CHAPTER

5

Sex Hormones and Sexual Differentiation

CHAPTER HIGHLIGHTS

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This Way

I have AIS, I guess,
because there is a god,
and he or she or both,
peered deep into my heart
to see
that all that I can be
is best expressed
in female form.

The alternative for me
would be XY, and I
would be virilized;
so all that's soft and tender
would instead surrender
to a strand of DNA.
In the lie of X and Y
I came to challenge the
immutability
of "he" and the certainty
of "she." Blended and infused,
a ruse of gender
that upends
a different fate.

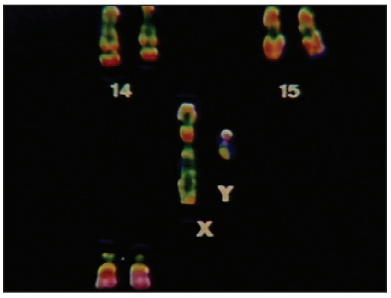
Non-functioning receptors
have rescued me

Not a failed mess
But a smashing success of nature!*

*Sherri Groveman, an intersex individual with Androgen Insensitivity Syndrome (AIS). In *Hermaphrodites with Attitude,* 1995, p. 2. (contact Info@isna.org).

One of the marvels of human biology is that the complex and different male and female anatomies—males with a penis and scrotum; females with a vagina, uterus, and breasts—arise from a single cell, the fertilized egg, which varies only in whether it carries two X chromosomes (XX) or one X and one Y (XY). Many of the structural differences between males and females arise before birth, during the **prenatal period,** in a process called *prenatal sexual differentiation.* Further differences also develop during puberty. This process of sexual differentiation—both prenatally and during puberty—will be examined in this chapter. First, however, another biological system, the endocrine (hormonal) system, needs to be considered, paying particular attention to the sex hormones, which play a major role in the differentiation process.

Sex Hormones



VIDEO

To learn more about the role of body chemistry in making us male or female, watch the "Hormones and Sexual Differentiation" video in Chapter 5 of your CD.

Hormones are powerful chemical substances manufactured by the *endocrine glands* and secreted directly into the bloodstream. Because they go into the blood, their effects are felt fairly rapidly and at places in the body quite distant from where they were manufactured. The most important sex hormones are **testosterone** (one of a group of hormones called **androgens**) and **estrogens** and **progesterone.** The thyroid, the adrenals, and the pituitary are examples of endocrine glands. We are interested here in the gonads, or sex glands: the testes in the male and the ovaries in the female. The **pituitary gland** and a closely related region of the brain, the **hypothalamus,** are also important, because the hypothalamus regulates the pituitary, which regulates the other glands, in particular the testes and ovaries. Because of its importance, the pituitary has been called the *master gland* of the endocrine system. The pituitary is a small gland, about the size of a pea, which projects down from the lower side of the brain. It is divided into two lobes: the anterior and the posterior lobe. The anterior lobe is the one that interacts with the gonads. The hypothalamus is a region at the base of the brain just above the pituitary (see Figure 5.1); it plays a part in regulating many vital behaviors such as eating, drinking, and sexual behavior,[1] and it is important in regulating the pituitary.

These three structures, then—the hypothalamus, pituitary, and gonads (testes or ovaries)—function together. They influence such important sexual functions as the menstrual cycle, pregnancy, the changes of puberty, and sexual behavior.

Prenatal period (pree-NAY-tul): The time from conception to birth.
Hormones: Chemical substances secreted by the endocrine glands into the bloodstream.
Testosterone: A hormone secreted by the testes in the male (and also present at lower levels in the female).
Androgens: The group of male sex hormones, one of which is testosterone.
Estrogens (ESS-troh-jens): The group of female sex hormones.
Progesterone (pro-JES-tur-ohn): A female sex hormone secreted by the ovaries.
Pituitary gland (pih-TOO-ih-tair-ee): A small endocrine gland located on the lower side of the brain below the hypothalamus; the pituitary is important in regulating levels of sex hormones.
Hypothalamus (hy-poh-THAL-ah-mus): A small region of the brain that is important in regulating many body functions, including the functioning of the sex hormones.

[1]One psychologist summarized the functions of the hypothalamus as being the four F's: fighting, feeding, fleeing, and, ahem, sexual behavior.

Figure 5.1 The hypothalamus-pituitary-gonad feedback loop in women, which regulates production of the sex hormones.

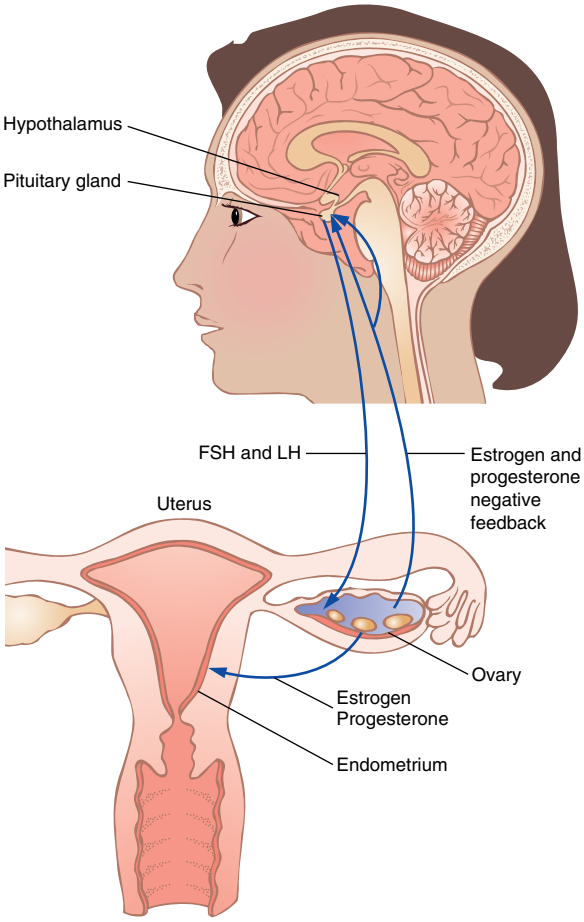
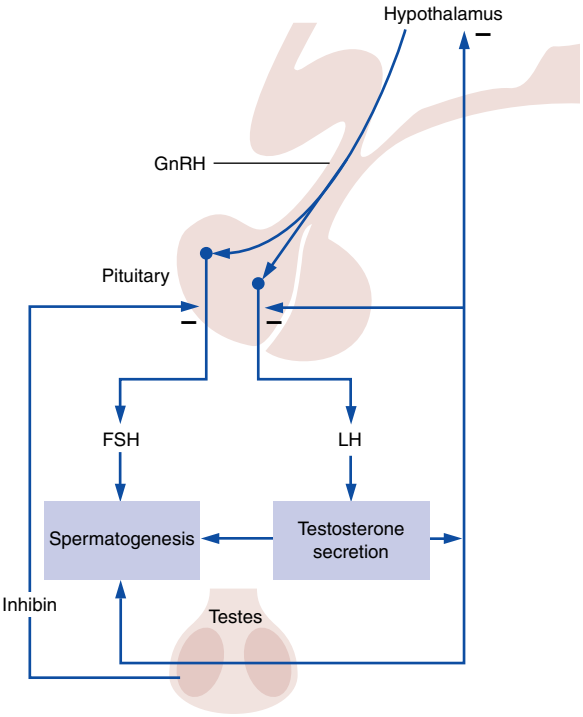


Figure 5.2 Schematic diagram of hormonal control of testosterone secretion and sperm production by the testes. The negative signs indicate that testosterone inhibits LH production, both in the pituitary and in the hypothalamus.



