole endometrium is now called the **decidua** (L. *deciduus*, falling off, shedding) and includes three areas (Figure 22–21):

- The **decidua basalis**, the area between the implanted embryo and the myometrium;
- The **decidua capsularis**, the region between the embryo and the uterine lumen that thins as the embryo gets larger; and
- The **decidua parietalis**, on the side of the uterus away from the embryo.

FIGURE 22–21 Extraembryonic membranes, decidua, and placenta.



(a) The membranous extraembryonic **amnion**, **chorion**, and **yolk sac** appear during the second week of development, with the embryonic disc between the amnion and yolk sac.

(b) After implantation the endometrium changes histologically and is called the **decidua**. It develops three different regions: **decidua basalis**, **capsularis**, and **parietalis**. **Chorionic villi** develop most profusely in the decidua basalis, which becomes the major portion of the **placenta**.

(c) Each of the many **chorionic stem villi** in the placenta contains a branch of the umbilical artery and vein, which form loops of microvasculature into smaller villus branches. The entire stem villus is bathed in maternal blood circulated by endometrial arteries and veins.

›› MEDICAL APPLICATION

The initial attachment of the embryo usually occurs on the ventral or dorsal walls of the body of the uterus. Sometimes the embryo attaches close to the internal os. In this case the placenta will be interposed between the fetus and the vagina, obstructing the passage of the fetus at parturition. This situation, called **placenta previa,** must be recognized by the physician, and the fetus must be delivered by cesarean section. Otherwise, obstructed parturition can lead to death of the fetus.

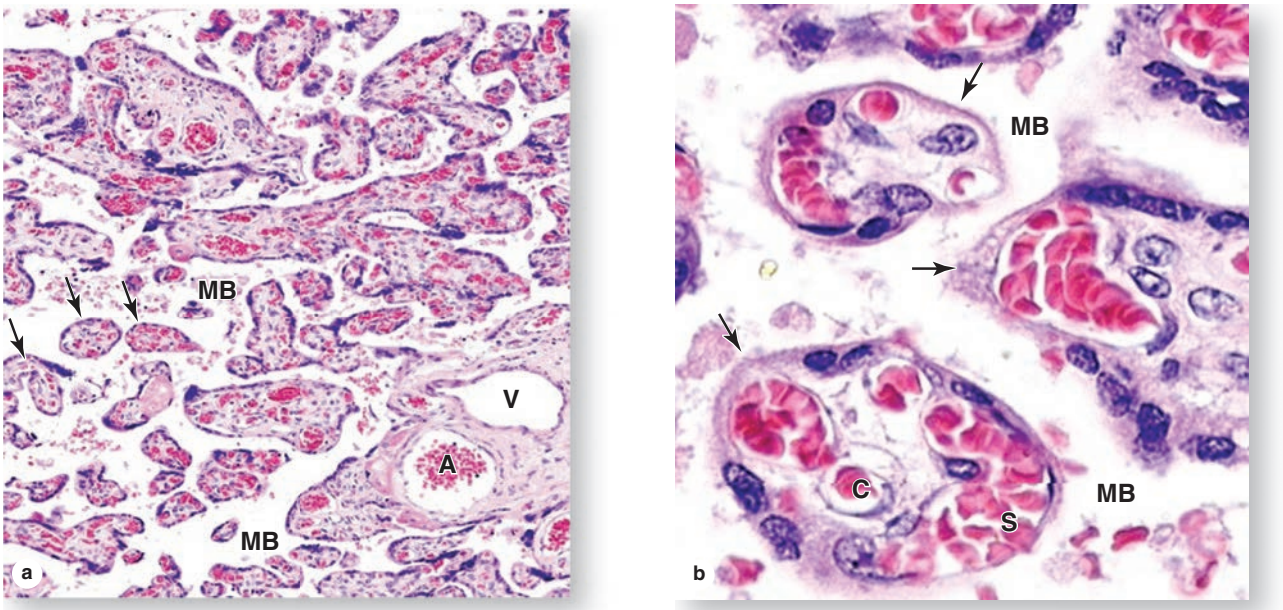
The **placenta** is the site of exchange for nutrients, wastes, O_2, and CO_2 between the mother and the fetus and contains tissues from both individuals. The embryonic part is the **chorion**, derived from the trophoblast and the maternal part is from the decidua basalis. Exchange occurs between embryonic blood in chorionic villi outside the embryo and maternal blood in lacunae of the decidua basalis. Chorionic villi of the developing placenta go through three stages:

- **Primary villi** appear 2 days after implantation as simple cords of proliferating cytotrophoblast cells covered by syncytiotrophoblast extend into lacunae containing maternal blood.
- **Secondary villi** begin to form on about the 15th day of embryonic development as the primary villi are invaded by extraembryonic mesenchyme.
- **Tertiary villi** develop within a few more days as mesenchyme in the secondary villi differentiates to form capillary loops continuous with the embryonic circulatory system.

