Human blastocyst (at right) emerging from its zona pellucida. The sex of the blastocyst has already been determined by the chromosomes it possesses, but it has not yet begun to differentiate as male or female (colorized scanning electron micrograph).
In Chapter 2 we discussed a number of central questions about sexuality from an evolutionary standpoint—Why are there two sexes? Why do males and females differ in anatomy and behavior? In this chapter we begin a discussion of these same questions from a developmental point of view. What are the actual processes that turn a barely visible blob of protoplasm—a fertilized egg—into an adult human being, complete with her or his unique physical appearance, character, and sexuality? Few questions have so perplexed philosophers and scientists over the centuries, and even today our answers are quite incomplete.

In this chapter we focus primarily on the development of physical differences between the sexes. In the process, we will see that many individuals deviate to some degree from the male and female stereotypes that are described in textbooks. In later chapters we will ask about the origin of sex differences in personality, feelings, and behavior—attributes that are often lumped under the category of “gender.” There we will find that these distinctions between the two sexes are even less sharp than the bodily differences.

**Humans Pass through Distinct Stages of Development**

It’s not possible to give an account of human development without drawing a distinction between its usual course and the various ways in which it can deviate from that course. The main text of this chapter describes typical sexual development, which progresses through several stages that are controlled by different biological mechanisms; Boxes 6.1 through 6.7 describe atypical sexual development, which can affect any of these stages. For a discussion of what should be considered “normal” in development, see Web Topic 6.1 The Meaning of “Normal.”
Fertilization Is the Fusion of One Sperm with One Ovum

We’ll begin with a brief general outline of human development before focusing specifically on sex. In the previous chapter, you learned how a secondary oocyte (or unfertilized ovum—Figure 6.1) is released from an ovarian follicle at ovulation and transported to the ampulla of the oviduct. Sperm also travel to the oviducts from their site of deposition in the vagina: They find their way primarily by ascending a gradient of increasing temperature (Suarez & Pacey, 2006), but they are helped along by active contractions of the uterus and oviducts. In fact, even inanimate particles placed on the cervix are transported to the uterus and oviducts within minutes (Zervomanolakis et al., 2007).

If sperm are present in the oviduct at the time of ovulation or arrive there within about 24 hours afterward, fertilization may occur—that is, a single sperm enters the ovum, producing a *zygote*. If fertilization does not occur within about 24 hours of ovulation the ovum dies, and the luteal phase continues on to menstruation.

Before fertilization can take place, the sperm must undergo two important processes: capacitation and the acrosome reaction (Figure 6.2). Capacitation involves the removal of masking proteins on the outer surface of the sperm by enzymes present in the uterus and oviducts. Capacitated sperm swim more forcefully and are capable of recognizing the presence of the ovum. Once capacitated, a single sperm can live only a few hours, so it must find an ovum or die. The many sperm from a single ejaculation undergo capacitation over a span of several days, however, so a woman can become pregnant from a sexual encounter that took place several days before she ovulates, as Chapter 11 will describe. Once capacitated, sperm are drawn to the ovum by a chemical attractant released by the ovum. This attractant is believed to be *bourgeonal* or a closely related compound; bourgeonal is an aromatic aldehyde used by the perfume industry on account of its floral odor (Spehr et al., 2003).

**FIGURE 6.1** An unfertilized ovum
The outer wrapping is the zona pellucida. The larger of the two inner structures is the oocyte (shown here halted during meiosis II). The smaller structure, at the 12 o’clock position, is the first polar body—the discarded set of chromosomes from meiosis I. (Micrograph courtesy of R. Yanagimachi.)

**fertilization** The entry of a sperm into an ovum, thus transforming the ovum into a genetically unique diploid organism capable of development (conceptus).

**zygote** A cell formed by the fusion of gametes: a fertilized ovum.

**capacitation** A chemical change in the surface of a sperm within the female reproductive tract that allows it to swim more forcefully and respond to the presence of the ovum.

**bourgeonal** An aromatic aldehyde that attracts spermatozoa to the ovum.

**FIGURE 6.2** Maturation of sperm in the female reproductive tract.

1. The sperm has completed meiosis in the testis, so it is already haploid.
2. At ejaculation, the sperm is covered in masking proteins that limit its responsiveness to its new environment.
3. While in the uterus or oviduct, the masking proteins are digested away (capacitation);…
4. …the sperm’s tail movements become more forceful, and it senses the presence of the ovum.
5. Once in contact with the ovum’s zona pellucida, the acrosome reaction occurs, exposing receptors that bind to the zona pellucida and releasing enzymes that digest a path through it.
The acrosome reaction occurs when sperm actually reach the zona pellucida—the protective membrane that surrounds the ovum. The sperm’s acrosome (see Chapter 4) fuses with its outer membrane, exposing receptors that bind to the zona pellucida as well as releasing protein-digesting enzymes that clear a path through the zona pellucida so that the sperm can reach the ovum’s plasma membrane.

