Unlike other physiological systems that serve to maintain homeostasis in an individual, reproductive physiology serves to perpetuate the species (sometimes at the expense of individuals). Furthermore, reproductive physiology differs tremendously between the genders, although control of sex steroid and gamete production in both is regulated by the release of two trophic hormones from the anterior pituitary: LH and FSH.

The Hypothalamus Secretes GnRH, which Acts on Gonadotrophs in the Anterior Pituitary

In both males and females, GnRH released into the portal system between the hypothalamus and anterior pituitary triggers the release of LH and FSH from the anterior pituitary. In both genders, these gonadotropins regulate sexual function.

Continuous release of GnRH causes an inhibition of LH and FSH secretion. Thus, administration of drugs with a similar structure as GnRH to maintain continuously-high levels of the peptide suppress sexual function. For example, implants that release GnRH analogs (such as Supprelin-LA) are used to delay sexual maturity in children with precocious puberty (a condition where sexual development begins at too early of an age).

Hence, sexual maturity is triggered when hypothalamic neurons that release GnRH begin to fire together at regular intervals. Curiously, GnRH secretion and release of LH and FSH from the anterior pituitary begin in utero, as sex steroids play an important role in sexual differentiation, particularly in males (testosterone is critical for the development of male sexual organs). Fetal plasma levels of testosterone are approximately the same as in adult males, and there is another peak just after birth. However, release of GnRH and gonadotropins cease within the first year, and the levels remain negligible until the start of puberty. GnRH release suppression is mediated through neurons that inhibit the GnRH-releasing hypothalamic neurons.

The mechanisms removing the suppression of the GnRH-releasing neurons during puberty are unknown. Premature activation of GnRH release results in precocious puberty.
LH Stimulates Leydig Cells in the Testis to Produce Testosterone

In males, **Leydig cells** (also called interstitial cells) are located in groups in the testis, adjacent to the **Sertoli cells** that “nurse” sperm cells through their maturation. Leydig cells are the primary source of testosterone production in the male. Testosterone (like all steroids) is synthesized from cholesterol by using a series of enzymes (see below; there is no need to memorize the biosynthesis pathways).

Biosynthesis Pathways for Steroids
LH binds to receptors on the surface of Leydig cells, which activates a G-protein coupled mechanism that increases the synthesis of enzymes and other proteins necessary for testosterone synthesis.

Sertoli cells have FSH receptors on their surface. Binding of FSH to these receptors triggers a G-protein coupled mechanism that results in the synthesis of a variety of proteins:

1. **Androgen-binding protein**, which is secreted into the luminal space near the developing sperm. This protein helps to keep testosterone levels very high near the developing sperm, which is required for their maturation.
2. **P-450 aromatase**, which converts testosterone into estradiol.
3. **Growth factors** that are required to nourish and support developing sperm cells and spermiogenesis, as well as the functions of Leydig cells.
4. **Inhibins** that have two functions: acting as a growth hormone in the testis and playing a major role in feedback inhibition of FSH production.

Hence, Leydig and Sertoli cells engage in crosstalk that is critical to maintain testicular function. Testosterone produced by Leydig cells is critical to support the Sertoli cells. Inhibins and growth factors produced by Sertoli cells are needed to support the Leydig cells. Estradiol produced by the Sertoli cells (from testosterone) stimulates testosterone production by the Leydig cells. Thus, both LH and FSH participate in regulating testosterone production: LH has a direct role and FSH has an indirect role.
Testosterone and Inhibin Provide Feedback Inhibition of the Hypothalamus and Pituitary

Release of LH and FSH results in the production of testosterone and inhibin, but the later two substances provide feedback inhibition to the hypothalamus and pituitary. Testosterone presumably acts in both the hypothalamus and pituitary. Since inhibin is a peptide, it cannot cross the blood-brain barrier, and presumably only acts in the anterior pituitary. The major effect of testosterone is to lower LH levels, whereas the major effect of inhibin is to lower FSH levels. However, due to the interactions of Leydig and Sertoli cells in the testis, lowering the release of either gonadotropin has effects on both testosterone production and spermiogenesis.

Interestingly, estradiol or high levels of progesterone can produce feedback inhibition of LH release in males, presumably because of the similarity in structure of testosterone and estradiol. Thus, if a male were to be artificially provided a female sex hormone, his testosterone production would be inhibited.

Functions of Testosterone

Since testosterone is a steroid, it acts by binding to intracellular receptors. Most cells in a male’s body have androgen receptors, such that testosterone has a large number of physiological effects. Testosterone binds to the intracellular androgen receptors directly in some cells, and in others the intracellular enzyme 5α-reductase converts testosterone to dihydrotestosterone prior to its binding with androgen receptor. Binding of steroid to androgen receptors has the following effects:

- **Development of male genitalia.** In the fetus, secretion of testosterone causes development of male sexual organs instead of female organs. In animals, injection of testosterone into a female fetus leads to development of male organs, and removal of testosterone results in a male fetus developing female sexual organs. Testosterone is also critical for the descent of the testes into the scrotum, which normally occurs in the last 2-3 months of gestation. Injection of testosterone into a male child born with normal but undescended testes usually results in the descent of the testes.
- **Enlargement of male genitalia and growth of body hair.**
- **Support of spermiogenesis.** The maturation of sperm is dependent on high levels of testosterone in the testis.
- **Baldness.** Baldness results from a genetic predisposition for the condition and the presence of testosterone. Males lacking testosterone will not become bald even if they are predisposed for the condition.
- **Deepening of the Voice.** Testosterone causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. As a result, a male’s voice becomes deeper.
• **Increased thickness of the skin and increased sebaceous function.** Testosterone is responsible for differences in skin characteristics between men and women. It also causes more secretions from sebaceous glands, particularly in the face, which predisposes males for acne.