By the end of the first month of the pregnancy, the placenta contains thousands of tertiary chorionic villi, each branching many times and each branch having one or more capillary loops (Figure 22–21c). Suspended in pools of maternal blood in the decidua, the chorionic villi provide an enormous surface area for metabolite exchange (Figure 22–22). Exchange of gases, nutrients, and wastes occurs between fetal blood in the capillaries and maternal blood bathing the villi, with diffusion occurring across the trophoblast layer and the capillary endothelium.

The placenta is also an endocrine organ, producing hCG, a lactogen, relaxin, and various growth factors, in addition to estrogen and progesterone. More detailed information on the developing embryo and placenta should be sought in embryology textbooks.

FIGURE 22–22 Term placenta.



The placenta contains chorionic villi of the fetus and maternal blood pooled in the decidua. **(a)** A full-term placenta has many villus stems, containing arteries (**A**) and (**V**) of the extraembryonic vasculature, and hundreds of smaller villus branches (**arrows**) that contain connective tissue and microvasculature. Maternal blood (**MB**) fills the space around the villi. (X50; H&E)

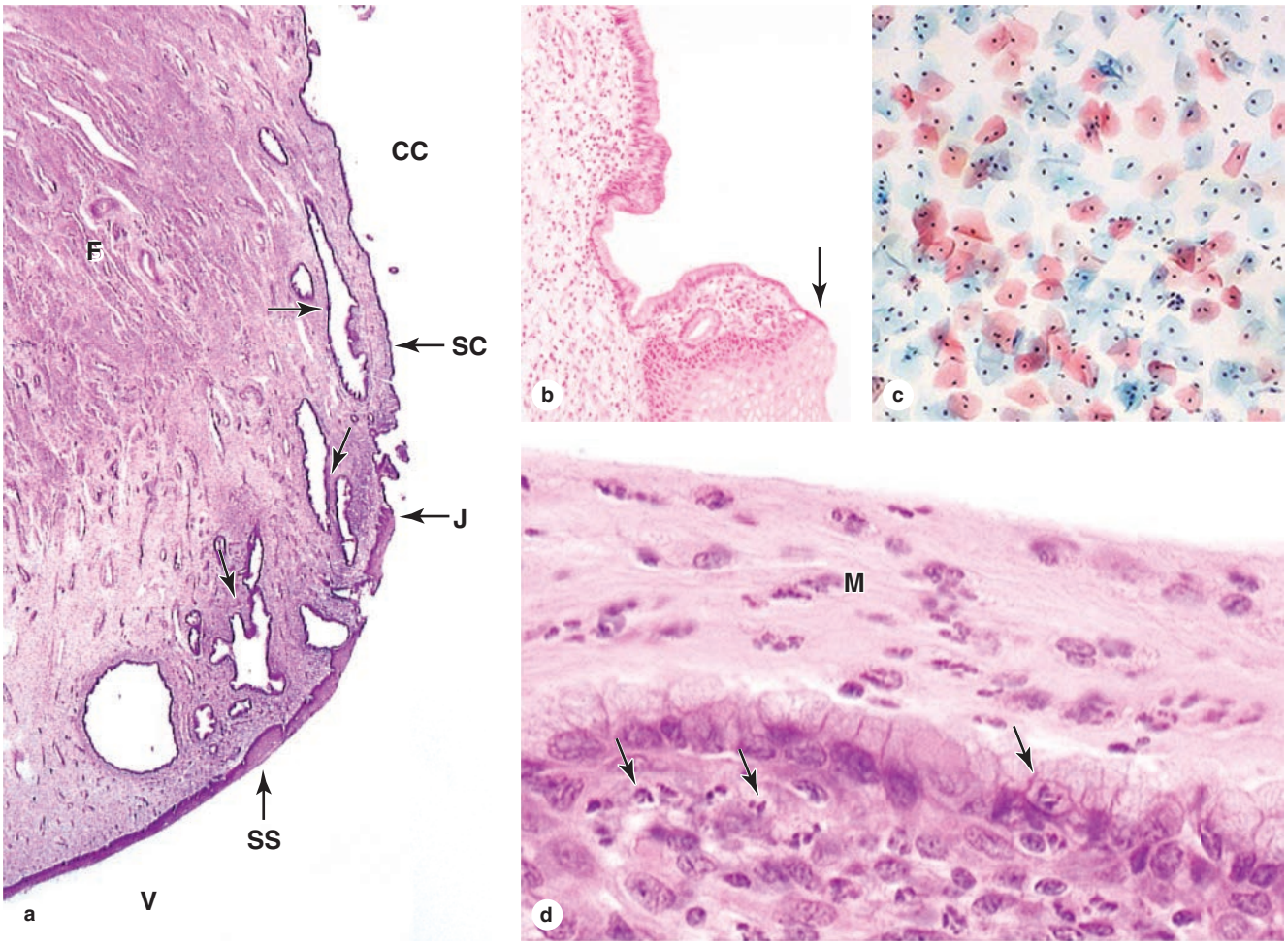
(b) Higher magnification of villus branches surrounded by maternal blood (**MB**) each containing capillaries (**C**) or sinusoids (**S**) with fetal blood. By the end of pregnancy cytotrophoblast cells have greatly decreased in number in many areas, leaving only a thin syncytiotrophoblast and basement membrane covering the villus in these regions (**arrows**). The extraembryonic blood vessels become closely associated with these areas of thin trophoblast for maximal diffusion of material between the two pools of blood. (X400; H&E)