Follicle-stimulating hormone (FSH): A hormone secreted by the pituitary; it stimulates follicle development in females and sperm production in males.
Luteinizing hormone (LH): A hormone secreted by the pituitary; it regulates estrogen secretion and ovum development in the female and testosterone production in the male.
GnRH (gonadotropin-releasing hormone): A hormone secreted by the hypothalamus that regulates the pituitary's secretion of gonad-stimulating hormones.
HPG axis: Hypothalamus-pituitary-gonad axis, the negative feedback loop that regulates sex-hormone production.

Sex Hormone Systems in the Male

The pituitary and the testes both produce hormones. The important hormone produced by testes is *testosterone*. Testosterone, a "male" or masculinizing sex hormone, has important functions in stimulating and maintaining the secondary sex characteristics (such as beard growth), maintaining the genitals and their sperm-producing capability, and stimulating the growth of bone and muscle.

The pituitary produces several hormones, two of which are important in this discussion: **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH).** These hormones affect the functioning of the testes. FSH controls sperm production and LH controls testosterone production.

Testosterone levels in males are relatively constant. These constant levels are maintained because the hypothalamus, pituitary, and testes operate in a negative feedback loop (Figure 5.2). The levels of LH are regulated by a substance called **GnRH (gonadotropin-releasing hormone),** which is secreted by the hypothalamus. (FSH levels are similarly regulated by GnRH.) The system comes full circle because the hypothalamus is sensitive to the levels of testosterone present, and thus testosterone influences the output of GnRH. This feedback loop is sometimes called the **HPG axis,** for *h*ypothalamus-*p*ituitary-*g*onad axis.

This negative feedback loop operates much like a thermostat-furnace system. If a room is cold, certain changes occur in the thermostat, and it signals the furnace to turn on. The action of the furnace warms the air in the room. Eventually the air becomes so warm that another change is produced in the thermostat, and it sends a signal to the furnace to turn

off. The temperature in the room then gradually falls until it produces another change in the thermostat, which then turns on the furnace, and the cycle is repeated. This is a *negative* feedback loop because *rises* in temperature turn *off* the furnace, whereas *decreases* in temperature turn *on* the furnace.

The hypothalamus, pituitary, and testes form a similar negative feedback loop, ensuring that testosterone is maintained at a fairly constant level, just as the temperature of a room is kept fairly constant. The pituitary's production of LH stimulates the testes to produce testosterone. But when testosterone levels get high, the hypothalamus reduces its production of GnRH; the pituitary's production of LH is then reduced, and the production of testosterone by the testes consequently decreases. When it has fallen, the hypothalamus again increases the production of GnRH and the process starts again.

While the level of testosterone in men is fairly constant, there is probably some cycling, with variations according to the time of the day and possibly according to the time of the month (see Chapter 6).

Although it has been clear for some time that there is a negative feedback loop between testosterone levels and LH levels, it has not been clear what regulates FSH levels. **Inhibin** is a substance produced in the testes (by cells called the Sertoli cells) that serves exactly that function—it acts to regulate FSH levels in a negative feedback loop (Plant et al., 1993).

Interest in inhibin has been intense because it shows great promise, at least theoretically, as a male contraceptive. That is, because inhibin suppresses FSH production, sperm production in turn is inhibited. Future developments in this field should be interesting.

Sex Hormone Systems in the Female

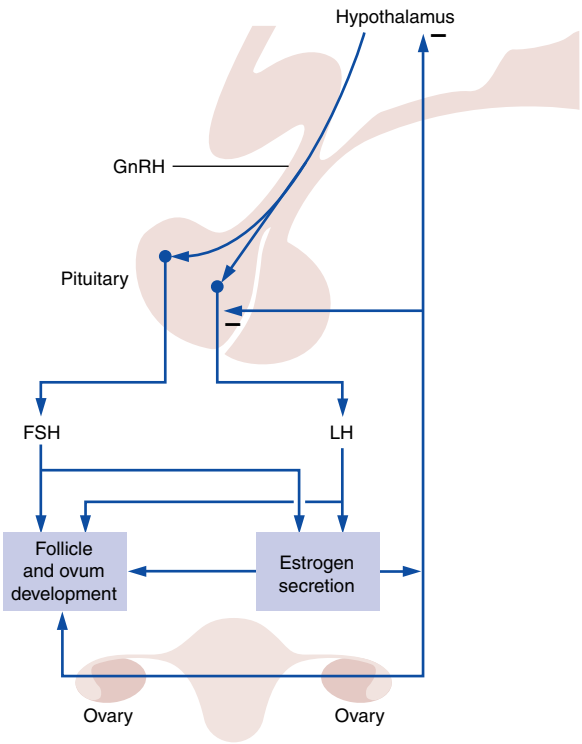
The ovaries produce two important hormones, *estrogen*[2] and *progesterone*. The functions of estrogen include bringing about many of the changes of puberty (stimulating the growth of the uterus and vagina, enlarging the pelvis, and stimulating breast growth). Estrogen is also responsible for maintaining the mucous membranes of the vagina and stopping the growth of bone and muscle, which accounts for the generally smaller size of females as compared with males.

In adult women the levels of estrogen and progesterone fluctuate according to the phases of the menstrual cycle (see Chapter 6) and during various other stages such as pregnancy and menopause. The levels of estrogen and progesterone are regulated by the two pituitary hormones, FSH and LH. Thus the levels of estrogen and progesterone are controlled by a negative feedback loop of the hypothalamus, pituitary, and ovaries similar to the negative feedback loop in the male (see Figure 5.3). For example, as shown on the right side of Figure 5.3, increases in the level of GnRH increase the level of LH, and the increases in LH eventually produce increases in the output of estrogen; finally, the increases in the level of estrogen inhibit (decrease) the production of GnRH and LH.

Inhibin: A substance secreted by the testes and ovaries which regulates FSH levels.

The pituitary produces two other hormones, *prolactin* and *oxytocin*. Prolactin stimulates secretion of milk by the mammary glands after a woman has given birth to a child. Oxytocin stimulates ejection of that milk from the nipples. Oxytocin also stimulates contractions of the uterus during childbirth.

Figure 5.3 Schematic diagram of hormonal control of estrogen secretion and ovum production by the ovaries (during the follicular phase of the menstrual cycle). Note how similar the mechanism is to the one in the male.



[2]We really should say *estrogens* because they are a group of hormones like the androgens. Estradiol is one of the estrogens. To keep things simple, we will just use the term *estrogen*.

The female sex hormone system functions much like the male sex hormone system. The ovaries and testes produce many of the same hormones, but in different amounts. The ovaries, like the testes, produce inhibin, which in turn forms a negative feedback loop with FSH production (Burger, 1993). The functioning of the female sex hormone system and the menstrual cycle will be considered in more detail in Chapter 6.

Prenatal Sexual Differentiation

Sex Chromosomes

As noted above, at the time of conception the future human being consists of only a single cell, the fertilized egg. The only difference between the fertilized egg that will become a female and the fertilized egg that will become a male is the sex chromosomes carried in that fertilized egg. If there are two X chromosomes, the result will typically be a female; if there is one X and one Y, the result will typically be a male. Thus, while incredibly tiny, the sex chromosomes carry a wealth of information that they transmit to various organs throughout the body, giving them instructions on how to differentiate in the course of development. The Y chromosome, because it is smaller, carries less information than the X.

Occasionally, individuals receive at conception a sex chromosome combination other than XX or XY. Such abnormal sex chromosome complements may lead to a variety of clinical syndromes, such as *Klinefelter's syndrome*. In this syndrome, a genetic male has an extra X chromosome (XXY). As a result, the testes are abnormal, no sperm are produced, and testosterone levels are low (Winter & Couch, 1995).