The moment a sperm actually fuses with the plasma membrane, an invisible but vital event takes place: The concentration of free calcium ions (Ca²⁺) within the ovum increases briefly. This increase, in turn, triggers the release of enzymes from the ovum that change the physical properties of the zona pellucida, making it difficult for any other sperm to pass through. (On the rare occasions when a second sperm enters the ovum, the resulting embryo does not survive.)

Within the next few minutes, another important event takes place: The ovum completes its second meiotic division (FIGURE 6.3). As with the first division, one daughter cell is just a tiny bag of discarded chromosomes, the second polar body; the other daughter cell inherits most of the cytoplasm. The ovum now contains two pronuclei: a pronucleus derived from the unfertilized ovum, containing a haploid set (a single set—see Chapter 2) of maternal chromosomes, and a pronucleus derived from the sperm, containing a haploid set of paternal chromosomes.

You might think that the most sensible thing to happen next would be for the two pronuclei to fuse, producing a diploid cell (a cell with the normal double set of chromosomes) with a single nucleus. Such a cell never forms, however. Instead, the two pronuclei undergo a round of DNA replication, so that each chromosome now consists of two identical chromatids. The pronuclear membranes break down, a mitotic spindle forms, the chromatids are pulled apart, and the cell divides. This is the first mitotic cell division of the new organism. Each daughter cell inherits one set of chromosomes from each of the two pronuclei, so these two cells, and all their descendants, are diploid. The polar bodies, containing the discarded chromosomes, eventually break down.

The term conception has the same meaning as fertilization. “Conception” is often used when speaking of the age of an embryo or fetus (e.g., “3 weeks post-conception”). Less commonly (and never in this book) “conception” is used to mean implantation (see below) or the secure establishment of pregnancy.

The conceptus implants in the uterine wall

The two-celled organism is called a conceptus. This term refers to the entire collection of cells derived from the fertilized ovum, regardless of whether or not they contribute to the tissues of the future fetus. The term “embryo” is not really appropriate at the 2-cell stage or for some time afterward, for reasons we’ll see shortly. Nevertheless,
The conceptus when it consists of about 16 to 32 cells arranged in a compact spherical mass.

A conceptus shortly before implantation, when it takes the form of a sphere of cells with a central cavity.

A gonadotropin secreted by the conceptus and by the placenta; it prevents regression of the corpus luteum.

The state of carrying a living, implanted conceptus, embryo, or fetus.

The term “embryo” is commonly used to refer to a conceptus from the 2-cell stage onward, especially in the context of in vitro fertilization.

The conceptus remains in the oviduct for about 3 days after ovulation, during which time it undergoes a few more rounds of cell division (FIGURE 6.4). The conceptus does not get any bigger, however; it remains confined within the original zona pellucida. The cytoplasm of the original ovum simply divides into smaller and smaller packets as the cells multiply. At the 4- or 8-cell stage, the conceptus’s genes become active for the first time. At about the 16-cell stage, the conceptus becomes a compact mass of cells known as a morula. Sometime around the fourth day, the conceptus is swept into the uterus by the action of the cilia lining the oviduct.

The conceptus—now containing about 32 cells—develops a central fluid-filled cavity, and the conceptus as a whole is now referred to as a blastocyst. On about the sixth day of development the blastocyst emerges from the zona pellucida and implants itself in the wall of the uterus (FIGURE 6.5). The implantation process requires the presence of both progesterone and estrogens, which are being secreted at this time by the corpus luteum in the mother’s ovary. As implantation progresses, the conceptus begins to secrete the hormone human chorionic gonadotropin (hCG). This protein hormone is structurally very similar to luteinizing hormone (LH), and it activates LH receptors on the cells of the maternal corpus luteum. By doing so, it “rescues” the corpus luteum from its normal regression at the end of the luteal phase. Thus, hCG is the signal to the mother’s body that implantation has occurred.