CERVIX

As noted earlier the **cervix** is the lower, cylindrical part of the uterus (see Figure 22–1). The cervix differs histologically from the rest of the uterus. The **endocervical mucosa** is a simple columnar epithelium on a thick lamina propria, with many large, branched, mucus-secreting **cervical glands**. It lacks spiral arteries, does not change its 2-3 mm thickness during the ovarian cycle, and is not shed during menstruation.

The cervical region around the external os projects slightly into the upper vagina and is covered by the **exocervical mucosa** with nonkeratinized stratified squamous epithelium continuous with that of the vagina. The junction between this squamous epithelium and the mucus-secreting columnar epithelium of the endocervix occurs in the **transformation zone**, an area just outside the external os that shifts slightly with the cyclical changes in uterine size (Figure 22–23). Periodic exposure of the squamous-columnar junction to the

FIGURE **22–23** Cervix.



(a) The mucosa of the cervical canal (**CC**) is continuous with the endometrium and like that tissue is lined by simple columnar epithelium (**SC**). This endocervical mucosa includes many large branched cervical mucous glands (**arrows**). At the external os, the point at which the cervical canal opens into the vagina (**V**), there is an abrupt junction (**J**) between the columnar epithelium and the stratified squamous epithelium (**SS**) covering the exocervix and vagina. Deeper, the cervical wall is primarily fibromuscular tissue (**F**). (X15; H&E)

(b) The epithelial junction (**arrow**) is seen more clearly. (X50; H&E)

(c) Exfoliative cytology of epithelial cells from the exocervical mucosa in a routine cervical smear. The squamous cells, stained on a slide by the Papanicolaou procedure using hematoxylin, orange G, and eosin, stain differently according to their content of keratins. Cells with atypical nuclei or other abnormalities can be detected by this method that is used routinely to check for cervical carcinoma. (X200; Papanicolaou stain)

(d) The endocervical mucosa is exposed to a relatively high population of microorganisms and normally has a large number of neutrophils and other leukocytes. Such cells occur in the lamina propria and epithelium (**arrows**), but they are also numerous and readily apparent in the layer of mucus (**M**), which was fixed in place here. (X400; H&E)

vaginal environment can stimulate reprogramming of epithelial stem cells, which occasionally leads to intraepithelial neoplasia at that site.

Under the influence of progesterone, the consistency of **cervical mucus** changes cyclically and plays a significant role in fertilization and early pregnancy. At ovulation, mucous secretion is abundant and watery, facilitating sperm movements into the uterus. In the luteal phase mucus is more viscous and hinders the passage of sperm. During pregnancy, the cervical glands proliferate and secrete highly viscous mucus that forms a plug in the cervical canal (Figure 22–21b).

The deeper wall of the cervix consists mainly of dense connective tissue, with much less smooth muscle than the rest of the uterus (Figure 22–23). The cervix becomes relatively rigid during pregnancy and helps retain the fetus in the uterus. Before parturition a process of **cervical effacement** occurs in which its connective tissue undergoes extensive remodeling and significant collagen removal, mediated in part by macrophages. As a result the cervix softens, the cervical canal dilates, and birth occurs more easily.

›› MEDICAL APPLICATION

The incidence of **cervical cancer** worldwide has been greatly reduced by widespread, routine screening by **exfoliative cytology** to examine for dysplasia of the cervical epithelium (Figure 22–23c). The test called the **Pap smear** after its developer George Papanicolaou, who introduced this diagnostic technique in the 1920s, uses cells that have been lightly scraped from cervix. Abnormal cells suggestive of precancerous changes in the epithelium are then detected microscopically. The epithelial dysplasia, which precedes **squamous cell neoplasia**, the most common type of cervical cancer, occurs in metaplastic cells of the transformation zone at a mean age of 54 years. The **human papillomas virus** (HPV) is strongly implicated in the pathogenesis of this cancer.