• **Increased protein production and muscle development.** Testosterone facilitates protein formation, as well as increases in the number of actin and myosin filaments in myofibrils (muscle hypertrophy).

• **Bone matrix increases and calcium retention.** Testosterone results in thicker bones with higher calcium deposits. It also results in altered development of the pelvis, such that the male pelvis differs in shape from the female pelvis.

• **Increases in metabolic rate.** Testosterone increases metabolic rate by as much as 15%.

• **Increases in hematocrit.** Testosterone raises the number of red blood cells in the blood.

• **Increases in sodium reabsorption.** Testosterone causes a modest increase in sodium reabsorption by the distal tubules of nephrons.

• **Psychological effects.** Testosterone increases sex drive, and can also induce aggressive drives.

Androgens can be produced in other tissues besides the testis. As we will see in the next lecture, the female ovary produces some androgens. The adrenal gland also produces androgens in both men and women, but the quantity is low (<5% of total androgen in an adult male’s body). In women, androgens are likely critical in stimulating axillary and public hair growth. Rare adrenocortical tumors can result in large amounts of androgen being secreted from the adrenal gland. Such tumors result in masculinization in women.

### Consequences of High and Low Testosterone Levels

Loss of testosterone after puberty does not result in a reversal of sexual characteristics (e.g., body hair does not disappear and the voice characteristics don’t change). However, it would be more difficult to increase muscle mass, and behavioral effects of testosterone (e.g., sex drive) are reduced measurably.

Abuse of anabolic steroids by athletes has been a serious problem. Increasing plasma levels of androgens does facilitate increasing muscle mass, but there are a number of deleterious side effects. Personality changes, including increased aggression (“roid rage”), are common. Taking anabolic steroids often also leads to sterility. Due to feedback inhibition, taking anabolic steroids results in a decrease in GnRH and LH release, such that Leydig cells no longer produce testosterone. Consequently, even though plasma androgen levels are much higher than normal, intratesticular levels are much lower. The lowered levels of intratesticular testosterone are inadequate to maintain sperm development, such that sterility occurs.

Testosterone-secreting tumors (due to a Leydig cell becoming cancerous) are rare, but do occur. Such tumors can result in over a 100X increase in blood testosterone levels. Leydig cell carcinoma has been reported in boys, and results in a sudden appearance of testosterone without feedback control. As a consequence, the boy rapidly develops secondary sexual characteristics.
Spermiogenesis

Spermiogenesis

Sperm development occurs in seminiferous tubules, which are formed from Sertoli cells that are linked together through tight junctions. The tight junctions are an integral part of an immunological barrier between the blood and the developing sperm, called the blood-testis barrier.

Mature spermatozoa are derived from germ cells through a series of complex transformations. The least mature cells are located adjacent to the basement membrane, whereas the most differentiated germ cells are located nearest the lumen.

The primordial germ cells migrate into the gonad during embryogenesis; these cells become immature germ cells called spermatogonia. Beginning at puberty and continuing thereafter throughout life, spermatogonia divide mitotically. The spermatogonia have the normal diploid complement of 46 chromosomes (2N): 22 pairs of autosomal chromosomes plus 1 X and 1 Y chromosome.

Some of the spermatogonia enter into their first meiotic division and become primary spermatocytes. At the prophase of this first meiotic division, the chromosomes undergo crossing over. At this stage, each cell has a duplicated set of 46 chromosomes (4N): 22 pairs of duplicated autosomal chromosomes, a duplicated X chromosome, and a duplicated Y chromosome. After completing this first meiotic division, the daughter cells become secondary spermatocytes, which have a haploid number of duplicated chromosomes (2N): 22 duplicated autosomal chromosomes and either a duplicated X or a duplicated Y chromosome. These secondary spermatocytes enter their second meiotic division almost immediately. This division results in smaller cells called spermatids, which have a haploid number of unduplicated chromosomes (1N).

Spermatids transform into spermatozoa in a process called spermiogenesis, which involves cytoplasmic reduction and differentiation of the tail pieces. Thus, maturation leads to an increase in cell number, with each primary spermatocyte producing four spermatozoa, two with an X chromosome and two with a Y chromosome.
Transformation of spermatogonia into functional spermatozoa requires ~74 days. Each stage of spermiogenesis has a specific duration. The life span of the germ cells is 16 to 18 days for spermatogonia, 23 days for primary spermatocytes, 1 day for secondary spermatocytes, and ~23 days for spermatids. The rate of spermiogenesis is constant and cannot be accelerated by hormones such as gonadotropins or androgens. Germ cells must move forward in their differentiation; if the environment is unfavorable and makes it impossible for them to pursue their differentiation at the normal rate, they degenerate and are eliminated.

In 20-year-old men, the production rate is ~6.5 million sperm per gram of testicular parenchyma per day. The rate falls progressively with age and averages ~3.8 million sperm per gram of testicular parenchyma per day in men 50 to 90 years old. This decrease is probably related to the high rate of degeneration of germ cells during meiotic prophase. Among fertile men, those aged 51 to 90 years exhibit a significant decrease in the percentage of morphologically normal and motile spermatozoa.