SRY: Stands for sex-determining region, Y chromosome.
Müllerian ducts: Ducts found in both male and female fetuses; in males they degenerate and in females they develop into the fallopian tubes, the uterus, and the upper part of the vagina.
Wolffian ducts: Ducts found in both male and female fetuses; in females they degenerate and in males they develop into the epididymis, the vas deferens, and the ejaculatory duct

The single cell divides repeatedly, becoming a two-celled organism, then a four-celled organism, then an eight-celled organism, and so on. By 28 days after conception, the embryo is about 1 centimeter (less than $^1/_2$ inch) long, but the male and female embryo are still identical, save for the sex chromosomes; that is, the embryo is still in the undifferentiated state. However, by the seventh week after conception, some basic structures have been formed that will eventually become either a male or a female reproductive system. At this point, the embryo has a pair of gonads (each gonad has two parts, an outer cortex and an inner medulla), two sets of ducts (the *Müllerian ducts* and the *Wolffian* ducts), and rudimentary external genitals (the *genital tubercle,* the *urethral folds,* and the *genital swelling*) (see Figure 5.4, top).

Gonads

In the seventh week after conception, the sex chromosomes direct the gonads to begin differentiation. In the male, the undifferentiated gonad develops into a testis at about 7 weeks. In the female, the process occurs somewhat later, with the ovaries developing at around 13 or 14 weeks.

An important gene that directs the differentiation of the gonads, located on the Y chromosome, is called **SRY,** for sex-determining region, Y chromosome (Page et al., 1987; Skaletsky et al., 2003). If SRY is present, testes differentiate and male development occurs (see Figure 5.5 for a summary of all the genes that regulate sexual differentiation). Researchers discovered this gene by studying cases of abnormal development—for example, adult women who had XY sex chromosomes and were infertile. The researchers found that these individuals were missing a section of the Y chromosome, precisely the section containing the SRY. The X chromosome carries a number of genes that control normal functioning of the ovaries (Winter & Couch, 1995). Surprisingly, a number of genes on the X chromosome affect cells in the testes that manufacture sperm (Wang et al., 2001).[3]

Prenatal Hormones and the Genitals

Once the ovaries and testes have differentiated, they begin to produce different sex hormones, which then direct the differentiation of the rest of the internal and external genital system (see Figure 5.4).

In the female the Wolffian ducts degenerate, and the **Müllerian ducts** turn into the fallopian tubes, the uterus, and the upper part of the vagina. The tubercle becomes the clitoris, the folds become the inner lips, and the swelling develops into the outer lips.

The testes secrete Müllerian inhibiting substance (MIS) (Vilain, 2000). MIS causes the Müllerian ducts to degenerate, while the **Wolffian ducts,** supported by testosterone, turn into the epididymis, the vas deferens, and the ejaculatory

[3]Scientists got so excited by this finding of genes on the X chromosome acting on the testes that they started calling them *transsexual genes.* Maybe you had to be there.

Figure 5.4 Development of the male and female external genitals from the undifferentiated stage. This occurs during prenatal development. Note homologous organs in the female and male.

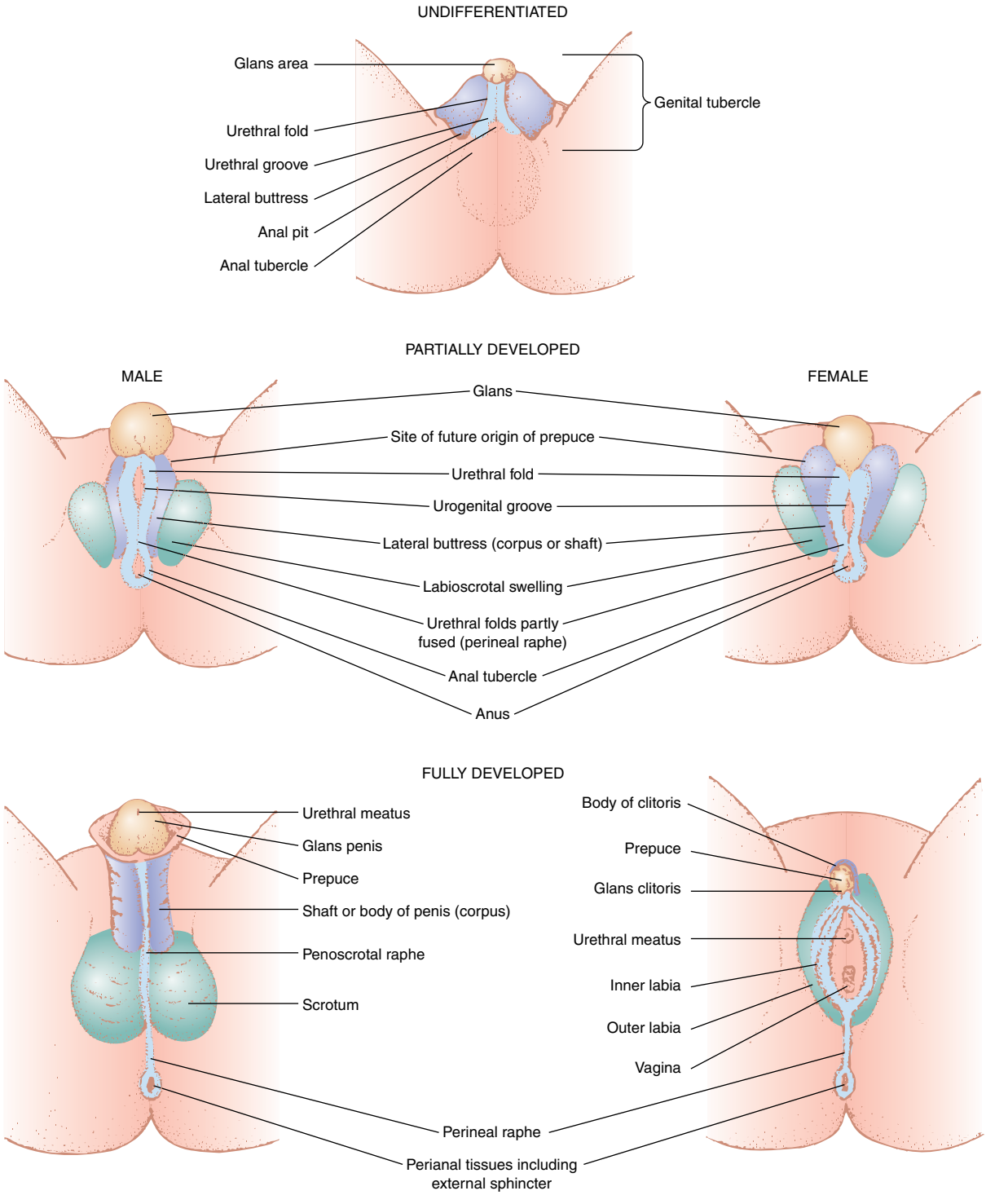
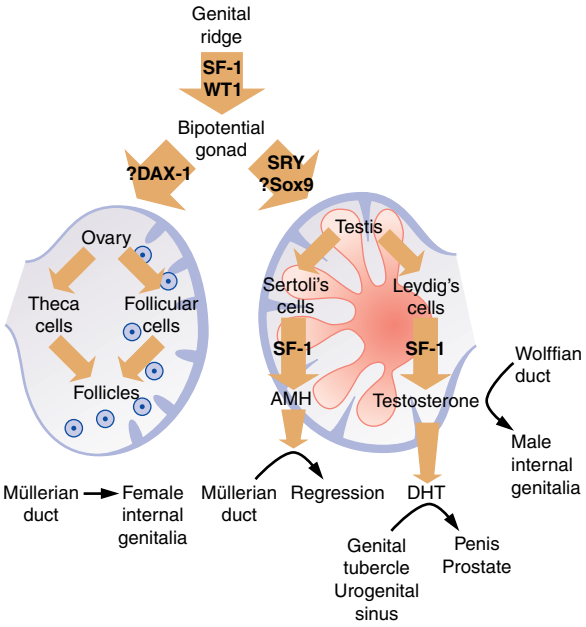


Figure 5.5 The possible functions of the genes linked so far to sexual differentiation in mammals: SRY, Sox9, AMH, WT1, SF-1, and DAX-1 (Marx, 1995).