› VAGINA

The wall of the **vagina** (L., *vagina*, sheath, scabbard) lacks glands and consists of a **mucosa**, a **muscular layer**, and an **adventitia**.

The epithelium of the vaginal mucosa is stratified squamous, with a thickness of 150-200 µm in adults (Figure 22–24). Stimulated by estrogens, the epithelial cells synthesize and accumulate glycogen. When the cells desquamate, bacteria metabolize glycogen to lactic acid, causing a relatively low pH within the vagina, which helps provide protection against pathogenic microorganisms. The lamina propria of the mucosa is rich in elastic fibers, with numerous narrow papillae projecting into the overlying epithelium (Figure 22–24). The mucosa normally contains lymphocytes and neutrophils in relatively large quantities.

Mucus in the vagina is produced by the cervical glands. During sexual arousal lubricating mucus is also provided by glands at the vaginal vestibule, including the paired **greater vestibular glands** (of Bartholin), which are homologous to the male bulbourethral glands.

The muscular layer of the vagina is composed mainly of two indistinct layers of smooth muscle, disposed as circular bundles next to the mucosa and as thicker longitudinal bundles near the adventitial layer (Figure 22–24). The dense connective tissue of the adventitia is rich in elastic fibers, making the vaginal wall strong and elastic while binding it to the surrounding tissues. This outer layer also contains an extensive venous plexus, lymphatics, and nerves.

›› MEDICAL APPLICATION

Atrophic vaginitis involves thinning or atrophy of the vaginal epithelium caused by diminished estrogen levels and occurs most often in postmenopausal woman. This change allows the more frequent inflammation and infections characteristic of this condition. Primary **squamous cell carcinoma** of the vagina occurs rarely, with most vaginal malignancies having spread secondarily from the cervix or vulva.

› EXTERNAL GENITALIA

The female **external genitalia**, or **vulva**, include several structures, all covered by stratified squamous epithelium:

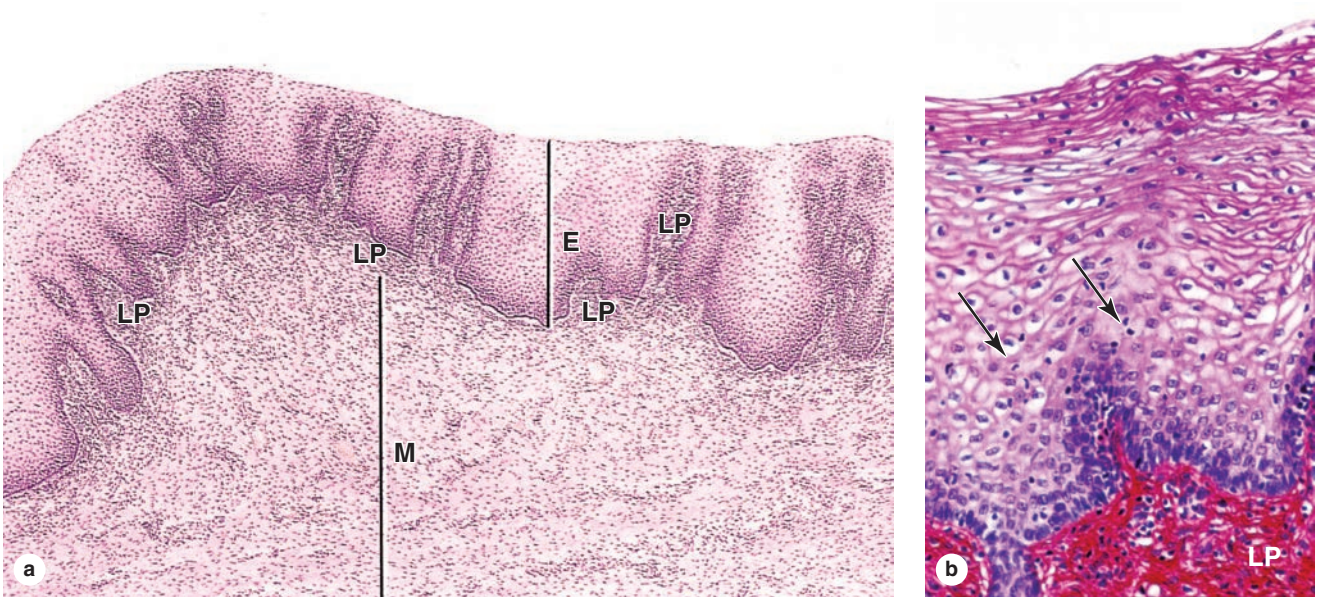
- The **vestibule**, a space whose wall includes the tubuloacinar vestibular glands;
- The paired **labia minora**, folds of skin lacking hair follicles but with numerous sebaceous glands;
- The paired **labia majora**, homologous and histologically similar to the skin of the scrotum; and
- The **clitoris**, an erectile structure homologous to the penis with paired corpora cavernosa.