**Sertoli Cells Support Spermiogenesis**

The Sertoli cells are large, convoluted cells extending from the basement membrane toward the lumen of the seminiferous tubule. As noted above, Sertoli cells produce a number of proteins necessary for the testis to function normally.

Developing sperm cells are surrounded by processes of Sertoli cell cytoplasm until they mature, which provides the necessary environment for this development. Gap junctions between the Sertoli cells and developing spermatozoa may represent a mechanism for transferring material between these two types of cells. Release of the spermatozoa from the Sertoli cell has been called spermiation. Spermatids progressively move toward the lumen of the tubule and eventually lose all contact with the Sertoli cell after spermiation.

Each spermatozoon is composed of a head and a tail. The head comprises the condensed nucleus of the cell with only a thin cytoplasmic and cell membrane layer around its surface. On the outside of the anterior two thirds of the head is a thick cap called the acrosome that is formed mainly from the Golgi apparatus. This contains a number of enzymes similar to those found in lysosomes of the typical cell, which play important roles in allowing the sperm to enter the ovum and fertilize it.

Back-and-forth movement of the tail (flagellar movement) provides motility for the sperm. The energy for this process is supplied in the form of ATP, which is synthesized by the mitochondria in the body of the tail. The normal motile, fertile sperm are capable of flagellated movement through the fluid medium at velocities of 1 to 4 mm/min. The activity of sperm is greatly enhanced in a neutral and slightly alkaline medium, as exists in the ejaculated semen, but it is greatly depressed in a mildly acidic medium. A strong acidic medium can cause rapid death of sperm.
Maturation and Storage of Sperm; Formation of Seminal Plasma

The seminiferous tubules open into a network of tubules, the rete testes, which serve as a reservoir for sperm. The rete testes are connected to the epididymis through the efferent ductules, which are located near the superior pole of the testicle. The epididymis is a highly convoluted single long duct, 4 to 5 meters in total length, on the posterior aspect of the testis. The epididymis can be divided anatomically into three regions: the head (the segment closest to the testis), the body, and the tail. Spermatozoa are essentially immotile on completion of spermiogenesis. Thus, transfer of spermatozoa from the seminiferous tubule to the rete testes and epididymis is passive. As noted earlier, ~74 days is required to produce spermatozoa, ~50 days of which is spent in the seminiferous tubule. After leaving the testes, sperm take 12 to 26 days to travel through the epididymis and appear in the ejaculate. While stored in the epididymis, sperm mature and acquire the ability for motility and fertilization.

The epididymis empties into the vas deferens, which is responsible for the movement of sperm along the tract. The vas deferens contains well-developed muscle layers that facilitate sperm movement. The vas deferens passes to the posterior and inferior aspect of the urinary bladder, where it is joined by the duct arising from the seminal vesicle; together, they form the ejaculatory duct, which joins the urethra. Sperm are stored in the epididymis as well as in the proximal end of the vas deferens prior to ejaculation.

Only 10% of the volume of semen is sperm cells. The remainder of the semen (i.e., 90%) is seminal plasma, the extracellular fluid of semen. The seminal plasma originates primarily from the accessory glands (the seminal vesicles, prostate gland, and the bulbourethral glands). The seminal vesicles contribute ~70% of the volume of semen, and the secretions of the prostate gland and bulbourethral glands contribute the rest. However, the composition of the fluid exiting the urethra during ejaculation is not uniform. The first fluid to exit is a mixture of spermatozoa with fluid from the epididymis and prostate. Subsequent emissions are composed of mainly secretions derived from the seminal vesicle. The first portion of the ejaculate contains the highest density of sperm; it also usually contains a higher percentage of motile sperm cells.

Due to the secretions, semen is isotonic or slightly alkaline (pH 7.3-7.7). The secretion contains a plethora of sugars and ions. The typical ejaculate volume is 2-6 ml and contains between 150 and 600 million spermatozoa.

Seminiferous epithelium is sensitive to elevated temperature, and will be adversely affected by temperatures as high as normal body temperature. Consequently, the testes are located outside the body in a sack of skin called the scrotum. The optimal temperature is maintained at 2 °C below body temperature. Hence, men with failure of the testis to descend into the scrotum, or men who consistently maintain elevated scrotal temperatures (e.g., professional cyclists), will have reduced or absent sperm count.
Physiology of Male Sexual Behavior

The testes, epididymis, male accessory glands, and erectile tissue of the penis receive dual sympathetic and parasympathetic innervation. As we discussed during earlier lectures, the parasympathetic nervous system mediates vasodilation in the penis that allows *Corpus cavernosum* to fill with blood, resulting in erection.

Parasympathetic activity also triggers secretory activity of the epithelia of the male accessory glands. Hence, cholinergic drugs (muscarinic agonists) induce the formation of copious amounts of secretions when these drugs are administered systemically, whereas cholinergic antagonists inhibit the secretions.

Emission begins with contraction of the smooth muscle in the vas deferens and the ampulla under the control of the sympathetic nervous system to cause expulsion of sperm into the internal urethra. The internal urinary sphincter also contacts to prevent backflow of semen into the bladder. Then, contractions of the muscular coat of the prostate gland followed by contraction of the seminal vesicles expel prostatic and seminal fluid also into the urethra, forcing the sperm forward. These fluids mix in the internal urethra with mucus secreted by the bulbourethral glands to form the semen.