Cryptorchidism: Undescended testes; the condition in which the testes do not descend to the scrotum as they should during prenatal development.

duct. The tubercle becomes the glans penis, the folds form the shaft of the penis, and the swelling develops into the scrotum.

The mechanism by which the internal and external genitals differentiate is the subject of much exciting new research. At least six different genes are involved in prenatal sexual differentiation (Figure 5.5), and a mutation in any one of them can cause an error in development (Vilain, 2000).

By four months after conception, the gender of the fetus is clear from the appearance of the external genitals (Figure 5.4).

Descent of the Testes and Ovaries

As these developmental changes are taking place, the ovaries and testes are changing in shape and position. At first, the ovaries and testes lie near the top of the abdominal cavity. By the tenth week they have grown and have moved down to the level of the upper edge of the pelvis. The ovaries remain there until after birth; later they shift to their adult position in the pelvis.

The male testes must make a much longer journey, down into the scrotum via a passageway called the *inguinal canal.* Normally this movement occurs around the seventh month after conception. After the descent of the testes, the inguinal canal closes off.

Two problems may occur in this process. First, one or both testes may have failed to descend into the scrotum by the time of birth, a condition known as *undescended testes,* or **cryptorchidism** (Santen, 1995). This occurs in about 2 percent of all males; most frequently, only one testis is undescended, the other being in the normal position. In most of these cases, the testes do descend by puberty, and so only about 1 in 500 adult men has undescended testes. If the testes do not descend spontaneously, however, the condition must be corrected by surgery or hormonal therapy. The optimum time for doing this is before age 5. Otherwise, if both testes have failed to descend, the man will be sterile because, as discussed in Chapter 4, the high temperature of the testes inside the body inhibits the production of sperm. Undescended testes are also more likely to develop cancer.

The second possible problem occurs when the inguinal canal does not close off completely. It may then reopen later in life, creating a passageway through which loops of the intestine can enter the scrotum. This condition, called *inguinal hernia,* can be remedied by simple surgery.

Brain Differentiation

During the prenatal period, when sex hormones are having a big impact on genital anatomy, they are also acting on the brain (Arnold, 2003). The results of many experiments with animals indicate that in certain regions there are differences between male and female brains. The primary sex-differentiated structure is the hypothalamus, in particular a region of it called the *preoptic area* (Collaer & Hines, 1995; Fitch & Bimonte, 2002). In humans, the evidence also indicates that differences exist between male and female brains in the preoptic area, although these differences may develop after birth rather than prenatally (Swaab et al., 1995).

One of the most important effects of this early sexual differentiation is the determination of the estrogen sensitivity of certain cells in the hypothalamus, cells that have *estrogen receptors* (Choi et al., 2001; McEwen, 2001). If testosterone is present during fetal development, these specialized cells in the hypothalamus become insensitive to estrogen. If estrogen is present, these cells become highly sensitive to levels of estrogen in the bloodstream. This sensitivity is crucial to the hypothalamic-pituitary-gonad feedback loop discussed earlier. Male hypo-

thalamic cells are relatively insensitive to estrogen levels, whereas female hypothalamic cells are highly sensitive to them. Male hypothalamic cells have more androgen receptors (Donahue et al., 2000).

New magnetic resonance imaging (MRI) studies are giving us a view into the brain of alive, awake humans, in contrast to earlier techniques that dissected the brains of, well, dead people and animals. The trade-off, at least for now, is that the MRI measures are relatively crude, simple assessments of the volume or size of certain regions. One of these studies found a larger volume of the hypothalamus and amygdala—both being brain regions with high densities of estrogen and androgen receptors—in men compared with women (Goldstein et al., 2001). Regions of the brain that have few estrogen and androgen receptors did not show these gender differences in size. Interestingly, a different MRI technique, the functional MRI, or fMRI, has detected increased activation in one region of the hypothalamus in men who were sexually aroused (Arnow et al., 2002).

Homologous Organs

The preceding discussion of sexual differentiation highlights the fact that although adult men and women appear to have very different reproductive anatomies, their reproductive organs have similar origins. When an organ in the male and an organ in the female both develop from the same embryonic tissue, the organs are said to be **homologous.** When the two organs have similar functions, they are said to be **analogous.** Table 5.1 summarizes the major homologies and analogies of the male and female reproductive systems. For example, ovaries and testes are both homologous (they develop from an indifferent gonad) and analogous (they produce gametes and sex hormones).

Atypical Prenatal Gender Differentiation

Gender is not a simple matter, a fact that is apparent from the preceding discussion. Most people, however, assume that it is. That is, people typically assume that if a person is female, she will be feminine; will think of herself as a woman; will be sexually attracted to men; will have a clitoris, vagina, uterus, and ovaries; and will have sex chromosomes XX. The parallel assumption is that all males are masculine; think of themselves as male; are sexually attracted to women; have a penis, testes, and scrotum; and have sex chromosomes XY.

Homologous organs (huh-MOLL-uh-gus): Organs in the male and female that develop from the same embryonic tissue.
Analogous organs (an-AL-uh-gus): Organs in the male and female that have similar functions.

A great deal of research over the last several decades challenges these assumptions and provides much information about sexuality and gender and their development. Before the results of this research are discussed, however, some background information is necessary.

We can distinguish among the following eight variables of gender (adapted from Money, 1987):[4]

1. *Chromosomal gender.* XX in the female; XY in the male.
2. *Gonadal gender.* Ovaries in the female; testes in the male.

[4]The distinction between the terms *gender* and *sex,* discussed in Chapter 1, is being maintained here.

Table 5.1 Homologous and Analogous Organs of the Male and Female Reproductive Systems

	Homologous Organs		*Analogous Organs*	
Embryonic Source	*In the Adult Male*	*In the Adult Female*	*In the Adult Male*	*In the Adult Female*
Gonad (medulla plus cortex)	Testes (from medulla)	Ovaries (from cortex)	Testes (from medulla)	Ovaries (from cortex)
Genital tubercle	Glans penis	Clitoris	Glans penis	Clitoris
Genital swelling	Scrotum	Outer lips		
Müllerian duct	Degenerates, leaving only remnants	Fallopian tubes, uterus, part of vagina		
Wolffian duct	Epididymis, vas deferens, seminal vesicles	Degenerates, leaving only remnants		
Urethral primordia	Prostate, Cowper's glands	Skene's glands, Bartholin glands	Prostate, Cowper's glands	Skene's glands, Bartholin glands

3a. *Prenatal hormonal gender.* Testosterone and MIS in the male but not the female before birth.

3b. *Prenatal and neonatal brain differentiation.* Testosterone present for masculinization, absent for feminization.

4. *Internal organs.* Fallopian tubes, uterus, and upper vagina in the female; prostate and seminal vesicles in the male.

5. *External genital appearance.* Clitoris, inner and outer lips, and vaginal opening in the female; penis and scrotum in the male.

6. *Pubertal hormonal gender.* At puberty, estrogen and progesterone in the female; testosterone in the male.