The mucosa of these structures, abundantly supplied with sensory nerves and tactile receptors also found in skin (see Chapter 18), is important in the physiology of sexual arousal.

› MAMMARY GLANDS

The **mammary glands** of the breasts develop embryologically as invaginations of surface ectoderm along two ventral lines, the milk lines, from the axillae to the groin. In humans one set of glands resembling highly modified apocrine sweat glands persists on each side of the chest. Each mammary gland consists of 15-25 **lobes** of the compound tubuloalveolar type whose function is to secrete nutritive milk for newborns. Each lobe, separated from the others by dense connective tissue with much adipose tissue, is a separate gland with its own excretory

FIGURE **22–24** **Vagina.**



The vagina has mucosal, muscular, and adventitial layers. **(a)** The lamina propria (**L**) is highly cellular and extends narrow papillae into the thick, nonkeratinized stratified squamous epithelium (**E**). The muscular layer (**M**) has bundles of smooth muscle arranged in a circular manner near the mucosa and longitudinally near the adventitia. (X60; H&E)

(b) Higher magnification of the epithelium and lamina propria (**LP**) shows invasion of leukocytes (**arrows**) between epithelial cells from the connective tissue. (X200; PSH)

lactiferous duct (Figure 22–25). These ducts, each 2-4.5-cm long, emerge independently in the **nipple**, which has 15-25 pore-like openings, each about 0.5 mm in diameter. The histologic structure of the mammary glands varies according to sex, age, and physiologic status.

Breast Development During Puberty

Before puberty, the mammary glands in both sexes are composed only of **lactiferous sinuses** near the nipple, with very small, branching ducts emerging from these sinuses. In girls undergoing puberty, higher levels of circulating estrogens cause the breasts to grow as a result of adipocyte accumulation and elongation of the duct system.

In nonpregnant adult women each mammary gland lobe consists of many **lobules**, sometimes called **terminal duct lobular units (TDLU)**. Each lobule has several small, branching ducts, but the attached secretory units are small and rudimentary (Figure 22–25). Lactiferous sinuses are lined with stratified cuboidal epithelium, and the lining of the lactiferous ducts and terminal ducts is simple cuboidal epithelium with many myoepithelial cells. Sparse fibers of smooth muscle also encircle the larger ducts. The duct system is embedded in loose, vascular connective tissue, and a denser, less cellular connective tissue separates the lobes. In the premenstrual phase of the reproductive cycle, connective tissue of the breast becomes somewhat edematous, making the breasts slightly larger.

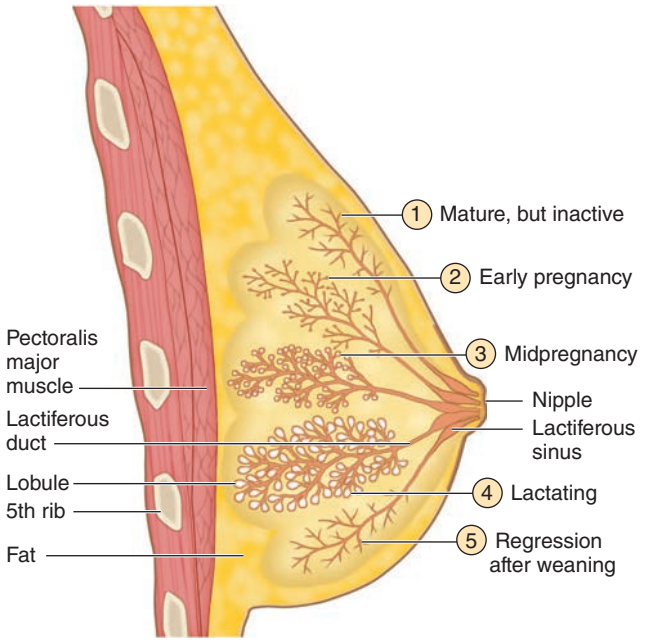
The **areola**, or skin surrounding and covering the nipple, contains sebaceous glands and abundant sensory nerves and is continuous with the mucosa of the lactiferous sinuses. The areola contains more melanin than skin elsewhere on the breast and darkens further during pregnancy. Connective tissue of the nipple is rich in smooth muscle fibers that run parallel to the lactiferous sinuses and produce nipple erection when they contract.