The ejaculatory process is a spinal cord reflex, although it is also under considerable cerebral control. Sensory impulses from the penis reach the sacral spinal cord and trigger activity in somatic motor neurons whose axons travel through the pudendal nerve. The resulting rhythmic contractions of the striated muscles of the perineal area—including the muscles of the pelvic floor, as well as the ischiocavernosus and bulbospongious muscles—forcefully propel the semen through the urethra through the external meatus.

**Hyperplasia of the Prostate**

For unknown reasons, the prostate begins to enlarge in older men. Over 80% of men over 80 have at least some prostate enlargement. Enlargement of the gland can compress the urethra, resulting in difficulty in both urination and ejaculation.

Although most prostate hyperplasia is benign, prostate cancer is common: prostate cancer is the second leading cause of cancer death in American men, behind only lung cancer. About 1 man in 36 will die of prostate cancer. Men of African descent have a higher incidence of prostate cancer.

Benign hyperplasia of the prostate is often treated with alpha blockers, which relax smooth muscle in the prostate that surrounds the urethra. Prostate hyperplasia is testosterone-dependent, as the condition never occurs in men lacking testosterone. Hence, drugs that block testosterone production are also used as treatments for prostate hyperplasia. Testosterone is reduced to dihydrotestosterone in the prostate, which appears to be the chemical that triggers prostate hyperplasia. Thus, blockers of the enzyme that converts testosterone to dihydrotestosterone (5α-reductase) are also effective in treating benign prostate hyperplasia. Such drugs include Proscar (finasteride) and Avodart (dutasteride). Interestingly, testosterone-related baldness in men requires conversion of testosterone to dihydrotestosterone. Thus, 5α-reductase inhibitors such as Propecia (finasteride) are approved to treat baldness.
Prostate-Specific Antigen (PSA) Test

A protein produced by prostate cells, prostate specific antigen (PSA), has been used to detect hyperplasia of the prostate (the levels of the protein increase in the blood when more prostate cells are present due to hyperplasia). Until recently, annual PSA screenings were recommended in men over 50 to detect prostate cancer. However, this test is highly susceptible to false positive results, as prostate infections or benign prostate hyperplasia also lead to elevated PSA levels. In addition, the baseline values vary widely in men, such that PSA results can be difficult to interpret.

As a result, many physicians now advise their older male patients to have a PSA test upon onset of symptoms of prostate hyperplasia (i.e., difficulty in urinating).

Other Medical Issues Affecting the Male Reproductive System

Erectile dysfunction as well as problems with ejaculation can stem from a variety of causes. Diseases such as diabetes and hypertension can result in damage to the vessels or nerves in the genitalia, resulting in erectile or ejaculatory problems. Nerves supplying the genitalia can also be damaged by colorectal, bladder, or prostate surgery. Such surgeries can also damage the innervation to the internal urinary sphincter, resulting in “retrograde ejaculation” (backflow of semen into the bladder).

A variety of medications can also have deleterious effects on male sexual function. Alpha adrenergic antagonists can reduce smooth muscle contractions required for ejaculation, and also result in retrograde ejaculation because the internal urinary sphincter no longer closes tightly. Many antidepressant drugs result in moderate to severe sexual dysfunction, likely due to effects on brain systems that trigger sexual responses. Interestingly, histamine H₂ receptor antagonists (which include drugs used to lower stomach acid and those used to treat motion sickness) can cause sexual dysfunction, because they interfere with vasodilation of the corpus cavernosum (the exact mechanism is unclear).

A number of congenital problems can result in infertility. In approximately a third of cases of infertility, men don’t produce sperm, but the reason is unknown (idiopathic infertility). It is likely this condition is due to failure of germ cells to migrate into the testis during development. Some men have an enlarged venous plexus in the scrotum (varicocele), which is much like varicose veins in the legs. As a result, the venous vales don’t close properly, and blood return from the testis is impaired. This can result in elevated temperatures in the scrotum, which results in impaired spermiogenesis.

The ducts that transport sperm such as the vas deferens can become kinked or damaged, resulting in an inability to ejaculate sperm. During a medical procedure called vasectomy, the vas deferens on each side is cut and tied, as a permanent method of birth control.
Female Reproductive Physiology

As in males, female reproductive physiology is regulated by GnRh release from the hypothalamus, and LH/FSH release from the pituitary. Like in males, GnRH release from the hypothalamus must be pulsatile in order for FSH and LH to be released from the pituitary. In addition, the female sex hormones (estradiol and progestins) have feedback regulation on the release of LH and FSH. However, the patterns of release of these hormones vary during the menstrual cycle, and the regulation of their secretion is more complex than in males.

In reproductive age women, cyclic changes in the reproductive organs occur approximately every 30 days. This is called the menstrual cycle. Probably the most important single event during the menstrual cycle is ovulation, or release of a mature ovum from the ovary. Unlike humans, some animals (including rabbits and cats) are induced ovulators, such that ovulation is induced by coitus.

The ovaries lie on the side of the pelvic cavity and contain developing follicles and corpora lutea in various stages of development.

The female accessory sex organs include the fallopian tubes, uterus, vagina, and external genitalia. The fallopian tube provides a pathway for the transport of ova from the ovary to the uterus. The distal end of the fallopian tube expands as the infundibulum, which ends in multiple fimbriae. The infundibulum is lined with epithelial cells that have cilia that beat toward the uterus. The activity of these cilia and the contractions of the wall of the fallopian tube, particularly around the time of ovulation, facilitate transport of the ovum.
The uterus is a complex, pear-shaped, muscular organ that is suspended by a series of supporting ligaments. It is composed of a fundus, a corpus, and a narrow caudal portion called the cervix. The external surface of the uterus is covered by serosa, whereas the interior, or endometrium, of the uterus consists of complex glandular tissue and stroma. The uterus is continuous with the vagina through the cervical canal. The cervix is composed of dense fibrous connective tissue and muscle cells. The cervical glands lining the cervical canal produce a sugar-rich secretion, the viscosity of which is conditioned by estradiol and progesterone.