Many conceptuses never implant, and these die within a few days. Failure of implantation can happen for a variety of reasons, including abnormalities in the conceptus (such as an incorrect number of chromosomes) or in the reproductive tract. In addition, the presence of nicotine (in women who smoke) interferes with the molecular “docking signals” between conceptus and endometrium, reducing the likelihood of implantation or triggering the loss of an already implanted conceptus (Zdravkovic et al., 2006).

When implantation fails, there is nothing to tell the mother that fertilization has ever occurred, and a woman who loses a conceptus prior to implantation is not considered to have been pregnant at all. Pregnancy is usually taken to begin after successful implantation and the hormonal rescue of the corpus luteum, rather than at fertilization. The fact that many conceptuses die prior to implantation may influence judgments about the morality of creating, experimenting on, or discarding human conceptuses.

The cells of the implanting blastocyst keep dividing, but as yet none of the cells is fated to give rise exclusively to fetal tissues.

FIGURE 6.4 Development of the human conceptus between fertilization and implantation. (A) Fertilized ovum showing male and female pronuclei, and polar bodies at top. (B) 2-cell stage. (C) 4-cell stage. (D) 8–16 cell stage. (E) Morula stage (16–32 cells). (F) Blastocyst stage. A central cavity (blastocoel) has formed. The inner cell mass contains the cells that will form the embryo and its membranes. The blastocyst is in the process of emerging from the zona pellucida.

FIGURE 6.5 Blastocyst in the process of implanting itself in the wall of the uterus (the endometrium), as seen in a colorized scanning electron micrograph.
The cells that line the outer rim of the blastocyst concern themselves with the process of implantation. A small cluster of cells gives rise to the protective membranes that will enwrap the fetus, most notably the sac called the amnion. The amnion contains amniotic fluid—the fetus’s watery environment for the duration of pregnancy.

**During embryonic life, the body plan and organ systems develop**

Finally, by about 2 weeks after conception, the precursors of the various nonfetal tissues have been established. There remains a small plate of tissue derived from the inner cell mass: the embryo. This is the tissue that will give rise to the fetus and ultimately to an independent human being. The embryo at this time consists of three stacked layers of different kinds of cells: ectoderm, mesoderm, and endoderm. The **ectoderm** will give rise to the skin, the nervous system, and a few other structures. The **endoderm** will give rise to the lining of the gut and its associated glands, as well as the lungs. The intervening layer, the **mesoderm**, will give rise to most other structures between the gut and the skin, such as the cardiovascular and musculoskeletal systems. In addition, small regions of mesoderm and endoderm will develop into the fetal side of the **placenta**—the vascular organ by which the fetus and its mother exchange gases, nutrients, and hormones—and the **umbilical cord**. The maternal side of the placenta develops from the endometrium (the inner lining of the uterus).

The embryonic phase of development begins about 15 days after conception and lasts until about 6 weeks after conception. During this month-long period the embryo transforms itself from a tiny plate of cells into a semblance of a human being, only 2 to 3 cm (about 1 inch) long but already in possession of all its major organ systems. A busy month indeed! (For a more detailed description of embryonic development, see **Web Topic 6.2 Principles of Embryonic Development**.)

Researchers have succeeded in isolating cells from the inner cell mass of human conceptuses (or embryos, as they are often called). These **embryonic stem cells** survive and divide in vitro (in a laboratory culture) and have the potential to develop into any specialized cell types, such as nerve cells or insulin-secreting cells. The possible medical use of embryonic stem cells is currently a topic of intense research.

**Fetal life involves growth and functional maturation**

The embryonic phase of development is complete by about 6 weeks after conception, at which point the embryo is referred to as a **fetus**. Subsequent fetal development involves mainly an increase in size (growth) and the functional maturation of body systems (**Figure 6.6**).
In several respects, the fetus takes control of its mother. For example, it secretes increasing levels of progesterone and estrogens. (More specifically, the fetal side of the placenta secretes progesterone, and the fetal adrenal gland secretes androgens that are then converted to estrogens by the placenta.) As a consequence, progesterone and estrogen levels in the mother’s blood rise to higher levels than at any other time in a woman’s life. These hormones ensure the maintenance of the uterus in a state conducive to pregnancy. Even though the corpus luteum in the mother’s ovary normally functions throughout pregnancy, its presence is not necessary after the placenta begins to secrete steroid hormones; in fact, pregnancy can continue after surgical removal of both ovaries. Another way in which these fetal hormones influence the mother to the fetus’s benefit is by promoting development of her breasts.