Breasts During Pregnancy & Lactation

The mammary glands undergo growth during pregnancy as a result of the synergistic action of several hormones, mainly estrogen, progesterone, prolactin, and the placental lactogen. These cause cell proliferation in secretory **alveoli** at the ends of the intralobular ducts (Figures 22–25 and 22–26). The spherical alveoli are composed of cuboidal epithelium, with stellate myoepithelial cells between the secretory cells and the basal lamina. The degree of glandular development varies among lobules and even within a single lobule.

While the alveoli and duct system grow and develop during pregnancy in preparation for lactation, the stroma

FIGURE 22–25 Mammary gland.



Shown here is the sequence of changes that occur in the alveolar secretory units and duct system of mammary glands before, during, and after pregnancy and lactation. (**1**) Before pregnancy, the gland is inactive, with small ducts and only a few small secretory alveoli. (**2**) Alveoli develop and begin to grow early in a pregnancy. (**3**) By midpregnancy, the alveoli and ducts have become large and have dilated lumens. (**4**) At parturition and during the time of lactation, the alveoli are greatly dilated and maximally active in production of milk components. (**5**) After weaning, the alveoli and ducts regress with apoptotic cell death.

becomes less prominent (Figures 22–26 and 22–27). The loose connective tissue within lobules is infiltrated by lymphocytes and plasma cells, the latter becoming more numerous late in pregnancy.

Late in pregnancy the glandular alveoli and ducts are dilated by an accumulation of **colostrum**, a fluid rich in proteins and containing leukocytes, which is produced under the influence of prolactin. Immunoglobulin A (IgA) antibodies are synthesized abundantly by plasma cells and transferred into colostrum, from which passive acquired immunity is conferred on the breast-fed newborn.

Following parturition, the alveoli of mammary glands start active milk production, or **lactation**, stimulated primarily by prolactin from the anterior pituitary (see Chapter 20). Epithelial cells of the alveoli enlarge and activate various processes involved in lactation:

- Large amounts of **protein** are synthesized, packaged into secretory vesicles, and undergo **merocrine secretion** into the lumen (Figure 22–28). Human milk contains about 1 g of protein per deciliter, including aggregated caseins (44% of the total protein), as well as soluble β-lactoglobulin and α-lactalbumin, all of which are a source of amino acids by the infant. Less abundant proteins in milk include many factors that assist digestion, several such as lactoferrin with antimicrobial activity, and various mitogenic growth factors important for gut development in the newborn.
- **Lipid droplets** form initially from short-chain fatty acids synthesized in the epithelial cells and grow by accretion of longer fatty acids and cholesterol originating from the diet or fat stores. They eventually undergo **apocrine secretion**, during which the droplets become enveloped with a portion of the apical cell membrane (see Figure 22–28). Milk contains 4 or 5 g of total fat per deciliter.
- **Lactose**, the major carbohydrate and energy source in milk, is synthesized in the Golgi apparatus and secreted with lactalbumin. Human milk contains over 7 g of lactose per deciliter, more than the combined total of proteins and lipids. Lactose is also responsible for generating the osmotic gradient that draws water and Ca^{2+} into the alveolar lumen.

Throughout lactation, secretion of proteins, membrane-bound lipid droplets, lactose, iron, and calcium is ongoing, with the products accumulating as milk in the lumens of the duct system (Figure 22–27).