The human vagina is ~10 cm in length and is a single, expandable tube. The vagina is lined by stratified epithelium and is surrounded by a thin muscular layer. During development, the lower end of the vagina is covered by the membranous hymen, which is partially perforated during fetal life. In some instances, the hymen remains continuous. The external genitalia include the clitoris, the labia majora, and the labia minora, as well as the accessory secretory glands, which open into the vestibule. The clitoris is an erectile organ, which is homologous to the penis and mirrors the cavernous ends of the glans penis.

**Gonadotropin Levels Alternate During Life**

![Gonadotropin Levels](image)

As in males, levels of LH and FSH vary widely through a female’s lifespan. Surges in the hormones occur in the fetus and just after birth, but then fall to extremely low levels. Part of the reason that children lack gonadotropins is extremely strong feedback inhibition. This feedback inhibition abates somewhat during adolescence, allowing gonadotropin levels to increase. During puberty, monthly oscillations in the levels of LH and FSH are initiated (more on this later). In the late 40s or early 50s, women lose the capability to generate sex steroids, and thus lose feedback inhibition of GnRH, LH, and FSH release. Consequently, LH and FSH secretion becomes very high.
The Menstrual Cycle

The menstrual cycle involves cyclic changes in two organs: the uterus and ovary. The ovarian cycle includes the follicular phase and the luteal phase, separated by ovulation. The endometrial cycle includes the menstrual, the proliferative, and the secretory phases of the uterine endometrium.

The Ovarian Cycle

As noted above, the development of follicles from the primordial to late preantral stage is relatively independent of the pituitary gonadotropins and occurs throughout the life of the female, including infancy, childhood, pregnancy and other periods when there are no menstrual cycles occurring. These follicles will not develop to tertiary follicles unless LH and FSH are present.

The end result of the ovarian cycle is the production of fertilizable ova. Unlike in males, the entire cohort of gametes available is present at birth in females. The basic unit in the ovary is the primordial follicle, an ovum surrounded by a single layer of granulosa cells. In this follicle, the ovum is about 40% of mature size. Each newly formed ovary has ~250,000-300,000 of these primordial follicles. From the time in utero onward the primordial follicles enter the actively growing pool. This movement of primordial follicles into the growth phase is termed "recruitment." The mechanism that initiates recruitment of a follicle is unknown.

Follicles enter the active pool either one at a time or in small groups termed "cohorts", differentiating a thecal layer and increasing the numbers of granulosa cells surrounding the "zona pellucida," a membrane that encloses the oocyte. Once recruited into the growing pool, they are called secondary or preantral follicles. From birth through adolescence, follicles reach the secondary stage and then become atretic (die) because further development to tertiary or antral follicles requires hormonal stimulation from the pituitary gland.

As noted above, the development of follicles from the primordial to late preantral stage is relatively independent of the pituitary gonadotropins and occurs throughout the life of the female, including infancy, childhood, pregnancy and other periods when there are no menstrual cycles occurring. These follicles will not develop to tertiary follicles unless LH and FSH are present.

The follicles are the source of the female sex hormones: estradiol and progestins. Although several progestins are produced, the most prominent of these is progesterone. Estradiol production dominates during the follicular phase, whereas progesterone production dominates during the luteal phase. The entire supply of follicles in the ovaries is depleted by the time a female reaches her early 50s. After that point, the female can no longer produce estrogen and progesterone, and enters menopause.
At the time of onset of menses, follicular steroid secretion is very low and with the low blood concentrations of estradiol and progesterone, pituitary secretion of LH and FSH increases due to the reduction in negative feedback. Follicles moving into the preantral stage during menses will be rescued by the rising levels of pituitary hormones and will progress to the antral stage.

The LH that is secreted acts on the LH receptors on the theca cells to stimulate the secretion of an androgen, dehydroepiandrosterone (DHEA), which metabolizes to androstenedione and testosterone. These androgens diffuse across the basement membrane separating the theca and granulosa layers and provide the critical substrate for estradiol synthesis by granulosa cells.

Under the stimulus of FSH binding to receptors on the granulosa cells, late preantral follicles accumulate fluid, develop a space called an antrum and generate the aromatase enzyme that converts androgen to estradiol. FSH also triggers rapid mitotic proliferation of the granulosa layer and a marked increase in the vascular supply to the theca layer of the rapidly growing follicle. In the final stages of FSH-stimulated maturation, the follicle (also called the Graafian follicle) reaches about 0.4 mm in diameter and the granulosa cells acquire LH receptor.