7. *Assigned gender.* The announcement at birth, "It's a girl" or "It's a boy," based on the appearance of the external genitals; the gender the parents and the rest of society believe the child to be; the gender in which the child is reared.

8. *Gender identity.* The person's private, internal sense of maleness or femaleness.

These variables might be subdivided into biological variables (the first six) and psychological variables (the last two).

In most cases, of course, all the variables are in agreement in an individual. That is, in most cases the person is a "consistent" female or male. If the person is a female, she has XX chromosomes, ovaries, a uterus and vagina, and a clitoris; she is reared as a female; and she thinks of herself as a female. If the person is a male, he has the parallel set of appropriate characteristics.

Intersex: An individual who has a mixture of male and female reproductive structures, so that it is not clear at birth whether the individual is a male or a female. Also called a *pseudohermaphrodite.*

Congenital adrenal hyperplasia (CAH): A condition in which a genetic female produces abnormal levels of androgens prenatally and therefore has male-appearing genitals at birth.

However, as a result of any one of a number of factors during the course of prenatal sexual development, the gender indicated by one or more of these variables may disagree with the gender indicated by others. When the contradictions are among several of the biological variables (1 through 6), the person is called an **intersex** or pseudohermaphrodite.[5] Biologically, the gender of such a person is ambiguous; the reproductive structures may be partly male and partly female, or they may be incompletely male or female. Approximately 2 percent of births have an intersex condition (Blackless et al., 2000).

[5]The term *hermaphrodite* is taken from Hermaphroditos, the name of the mythological son of Hermes and Aphrodite. The latter was the Greek goddess of love.

Figure 5.6 Dr. John Money, a controversial pioneer in research on and treatment of intersex individuals.

A number of syndromes can cause intersex, some of the most common being congenital adrenal hyperplasia, progestin-induced pseudohermaphroditism, and the androgen-insensitivity syndrome. In **congenital adrenal hyperplasia** (**CAH**, also called *adrenogenital syndrome*), a genetic female develops ovaries normally as a fetus; later in the course of prenatal development, however, the adrenal gland begins to function abnormally (as a result of a recessive genetic condition unconnected with the sex chromosomes), and an excess amount of androgens is produced. Prenatal sexual differentiation then does not follow the normal female course. As a result, the external genitals are partly or completely male in appearance; the labia are partly or totally fused (and thus there is no vaginal opening), and the clitoris is enlarged to the size of a small penis or even a full-sized one. Hence at birth these genetic females are sometimes identified as males. Long-term follow-ups indicate that CAH girls have a female gender identity and generally function well as girls and women (Wisniewski et al., 2000).

Progestin-induced pseudohermaphroditism is a similar syndrome which resulted from a drug, progestin, that was at one time given to pregnant women to help them maintain the pregnancy if they were prone to miscarriage. (The drug is no longer prescribed because of the following effects.) As the drug circulated in the mother's bloodstream, the developing fetus was essentially

exposed to a high dose of androgens. (Progestin and androgens are quite similar biochemicals, and in the body the progestin acted like androgen.) In genetic females this produced an abnormal, masculinized genital development similar to that found in CAH.

The reverse case occurs in **androgen-insensitivity syndrome (AIS)** (Wisniewski et al., 2000). In this syndrome a genetic male produces normal levels of testosterone; however, as a result of a genetic condition the body tissues are insensitive to the testosterone, and prenatal development is feminized. Thus the individual is born with the external appearance of a female: a small vagina (but no uterus) and undescended testes. The individual whose poem appeared at the beginning of this chapter has AIS.

Intersex persons provide good evidence of the great complexity of sex and gender and their development. Many variables are involved in gender and sex, and there are many steps in gender differentiation, even before birth. Because the process is complex, it is vulnerable to disturbances, creating conditions such as intersex. Indeed, the research serves to question our basic notions of what it means to be male or female. In CAH, is the genetic female who is born with male external genitals a male or a female? What makes a person male or female—chromosomal gender? External genital appearance? Gender identity?

A related phenomenon was first studied in a small community in the Dominican Republic (Imperato-McGinley et al., 1974). Due to a genetic-endocrine problem, a large number of genetic males were born there who, at birth, appeared to be females. The syndrome is called *5-Alpha Reductase Syndrome*. They had a vaginal pouch instead of a scrotum and a clitoris-sized penis. The uneducated parents, according to the researchers, were unaware that there were any problems, and these genetic males were treated as typical females. At puberty, a spontaneous biological change causes a penis to develop. Significantly, their psychological identity also changed. Despite rearing as females, their gender identity switched to male, and they developed heterosexual interests. In their culture, these people are called Guevodoces ("penis at 12").

Anthropologist Gilbert Herdt (1990) is critical of the research and interpretations about the Guevodoces. The major criticism is that the Western researchers assumed that this culture is a two-gender society, like the United States, and that people have to fall into one of only two categories, either male or female. Anthropologists, however, have documented the existence of three-gender societies—that is, societies in which there are three, not two, gender categories—and the society in which the Guevodoces grow up is a three-gender society. The third gender is the Guevodoces. Their gender identity is not male or female but Guevodoce. The 5-Alpha Reductase Syndrome has also been found among the Sambia of New Guinea, who also have a three-gender culture. Again we see the profound effect of culture on our most basic ideas about sex and gender.

Androgen-insensitivity syndrome (AIS): A genetic condition in which the body is unresponsive to androgens so that a genetic male may be born with a female-appearing body.
Puberty: The time during which there is sudden enlargement and maturation of the gonads, other genitalia, and secondary sex characteristics, so that the individual becomes capable of reproduction.

Sexual Differentiation during Puberty

Puberty is not a point in time but rather a process during which there is further sexual differentiation. It is the stage in life during which the body changes from that of a child into that of an adult, with secondary sexual characteristics (such as breasts or a beard) and the ability to reproduce sexually. **Puberty** can be scientifically defined as the time during which there is sudden enlargement and maturation of the gonads, other genitalia, and secondary sex characteristics, leading to reproductive capacity (Tanner, 1967). It is the second important period—the other being the prenatal period—during which sexual differentiation takes place. Perhaps the most important single event in the process is the first ejaculation for the male and the first menstruation for the female, although the latter is not necessarily a sign of reproductive capability, since girls typically do not produce mature eggs until a year or two after the first menstruation.

The physiological process that underlies puberty in both genders is a marked increase in levels of sex hormones. Thus the hypothalamus, pituitary, and gonads control the changes.

Adolescence is a socially defined period of development that bears some relationship to puberty. Adolescence represents a psychological transition from the behavior and attitudes of a child to the behavior, attitudes, and responsibilities of an adult. In the United States it corresponds roughly to the years from age 10 to age 20. Modern American culture has an unusually long period of adolescence (Steinberg, 2002). A century ago, adolescence was much shorter; the lengthening of the educational process has served to prolong adolescence. In some cultures, in fact, adolescence

Focus 5.1

The Debate over the Treatment of Intersex Individuals

When Chris was born, her clitoris was 1.7 cm long. That's about halfway between the length of the average newborn clitoris and the average newborn penis. She had a scrotum but no testes in it. The physician was unsure whether she was a girl or a boy. A blood test revealed that her sex chromosomes were XY. After 24 hours of consultations, during which her parents were in agony, the physician decided that Chris should be a girl because it would be impossible for her to function as a boy with such strange genitals. While a baby, she had several surgeries, one to remove her testes, which were still in her abdomen. Her clitoris was surgically reduced in size when she was 5, old enough to remember it. Today she is 27 and angry about what she considers the mutilations of her body. She now knows that she has androgen-insensitivity syndrome. So much of her clitoris was removed that she is not able to have an orgasm.