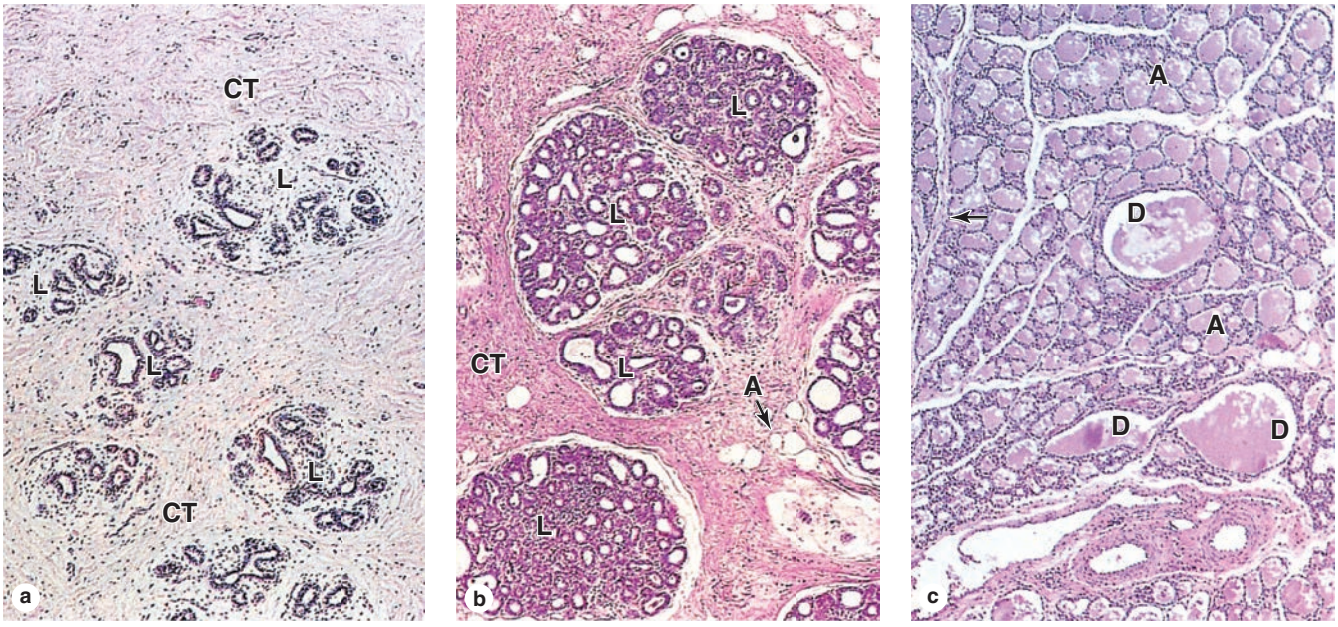
›› MEDICAL APPLICATION

When a woman is breast-feeding, the nursing action of the child stimulates tactile receptors in the nipple, resulting in liberation of the posterior pituitary hormone **oxytocin**. This hormone causes contraction of the smooth muscle of the lactiferous sinuses and ducts, as well as the myoepithelial cells of alveoli and ducts, resulting in the **milk**-ejection reflex. Negative emotional stimuli, such as frustration, anxiety, or anger, can inhibit the liberation of oxytocin and thus prevent the reflex.

Postlactational Regression in the Mammary Glands

When breast-feeding is stopped (weaning), most alveoli that developed during pregnancy and lactation degenerate. Epithelial cells undergo apoptosis, autophagy, or sloughing (Figure 22–29), with dead cells and debris removed by macrophages. The duct system of the gland returns to its general appearance in the inactive state (Figure 22–25). After menopause, alveoli and ducts of the mammary glands are reduced further in size and there is loss of fibroblasts, collagen, and elastic fibers in the stroma.

FIGURE 22–26 Alveolar development in the breast during pregnancy.



(a) The mammary glands of adult, nonpregnant women are inactive, with small ducts and few lobules (**L**) having secretory alveoli which are not well-developed. The structure with the large lumen in each lobule is part of the duct; the smaller structures are the small, undeveloped alveoli. The breasts are composed largely of connective tissue (**CT**), having considerable fat.

(b) The glands become active during pregnancy, with the duct system growing rapidly and the secretory units of each lobule becoming much larger and more extensively branched. In this micrograph adipocytes (**A**) are included, but these are only a small fraction of those present.

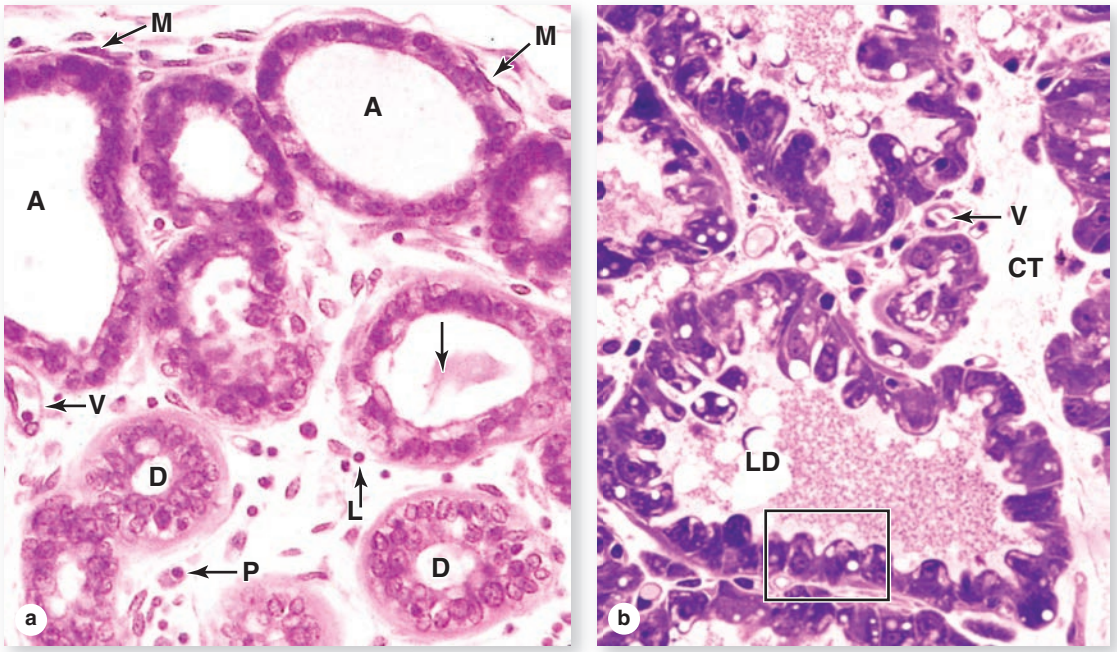
(c) During lactation, the lobules are greatly enlarged and the lumens of both the numerous glandular alveoli (**A**) and the excretory ducts (**D**) are filled with milk. The intralobular connective tissue is more sparse and difficult to see, except for small septa (arrows). (All X60, H&E)