The FSH-stimulated aromatase activity increases throughout the follicular phase and thus estradiol concentrations rise rapidly, particularly during the second half of the follicular phase. This rise in estradiol late in the follicular phase is a negative feedback signal to the pituitary, causing a decline in FSH. Because granulosa cells have acquired LH receptor in the Graafian follicle (but these receptors are not present in the granulosa layer at earlier stages), the granulosa cells can respond to both FSH and LH to increase intracellular cAMP and continue growing. On the other hand, follicles that have begun to grow but do not yet have LH receptor will become atretic with the fall in FSH. Typically, only one follicle has reached the stage of acquiring LH receptors when FSH levels decrease in the later follicular phase. This is the ‘selection’ mechanism that ensures that only one follicle will reach maturity and ovulate, even though several follicles may have responded to the peri-menstrual increase in gonadotropin.
Feedback Regulation of LH and FSH Secretion in Females

In addition to estradiol, a second steroid hormone, **progesterone**, is also produced in the ovary. Progesterone is not present until near the end of the follicular phase, when the granulosa cells develop the capacity of producing the hormone. Progesterone secretion is not high until after ovulation (the luteal phase), when the follicular cells remaining after the ovum is expelled reorganize into the **corpus luteum** (“yellow body”).

The ovarian steroids—the estrogens and progestins—exert both negative and positive feedback on the hypothalamic-pituitary axis. Whether the feedback is negative or positive depends on both the concentration of the gonadal steroids and the duration of the exposure to these steroids (i.e., the time in the menstrual cycle). In addition, the ovarian peptides—the **inhibins**—also feedback on the anterior pituitary.

Throughout most of the menstrual cycle, the estrogens and progestins that are produced by the ovary feedback negatively on both the hypothalamus and the gonadotrophs of the anterior pituitary. The net effect is to reduce the release of both LH and FSH. The estrogens exert negative feedback at both low and high concentrations, whereas progesterone is effective only at high concentrations. Estrogens also inhibit GnRH release from the hypothalamus. Granulosa cells additionally release peptides: **inhibins**. FSH stimulates the release of inhibins, as does LH when granulosa cells acquire LH receptors. As discussed below, the inhibins inhibit FSH release.

Curiously, after estradiol levels reach a threshold and remain there for ~2 days, the hypothalamic-pituitary axis reverses its sensitivity to estradiol. In other words, estradiol comes to have a positive effect on LH secretion. This promotes the **LH surge**, when LH levels rise at a very high rate. Rising levels of progesterone during the late follicular phase also contribute to eliciting the LH surge. There is also a simultaneous spike in FSH release.

As noted above, Inhibins are released from the corpus luteum after ovulation. These peptides have the same effects in females as in males: inhibiting FSH release, and to a lesser extent LH release. Inhibins may play a particularly important role in decreasing FSH and LH at the end of luteal phase.
Ovulation

The LH surge induces a number of effects that result in ovulation, or expulsion of the ovum:

1. The synthesis of enzymes in the granulosa cells change, such that the cells start releasing progesterone instead of estrogen.
2. The theca cells of the follicle begin to release proteolytic enzymes.
3. Prostaglandins are released, causing fluid movement into the follicle, resulting in swelling.

The Corpus Luteum

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca cells change rapidly into **lutein cells**. They enlarge in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance. This process is called **luteinization**, and the total mass of cells together is called the corpus luteum. A well-developed vascular supply also grows into the corpus luteum.

The transformed granulosa cells produce large amounts of progesterone, whereas the transformed theca cells produce androgens (as well as some progesterone); the androgens are converted to estradiol by aromatase in the corpus luteum. Thus, the corpus luteum secretes both progesterone and estradiol, with progesterone dominating.

The high levels of estrogen and progesterone, coupled with the release of inhibins from the granulosa cells, results in an inhibition of LH and FSH release from the anterior pituitary. Loss of these hormones results in an atrophy of the corpus luteum. Final atrophy of the corpus luteum normally occurs after ~12 days of corpus luteum life, which is around the 26th day of the normal female sexual cycle, 2 days before menstruation begins. At this time, the sudden cessation of secretion of estrogen, progesterone, and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH permit the development of new follicles, beginning a new ovarian cycle. The paucity of secretion of progesterone and estrogen at this time also leads to menstruation by the uterus (see below).

**SUMMARY**

1. Ovarian follicles are constantly being recruited into development, but completion of that development requires the presence of substantial amounts of LH and FSH. Only follicles that begin development in the menstrual phase are exposed to adequate levels of the pituitary hormones at the correct time to be “rescued”. Usually only one follicle per cycle completes development.
2. In the follicular phase, the follicle releases considerable estradiol, which increases as the follicle grows.
3. Through mechanisms that are not well understood, near the end of the follicular phase, the increasing estradiol levels induce an LH surge, as well as a rise in FSH.
4. The LH surge induces ovulation.
5. The follicular cells remaining after ovulation develop into the corpus luteum, which secretes substantial progesterone as well as some estradiol.
6. As FSH and LH levels decrease after ovulation, the corpus luteum degenerates and estrogen and progesterone levels fall.
7. Loss of sex steroids results in menstruation.
Endometrial Cycles

The hormones released from the ovary have profound effects on the endometrium of the uterus.

The Menstrual Phase. If the oocyte was not fertilized and pregnancy did not occur during the menstrual cycle, estradiol and progesterone secretion decrease with the atrophy of the corpus luteum. As hormonal support of the endometrium is withdrawn, the vascular and glandular integrity of the endometrium degenerates, the tissue breaks down, and menstrual bleeding ensues. This is defined as day 1 of the menstrual cycle.

The Proliferative Phase. Proliferation and differentiation of the endometrium are stimulated by estradiol that is secreted by the developing follicles. As noted above, levels of estradiol rise early in the follicular phase and peak just before ovulation. Estradiol binds to a nuclear receptor in the endometrial cell, and the activated receptor modulates the transcription rates of specific genes. The expression of these genes results in the production of paracrine factors necessary for maturation and growth of the endometrium. Estrogen causes the endometrium to become highly developed, and to thicken from ~0.5 mm to 5 mm. Estrogen also induces the synthesis of progestin receptors in endometrial tissue. Levels of progestin receptors peak at ovulation, when estrogen levels are highest, to prepare the cells for the high progestin levels of the luteal phase of the cycle.