Chris (a composite of several case histories in the scientific literature) is an intersex individual; that is, her genitals have combined male, female, or ambiguous elements. She was treated according to a protocol that became standard beginning in the 1960s and persists to the present day. This protocol was based on the pioneering research of Dr. John Money and others. According to him, individuals such as Chris, whom he called "pseudohermaphrodites," could successfully be assigned to either gender, provided that it was done before 18 months of age and that the necessary surgeries and follow-up medical treatments (such as hormone treatment) occurred. Money's research indicated that individuals treated with the standard protocol grew up to be healthy and well adjusted.

In the last decade, however, intersex individuals have come out of the closet and formed an activist organization, the Intersex Society of North America (ISNA).* Intersex activists argue that they have cases of genital *variability,* not genital abnormality. The medical standard is that an infant's organ that is 0.9 cm or less is a clitoris and 2.5 cm or more is a penis. Activists argue that these cutoffs are arbitrary. What is wrong with a clitoris that is 1.7 cm long? Perhaps the only thing wrong with it is that it makes doctors, and perhaps parents, embarrassed. Issues of medical ethics are raised: Should essentially cosmetic surgery be performed on a baby who cannot give informed consent? Should parents be encouraged to lie to their child?

Sex researcher Milton Diamond conducted long-term follow-ups on several individuals treated using Money's standard protocol. He found that, contrary to the glowing picture of perfect adjustment painted by Money and others, these intersex individuals had serious adjustment problems that they traced directly to the medical "management" of their condition. Diamond's research has sparked a debate over the proper treatment of intersex individuals. Diamond has proposed a protocol in which he urges physicians, in cases of intersex infants, (1) to make their most informed judgment about the child's eventual gender identity (CAH girls, for example, almost invariably have a female identity) and counsel the parents to rear the child in that gender; (2) not to perform surgeries that might later need to be reversed; and (3) to provide honest counseling and education to the parents and child as he or she grows up so that the child can eventually make an informed decision regarding treatment.

does not exist; the child shifts to being an adult directly, with only a *rite de passage* in between.

Before describing the changes that take place during puberty, we should note two points. First, the timing of the pubertal process differs considerably for males and females. Girls begin the change around 8 to 12 years of age, while boys do so about two years later. Girls reach their full height by about age 16, while boys continue growing until about age 18 or later. The phenomenon of males and females being out of step with each other at this stage creates no small number of crises for the adolescent. Girls are interested in boys long before boys are aware that girls exist. A girl may be stuck with a date who barely reaches her armpits, while a boy may have to cope with someone who is better qualified to be on the basketball team than he is.

Second, there are large individual differences (differences from one person to the next) in the age at which the processes of puberty take place.

More systematic studies following up on intersex individuals quickly followed. Micropenis is a condition in which a genetic, XY male is born with a very small penis. One study followed up 18 of these individuals in adulthood; 13 had been reared as boys and 5 as girls (Wisniewski et al., 2001). All of the individuals raised as men reported good or fair erections, but 50 percent were dissatisfied with their genitals. In contrast, 80 percent of the individuals raised as women were dissatisfied with their genitals and 40 percent had no sexual interest or experience. Whether reared male or female, all were satisfied with their gender. In this case, it seems that rearing as a male worked better.

Another study examined the success of "feminizing" genital surgery; that is, performing surgery to reduce the size of an overlarge clitoris or to create or enlarge a vagina, as might happen with CAH girls (Creighton et al., 2001). Of the surgeries done in childhood, 41 percent were judged as having a poor outcome, supporting Diamond's recommendations against these early surgeries. Another study of intersex women—many of them with CAH—who had had clitoral surgery in childhood indicated approximately twice as many of them (39 percent) being unable to orgasm, compared with a control group (20 percent) of intersex women who had not had clitoral surgery (Minto et al., 2003).

Recognizing these new developments, the American Academy of Pediatrics (2000) issued guidelines for primary care pediatricians on how to care for newborns with ambiguous genitals. They include what tests to run to determine the cause of the ambiguous genitals, when the baby should be referred to a center specializing in intersexuality, and what factors should be used to decide the sex of rearing. These factors include fertility potential (for example, a CAH girl is potentially fertile and should be raised as a girl) and capacity for normal sexual functioning. Only with long-term studies will we learn whether these new treatments will yield better results for intersex individuals.

Figure 5.7 Cheryl Chase, an intersex activist.

*For information about the ISNA and other sexuality organizations, including its Web site, see the Directory of Resources at the end of this book.

Sources: American Academy of Pediatrics (2000); Creighton et al. (2001); Creighton & Minto (2001); Diamond (1996, 1999); Diamond & Sigmundson (1997); Kessler (1998); Meyer-Bahlburg et al. (2004); Money & Ehrhardt (1972); Wisniewski et al. (2000, 2001).

Thus there is no "normal" time to begin menstruating or growing a beard. Accordingly, we give age ranges in describing the timing of the process.

Changes in the Female

A summary of the physical changes of puberty in males and females is provided in Table 5.2. The first sign of puberty in the female is the beginning of breast development, generally at around 7 to 13 years of age (Herman-Giddens et al., 1997). The ducts in the nipple area swell, and there is growth of fatty and connective tissue, causing the small, conical buds to increase in size. These changes are produced by increases in the levels of the sex hormones by a mechanism that will be described below.

As the growth of fatty and supporting tissue increases in the breasts, a similar increase takes place at the hips and buttocks, leading to the

Table 5.2 Summary of the Changes of Puberty and Their Sequence

Girls			Boys		
Characteristic	*Age Range for First Appearance (Years)*	*Major Hormonal Influence*	*Characteristic*	*Age Range for First Appearance (Years)*	*Major Hormonal Influence*
1. Growth of breasts	7–13	Pituitary growth hormone, estrogens, progesterone, thyroxine	1. Growth of testes, scrotal sac	10–13.5	Pituitary growth hormone, testosterone
2. Growth of pubic hair	8–14	Adrenal androgens	2. Growth of pubic hair	10–15	Testosterone
3. Body growth	9.5–14.5	Pituitary growth hormone, adrenal androgens, estrogens	3. Body growth	10.5–16	Pituitary growth hormone, testosterone
4. Menarche	10–16.5	GnRH, FSH, LH, estrogens, progesterone	4. Growth of penis	11–14.5	Testosterone
			5. Change in voice (growth of larynx)	About the same time as penis growth	Testosterone
5. Underarm hair	About two years after pubic hair	Adrenal androgens	6. Facial and underarm hair	About two years after pubic hair	Testosterone
6. Oil- and sweat-producing glands (acne occurs when glands are clogged)	About the same time as under-arm hair	Adrenal androgens	7. Oil- and sweat-producing glands, acne	About the same time as under-arm hair	Testosterone

Source: Goldstein (1976), pp. 80–81.

Menarche (MEN-ar-key): First menstruation.

rounded contours that distinguish adult female bodies from adult male bodies. Individual females have unique patterns of fat deposits, so there are also considerable individual differences in the resulting female shapes.

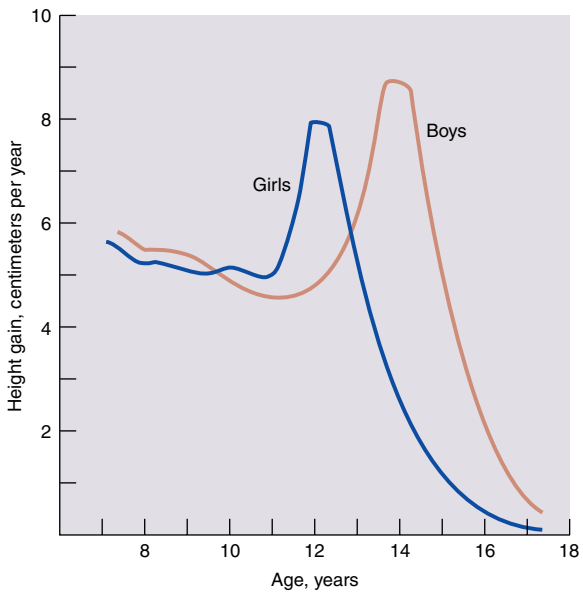
Another visible sign of puberty is the growth of pubic hair, which occurs shortly after breast development begins. About two years later, axillary (underarm) hair appears.