›› MEDICAL APPLICATION

Breast cancer is almost always derived from epithelial cells in the terminal lobules of the glands. The most common form is invasive **ductal carcinoma** in which neoplastic cells of intralobular ducts or small branches of lactiferous ducts invade the surrounding stroma, forming a fixed, palpable mass. Cell spreading (or metastasizing) from the carcinoma via the circulatory or lymphatic vessels to critical organs such as the lungs or brain is responsible for the mortality associated with breast cancer. If the treatment is **mastectomy**, axillary lymph nodes are usually also removed surgically and examined histologically for the presence of metastatic mammary carcinoma cells. Early detection (eg, through self-examination, mammography, ultrasound, and other techniques) and consequent early treatment have significantly reduced the mortality rate.

Bacterial infection of a mammary gland, or acute mastitis, may occur in the lactating or involuting breast, usually after obstruction by milk left within small components of the duct system.

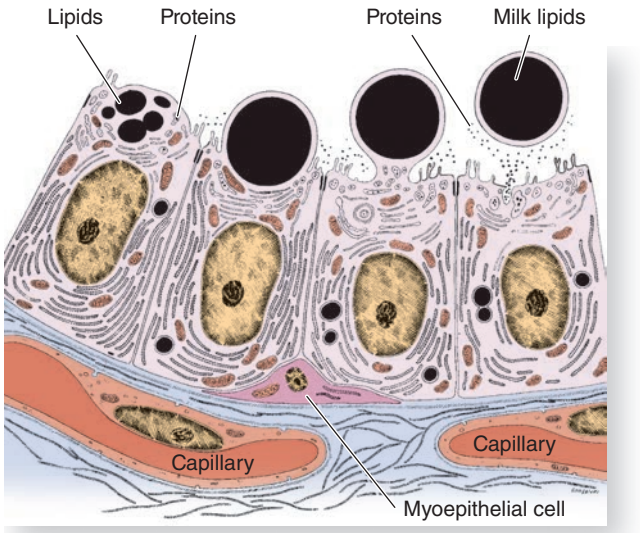
FIGURE 22–27 Actively developing and lactating alveoli.



Glandular alveoli develop completely only during pregnancy and begin milk production near the end of pregnancy. **(a)** Alveoli (**A**) develop as spherical structures composed of cuboidal epithelial cells surrounded by the contractile processes of myoepithelial cells (**M**). Development occurs at different rates throughout the breast. Late in pregnancy lymphocytes (**L**) leave venules (**V**), accumulate in the intralobular connective tissue, and differentiate as plasma cells (**P**) secreting IgA. Intralobular ducts (**D**) are lined by epithelium containing secretory cells, nonsecretory cells, and plasma cells; larger lumens may show milk (**arrow**). (X400; H&E)

(b) Secretory cells of the lactating gland are more columnar and contain variously sized lipid droplets, which are also visible in the milk (**LD**). Connective tissue (**CT**) contains small blood vessels (**V**). Secretory cells in the enclosed area are shown diagrammatically in Figure 22–28. (X400; PT)

FIGURE 22–28 Secretion in the mammary gland.



Alveolar cells of the lactating mammary gland are highly active in protein synthesis and lipid synthesis. Most proteins are packaged into secretory vesicles in the Golgi apparatus and secreted at the apical end of the cells by typical exocytosis or merocrine secretion. Lipids coalesce as free cytoplasmic droplets and eventually undergo apocrine secretion, in which they are extruded from the cell along with a portion of the apical cell membrane (and often a small amount of attached cytoplasm.) Both types of secretion are shown here in a sequence moving from left to right.