The Secretory Phase. During the early luteal phase of the ovarian cycle, progesterone halts the proliferative phase of the endometrial cycle. Progesterone also stimulates the glandular components of the endometrium and thus induces secretory changes in the endometrium. The epithelial cells exhibit a marked increase in secretory activity, as indicated by increased amounts of endoplasmic reticulum and mitochondria. The endometrial glands become engorged with secretions. They are no longer straight; instead, they become tortuous and achieve maximal secretory activity at approximately day 20 or 21 of the menstrual cycle. Vascularization of the endometrium also increases.

During the late luteal phase of the menstrual cycle, when levels of both estrogens and progestins diminish, a series of responses results in the loss of most of the endometrium. Arteries in the endometrium con-
strict, and hydrolases are released from lysosomes. As endometrial cells die and the tissue sloughs, bleeding occurs. However release of fibrinolysins (enzymes that attack and inactivate fibrin molecules) prevent clotting from occurring.

**Cervical Mucus.** Changes also occur in the cervix (the area of the uterus that is continuous with the vagina) during the menstrual cycle. Several hundred glands in the cervix produce mucus, with the volume changing from 20–60 mg a day during the early follicular phase (proliferative phase) to 600 mg/day around the time of ovulation. The mucus is viscous as it contains large proteins known as mucins. The viscosity and water content varies during the menstrual cycle; mucus is composed of around 93% water, reaching 98% at midcycle.

These changes allow the mucus to function either as a barrier or a transport medium to spermatozoa. At midcycle around the time of ovulation (a period of high estrogen levels) the mucus is thin and serous to allow sperm to enter the uterus, and is more alkaline and hence more hospitable to sperm. The mucus has a stretchy characteristic described as *Spinnbarkeit* most prominent around the time of ovulation. The mucins present form channels that facilitate the movement of sperm further into the uterus.

At other times in the cycle, the mucus is thick and more acidic due to the effects of progesterone. This "infertile" mucus acts as a barrier to sperm entering the uterus. Thick mucus also prevents pathogens from interfering with a nascent pregnancy.

A cervical mucus plug, called the operculum, forms inside the cervical canal during pregnancy. This provides a protective seal for the uterus against the entry of pathogens and against leakage of uterine fluids. The mucus plug is also known to have antibacterial properties. This plug is released as the cervix dilates, either during the first stage of childbirth or shortly before. It is visible as a blood-tinged mucous discharge.

**Fallopian Tubes.** During the Proliferative Phase, estradiol causes the glandular tissues of this fallopian tubes to proliferate. Especially important, estradiol causes the number of ciliated epithelial cells that line the fallopian tubes to increase. Also, activity of the cilia is considerably enhanced. These cilia always beat toward the uterus, which helps propel the fertilized ovum in that direction. During the Secretory Phase, progesterone promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube before implantation.

**Additional Roles of the Sex Steroids in Females**

**Estrogens**

At adolescence, estrogen causes the female sex organs to change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus, and vagina all increase several times in size. Also, the external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and enlargement of the labia minora. In addition, estrogens change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection than is the prepubertal cuboidal cell epithelium. Estrogens also initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, progesterone and prolactin are needed to convert the breasts into milk-producing organs.
At the onset of adolescence, estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth. However, later in adolescence, estrogens are responsible for closure of the epiphyseal plate in both men and women. In men, testosterone must be converted to estradiol via aromatase present in bone. The inefficiency of this process results in closure of the epiphyseal plate later in males than females. Hence, males tend to grow taller than females.

Estrogens stimulate protein synthesis in women, but estrogens are not as potent as androgens. Thus, it is more difficult for women than men to accumulate significant muscle mass. Estrogens increase the whole-body metabolic rate slightly, but only about one third as much as the increase caused by the male sex hormone testosterone. They also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in the female body is greater than that in the male body. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause the deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure.

Estrogens cause the skin to develop a texture that is soft and usually smooth, but even so, the skin of a woman is thicker than that of a child or a castrated female. Also, estrogens cause the skin to become more vascular; this is often associated with increased warmth of the skin and also promotes greater bleeding of cut surfaces than is observed in men.

**Progestins**

Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. However, progesterone does not cause the alveoli to secrete milk, which is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland. Progesterone also causes the breasts to swell. Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the tissue.

**Androgens**

As discussed above, follicular theca cells produce androgens, which are mainly converted to estradiol by aromatase. However, this conversion is not 100% efficient, so some androgens from the ovary do circulate in the bloodstream and have effects throughout the female body. In addition, androgens arise from the adrenal glands in both men and women.

Approximately 8% of women suffer from androgen excess, which produces a number of unpleasant effects. The leading complaint is hirsutism, or unwanted hair that can occur on the face, upper chest, abdomen, inner aspects of the thighs, and the upper and lower back. In addition, hair loss (baldness) can occur with androgen excess if a female has a genetic predisposition for the condition. Acne is another unpleasant side effect that is particularly prominent in adolescent females with androgen excess.