Body growth increases sharply during puberty, during the approximate age range of 9.5 to 14.5 years. The growth spurt for girls occurs about two years before the growth spurt for boys (Figure 5.8). This is consistent with girls' general pattern of maturing earlier than boys. Even prenatally, girls show an earlier hardening of the structures that become bones.

Estrogen eventually applies the brakes to the growth spurt in girls; the presence of estrogen also causes the growth period to end sooner in girls, thus accounting for the lesser average height of adult women as compared with adult men.

At about 12 to 13 years of age, the **menarche** (first menstruation) occurs. The girl, however, is

Figure 5.8 The adolescent spurt of growth for boys and girls. Note that girls experience their growth spurt earlier than boys do.



not capable of becoming pregnant until ovulation begins, typically about two years after the menarche. The first menstruation is not only an important biological event but also a significant psychological one. Various cultures have ceremonies recognizing its importance. In some families, it is a piece of news that spreads quickly to the relatives. Girls themselves display a wide range of reactions to the event, ranging from negative ones, such as fear, shame, or disgust, to positive ones, such as pride and a sense of maturity and womanliness.

Some of the most negative reactions occur when the girl has not been prepared for the menarche, which is still the case surprisingly often. Parents who are concerned about preparing their daughters for the first menstruation should remember that there is a wide range in the age at which it occurs. It is not unusual for a girl to start menstruating in the fifth grade, and instances of the menarche during the fourth grade, while rare, do occur.

What determines the age at which a girl first menstruates? One explanation is the *percent body fat hypothesis* (Frisch & McArthur, 1974; Hopwood et al., 1990). During puberty, deposits of body fat increase in females. According to the percent body fat hypothesis, the percentage of body weight that is fat must rise to a certain level for menstruation to occur for the first time and for it to be maintained. Thus very skinny adolescent girls would tend to be late in the timing of first menstruation. **Leptin,** a protein manufactured in the body, seems to be related to the onset of puberty in girls and in boys as well, although scientists have not yet sorted out the details (Apter, 2003; Phillip & Lazar, 2003; Wilson et al., 2003). In prepubertal girls and boys, leptin levels rise as body fat increases. Leptin stimulates the growth of skeletal bone and the release of LH.

The percent body fat hypothesis also helps to make sense of two related phenomena: the cessation of menstruation in anorexics and the cessation of menstruation in women distance runners. *Anorexia nervosa* is a condition in which the person—most commonly an adolescent girl—engages in compulsive, extreme dieting, perhaps to the point of starving herself to death. As anorexia progresses, the percentage of body fat declines and menstruation ceases. It is also fairly common for women who are runners, and all women who exercise seriously to the point where their body fat is substantially reduced, to cease menstruating. For both anorexics and female runners, it seems that when the percentage of body fat falls below a critical value, the biological mechanisms that control the menstrual cycle shut down menstruation.[6]

Before leaving the topic of running, we should note that there is some evidence that serious exercise also affects the male reproductive system. One study of male distance runners found that their testosterone levels were only about 68 percent as high, on the average, as a control group's testosterone levels (Wheeler et al., 1984). There are some reports of male long-distance runners complaining of a loss of sex drive, but it is unclear whether this results from reduced testosterone levels or from the perpetual feelings of fatigue that such runners have from their intensive training (Wheeler et al., 1984).

Other body changes in girls during puberty include a development of the blood supply to the clitoris, a thickening of the walls of the vagina, and a rapid growth of the uterus, which doubles in size between the tenth and the eighteenth years. The pelvic bone structure grows and widens, contributing to the rounded shape of the female and creating a passageway large enough for an infant to move through during birth.

The dramatic changes that occur during puberty are produced, basically, by the endocrine system and its upsurge in sex hormone production during puberty. The process begins with an increase in secretion of FSH by the pituitary gland. FSH in turn stimulates the ovaries to produce estrogen. Estrogen is responsible for many of the changes that occur; it stimulates breast growth and the growth of the uterus and vagina.

Leptin: A protein produced in the body that is related to the onset of puberty.
Adrenal glands (uh-DREE-nul): Endocrine glands located just above the kidneys; in the female they are the major producers of androgens.
Adrenarche (AD-ren-ar-key): A time of increased secretion of adrenal androgens, usually just before age eight.

Also involved in puberty are the paired **adrenal glands,** which are located just above the kidneys. In the female, the adrenal glands are the major producer of androgens, which exist at low levels in females. Adrenal androgens stimulate the growth of pubic and axillary hair and are related to the female sex drive. **Adrenarche**—the time of increasing secretion of adrenal androgens—generally begins slightly before age 8 (Grumbach & Styne, 1998).

Changes in the Male

As noted above, puberty begins at about 10 or 11 years of age in boys, about two years later than it does in girls. The physical causes of puberty in

[6]On the other hand, programs of moderate, regular aerobic exercise have been shown to reduce menstrual problems such as cramps (Golub, 1992).

boys parallel those in girls. They are initiated by increased production of FSH and LH by the pituitary. At the beginning of puberty, the increase in LH stimulates the testes to produce testosterone, which is responsible for most of the changes of puberty in the male.

The first noticeable pubertal change in males is the growth of the testes and scrotal sac, which begins at around 10 to 13 years of age as a result of testosterone stimulation. The growth of pubic hair begins at about the same time. About a year later the penis begins to enlarge, first thickening and then lengthening. This change also results from testosterone stimulation. As the testes enlarge, their production of testosterone increases even more; thus there is rapid growth of the penis, testes, and pubic hair at ages 13 and 14.

The growth of facial and axillary hair begins about two years after the beginning of pubic-hair growth. The growth of facial hair begins with the appearance of fuzz on the upper lip; adult beards do not appear until two or three years later. Indeed, by age 17, 50 percent of American males have not yet shaved. These changes also result from testosterone stimulation, which continues to produce growth of facial and chest hair beyond 20 years of age.

Erections increase in frequency. The organs that produce the fluid of semen, particularly the prostate, enlarge considerably at about the same time the other organs are growing. By age 13 or 14 the boy is capable of ejaculation.[7] By about age 15, the ejaculate contains mature sperm and the male is now fertile. The pituitary hormone FSH is responsible for initiating and maintaining the production of mature sperm.

Beginning about a year after the first ejaculation, many boys begin having nocturnal emissions, or "wet dreams." For the boy who has never masturbated, a wet dream may be his first ejaculation.

At about the same time penis growth occurs, the larynx ("voice box") also begins to grow in response to testosterone. As the larynx enlarges, the boy's voice drops, or "changes." Typically the transition occurs at around age 13 or 14. Because testosterone is necessary to produce the change in voice, castration before puberty results in a male with a permanently high voice. This principle was used to produce the castrati, who sang in the great choirs of Europe during the eighteenth century. They began as lovely boy sopranos, and their parents or the choirmaster, hating to see their beautiful voices destroyed at puberty, had them castrated so that they remained permanent sopranos. Contrary to popular belief, castration in adulthood will not produce a high voice, because the larynx has already grown.

A great spurt of body growth begins in males at around 11 to 16 years of age (Figure 5.9). Height increases rapidly. Body contours also change. While the changes in girls involve mainly the increase in fatty tissue in the breasts and hips, the changes in boys involve mainly an increase in muscle mass. Eventually testosterone brings the growth process to an end, although it permits the growth period to continue longer than it does in females.

Puberty brings changes and also problems. One is *acne,* which is stimulated by androgens and affects boys more frequently than girls. *Acne* is a distressing skin condition that is caused by a clogging of the sebaceous (oil-producing) glands, resulting in pustules, blackheads, and redness on the face and possibly the chest and back. Generally, acne is not severe enough to be a medical problem, although its psychological impact may be great. In order to avoid scarring, severe cases should be treated by a physician, the treatment typically being ultraviolet light, the drug Retin-A, and/or antibiotics. The drug Accutane is highly effective for severe cases. However, it must be used cautiously, because it may have serious side effects, including birth defects if taken by a pregnant woman.

Gynecomastia (breast enlargement) may occur temporarily in boys, creating considerable embarrassment. About 80 percent of boys in puberty experience this growth, which is probably caused by small amounts of female sex hormones being produced by the testes. Obesity may also be a temporary problem, although it is more frequent in girls than boys.

In various cultures around the world, puberty rites are performed to signify the adolescent's passage to adulthood. In the United States the only remaining vestiges of such ceremonies are the Jewish bar mitzvah for boys and bat mitzvah for girls and, in Christian churches, confirmation. In a sense, it is unfortunate that we do not give more formal recognition to puberty. Puberty rites probably serve an important psychological function in that they are a formal, public announcement of the fact that the boy or girl is passing through an important and difficult period of change. In the absence of such rituals, the young person may think that his or her body is doing strange things and may feel very much alone. This may be particularly problematic for boys, who lack an obvious sign of puberty like the first menstruation (the first ejaculation is probably the closest analogy) to help them identify the stage they are in.

[7]Note that orgasm and ejaculation are two separate processes, even though they generally occur together, at least in males after puberty. But orgasm may occur without ejaculation, and ejaculation may occur without orgasm.

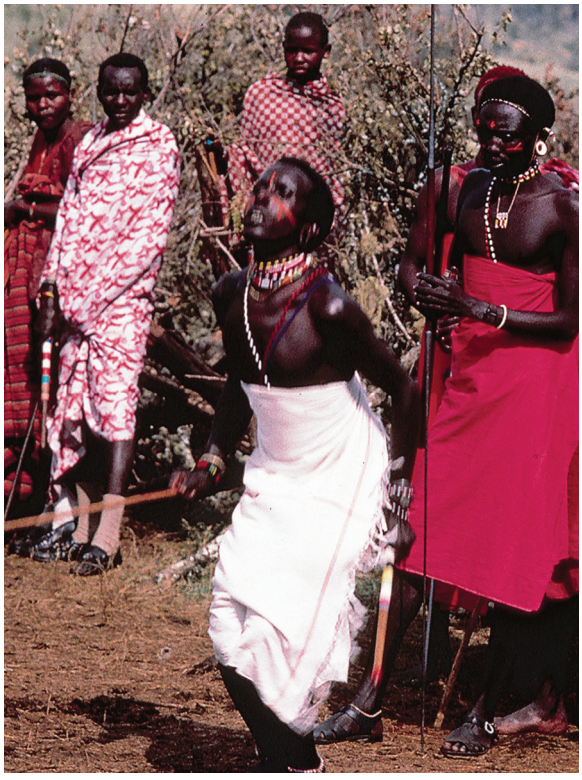
Figure 5.9 There is great variability in the onset of puberty and its growth spurt. Both girls are the same age. All boys are the same age.

(a)

(b)

Figure 5.10 Most cultures celebrate puberty, but cultures vary widely in the nature of the celebration. (*a*) American Jewish youth celebrate a bar mitzvah (for boys) or bat mitzvah (for girls). (*b*) The Samburu youth of Kenya celebrate a male circumcision ritual.

(a)



(b)

SUMMARY

The major sex hormones are testosterone, which is produced in the male by the testes, and estrogen and progesterone, which are produced in the female by the ovaries. Levels of the sex hormones are regulated by two hormones secreted by the pituitary: FSH (follicle-stimulating hormone) and LH (luteinizing hormone). The gonads, pituitary, and hypothalamus regulate one another's output through a negative feedback loop. Inhibin regulates FSH levels.

At conception males and females differ only in the sex chromosomes (XX in females and XY in males). As the fetus grows, the SRY gene on the Y chromosome directs the gonads to differentiate into the testes. In the absence of the SRY gene, ovaries develop. Different hormones are then produced by the gonads, and these stimulate further differentiation of the internal and external reproductive structures of males and females. A male organ and a female organ that derive from the same embryonic tissue are said to be homologous to each other.

Intersex conditions are generally the result of various syndromes (such as CAH) and accidents that occur during the course of prenatal sexual differentiation. Currently there is a debate over the best medical treatment of these individuals. The Guevodoces provide an interesting case of gender change at puberty.

Puberty is initiated and characterized by a great increase in the production of sex hormones. Pubertal changes in both males and females include body growth, the development of pubic and axillary hair, and increased output from the oil-producing glands. Changes in the female include breast development and the beginning of menstruation. Changes in the male include growth of the penis and testes, the beginning of ejaculation, and a deepening of the voice.

QUESTIONS FOR THOUGHT, DISCUSSION, AND DEBATE

1. Of the physical changes of puberty, which are the most difficult to cope with?
2. The society in the Dominican Republic in which the Guevodoces are born (see page 105) is a three-gender society, unlike the two-gender society of the dominant U.S. culture. What would the United States be like if it was a three-gender society? Who would be classified in the third gender? Would their lives be better or worse as a result? Could we have a four-gender society? Who would be classified in the fourth gender? (For further information, see Herdt, 1990.)
3. Teresa has just given birth to her first baby. The doctor approaches her with a worried expression and says that her baby's genitals are unusual and some decisions will have to be made. The phallus is too big for a clitoris, but too small for a penis. What should Teresa do? What other information should she obtain from the doctor before making a decision?

SUGGESTIONS FOR FURTHER READING

Fausto-Sterling, Anne (2000). *Sexing the body.* New York: Basic Books. The author, a developmental geneticist, has written a provocative book that calls into question our most basic understandings of differentiation of the sexes, both physically and psychologically.

Kessler, Suzanne J. (1998). *Lessons from the intersexed.* New Brunswick, NJ: Rutgers University Press. Kessler, a psychologist, reports on her years of research with intersex individuals and the medical and psychological professionals who treat them, and proposes new approaches in dealing with the condition.

Larsen, P. Reed et al. (2003). *Williams textbook of endocrinology.* 10th ed. Philadelphia: Saunders. An outstanding endocrinology text, with a particularly good chapter on sexual differentiation.

Steinberg, Laurence (2002). *Adolescence.* 6th ed. New York: McGraw-Hill. This is the definitive textbook on adolescence, written by a leading researcher.

WEB RESOURCES

http://www.isna.org
The Intersex Society of North America home page.

http://www.teenpuberty.com
Teen Puberty; includes health information about pubertal changes; intended for adolescents.

http://www.urologyhealth.org/pediatric
American Urological Association; discussion of pediatric abnormalities contains information regarding abnormal sexual differentiation.

http://www.oxytocin.org/oxytoc
Information and articles about oxytocin and its roles in orgasm, childbirth, and bonding.

http://www.cah.org.uk
Congenital Adrenal Hyperplasia Support Group.

http://www.medhelp.org/www/ais
Androgen Insensitivity Syndrome Support Group.