In women, it is rare for androgen levels to reach adequate concentration in the blood to produce masculinization: large increase in muscle mass, deepening of the voice, breast atrophy. If these symptoms occur, they are likely due to the presence of an androgen-secreting tumor or the use of anabolic steroids.
As noted in the previous lecture, LH-secreting cells contain aromatase, which converts testosterone to estradiol. Thus, anabolic steroids result in feedback inhibition of LH/FSH release, such that follicles will fail to develop normally. Women who take anabolic steroids will not ovulate or have normal menstrual cycles.

Menopause

Oogenesis in the female differs in several ways from spermiogenesis in the male:

1. In the female, the mitotic proliferation of germ cells takes place entirely before birth, whereas in the male, spermatogonia proliferate only after puberty and then throughout life.
2. The meiotic divisions of a primary oocyte in the female produce only one mature ovum, whereas in the male, the meiotic divisions of a primary spermatocyte produce four mature spermatozoa.
3. In the female, the second meiotic division is completed only on fertilization (covered in the next lecture) and thus no further development of the cell takes place after the completion of meiosis, whereas in the male, the products of meiosis (the spermatids) undergo substantial further differentiation to produce mature spermatozoa.

As a consequence, females will eventually “run out” of follicles. When this occurs (at a mean age of 51.5 years), they largely lose the capacity for synthesis of estradiol, progesterone, and inhibins. As a consequence, there is no longer negative feedback to the pituitary, so LH and FSH levels rise. Changes in the production of these hormones has a number of physiological and medical implications.

Interestingly, the levels of ovarian hormones start to drop significantly, and pituitary hormones increase measurably, well before the follicles are depleted. Such changes are usually evident by the time a female reaches 35. The mechanism is unclear.

Loss of female sex steroids has a number of undesired effects. The modest stimulation of metabolic rate and protein synthesis provided by estradiol disappears, such that weight gain is common (unless caloric intake is suppressed). In addition, the estrogen deficiency leads to (1) increased osteoclastic activity in the bones, (2) decreased bone matrix, and (3) decreased deposition of bone calcium and phosphate. In some women this effect is extremely severe, and the resulting condition is osteoporosis.

The most common complaint from women entering menopause relates to actual or perceived changes in body temperature, referred to as “hot flashes.” The physiological underpinnings of the hot flashes are not well understood, but sudden bouts of flushing and sweating are often distressful. Hot flashes also occur at night, and can result in insomnia.

Estradiol affects neuronal function, and thus psychological effects of menopause may also be evident. The effects can include insomnia, mood changes, and depression.

Hormonal replacement therapy (HRT) has been used to treat the symptoms of menopause. However, such therapies have both risks and benefits. While ameliorating most of the symptoms of menopause, a variety of studies have shown that HRT increases the risk of strokes, myocardial infarction, and breast cancer. In addition, estrogen replacement therapy (without progesterone) maintains the uterus in a tonic proliferative phase and increases the risk of endometrial cancer. This risk is avoided when the HRT includes both estrogen and progesterone.

After considering all evidence, the FDA recommends using the lowest effective dose of hormones during HRT, and discontinuing therapy as soon as possible.
Selective Estrogen Receptor Modulators (SERMs). There are alternatives to HRT for treating some of the problems associated with menopause. For example, bisphosphonates can reduce the risk of osteoporosis. Selective estrogen receptor modulators are newer treatments for menopause, and a variety of other conditions that are affected by the presence of estradiol (e.g., breast cancer, which is stimulated by estrogens). SERMs can act as an estrogen agonist in some tissues but as an estrogen antagonist in others. A variety of such drugs have been developed, and their actions in different tissues vary.

One of the older SERMs is tamoxifen, which has been used to treat breast cancer, as it acts as an estrogen receptor antagonist in the breast. However, in bone the drug serves as an estrogen agonist, and thus provides no risk of osteoporosis. Unfortunately, tamoxifen also acts as an estrogen agonist in the uterus, and its use has been linked to the induction of endometrial cancer. It also increases the risk for stroke, and due to these risks the use of the drug has diminished in the USA (although tamoxifen remains a leading breast cancer treatment in many countries).

Another SERM used for menopause treatment is EVISTA (raloxifene hydrochloride). Raloxifene is an effective treatment for osteoporosis (through its actions as an estrogen receptor agonist), but does not carry the cancer risk associated with tamoxifen. However, raloxifene is associated with a small increase in cardiovascular disease.

Research is actively ongoing to develop the "perfect SERM," which alleviates the symptoms of menopause without the risks of HRT.

Female Sexual Response

The female sexual response occurs through coordinated activity of the parasympathetic, sympathetic, and somatic nervous systems. Dilatation of blood vessels in the erectile tissues causes engorgement with blood and erection of the clitoris, as well as distention of the peri-introital tissues and subsequent narrowing of the lower third of the vagina. Parasympathetic fibers emanating from the sacral spinal cord innervate these erectile tissues, just as in men. Furthermore, the responses are mediated through release of nitric oxide, as in males. In addition, the parasympathetic system innervates Bartholin’s glands, which empty into the introitus, as well as the vaginal glands. Parasympathetic activation of these glands provides for lubrication to minimize the friction of intercourse. Drugs that block these parasympathetic responses interfere with female sexual function.

Sympathetic and somatic reflexes during the female sexual response facilitate the movement of sperm upwards in the reproductive tract to maximize the likelihood of fertilization of the ovum. Drugs that block sympathetic activity can thus also interfere with the female sexual response.

The sexual responses in both men and women are highly dependent on cerebral activity. Antidepressant drugs such as SSRIs often interfere with sexual responses in both genders.