The fetus is not just smaller than an infant, but it is also different from one—especially in terms of its adaptation to life in the uterus. Its cardiovascular system, in particular, is organized quite differently: In the air-breathing child half the heart’s output goes to the lungs, but in the fetus the lungs serve no function, and they receive little blood. Also, the fetus’s hemoglobin—the oxygen-carrying molecule in its blood—is different from adult hemoglobin and is designed to operate at lower oxygen levels.

Yet the fetus also does many things that are surprisingly like the actions of an already-born child. It moves, of course—as a mother first notices around week 14 to 16 of pregnancy. Its kicks are most noticeable, but the fetus may also make more controlled movements, such as placing its thumb in its mouth. It responds to stimuli such as loud sounds with an increase in heart rate. It drinks copious amounts of amniotic fluid and voids dilute urine back into the fluid—any waste products cross the placenta and are eventually excreted in the mother’s urine. The fetus wakes and sleeps, and during sleep it has episodes of rapid eye movement (REM sleep—the phase that, in children and adults, is associated with vivid dreaming). During REM sleep the fetus contracts its diaphragm periodically: These “breathing” movements are essential for normal lung development.

The fetus is not yet a child, however. In particular, the development of the cerebral cortex, and its connections to other parts of the nervous system, is very incomplete, even at birth. It is plausible—though by no means documented—that a fetus can consciously experience pain, but it cannot establish durable memories. According to one study, however, late-term fetuses can distinguish between their mother’s voice and that of a female stranger, responding with an increase in heart rate to the former and a decrease to the latter (Kisilevsky et al., 2003).

Pregnancy and childbirth are described from the parents’ perspective in Chapter 11. Birth is not the end of development, of course. The phase that marks the onset of reproductive maturity is puberty, which we discuss in some detail toward the end of this chapter.

Genetic Sex Is Determined at Fertilization

Our understanding of sex determination is founded on a classic series of studies conducted by the French embryologist Alfred Jost in the 1940s (Jost, 1953). Jost removed the gonadal tissue from fetal rabbits very early in development (FIGURE 6.7). He found that, regardless of their genetic sex, these rabbits developed as females, albeit without ovaries. Jost concluded that male development involves a gene or genes that trigger the development of testes, which in turn release hormonal signals that masculinize the rest of the body. Female development, Jost correctly reasoned, is a “default” pathway—one that goes forward in the absence of specific genetic instructions to the contrary.
Sex is usually determined by the presence or absence of the Y-linked gene SRY

During the 1950s, the chromosomal basis of sex in mammals, including humans, was worked out. As already described in Chapter 2, males were found to include individuals with certain complements of sex chromosomes: XY (the usual pattern), plus unusual patterns such as XXY, XXXY, and XYY. Females were found to include individuals with certain other patterns: XX (the usual pattern), plus unusual patterns such as X and XXX. (The developmental consequences of these patterns are described in BOX 6.1.) In other words, any embryo that possesses at least one Y chromosome develops as a male; all others develop as females. (Below, we mention some unusual exceptions to this rule.) These findings mean that the father’s genetic contribution to the conceptus determines its sex because the fertilizing sperm contributes either an X or a Y chromosome, whereas the ovum always contributes an X chromosome. When researchers put these chromosomal observations together with Jost’s experimental results, it seemed that there should be a Y-linked gene (a gene located on the Y chromosome) that makes an embryo male by triggering the development of a testis and that the absence of this gene should permit an embryo to develop as a female. The identification of this gene, however, had to wait many years for the development of molecular genetic techniques applicable to the human genome.

In 1990, a British group reported success (Sinclair et al., 1990). They had studied the very rare individuals who disobeyed the chromosomal rules described above: people with XX chromosomes who nevertheless were male and people with XY chromosomes who nevertheless were female (FIGURE 6.8). It turned out that, in some of the XX males, a tiny fragment of a Y chromosome had “jumped” onto an X chromosome. (This must have happened during the development of the sperm that gave rise to these individuals.) Correspondingly, some of the XY females were missing the same tiny fragment from their Y chromosome. The British researchers identified a gene in this small region of the Y chromosome and named it SRY (for “Sex-determining Region of the Y chromosome”). Thus SRY is the gene that makes an embryo male, and embryos lacking SRY develop as females.

SRY and other genes direct the development of the gonads

It seems likely, then, that SRY somehow instructs the embryo to develop a testis. How does that happen? Both the testes and the ovaries develop from common, undifferentiated precursor structures called the genital ridges, which are clusters of mesodermal cells on either side of the aorta. To the side of each genital ridge is a transitory, kidney-like structure, the mesonephros, that ends up donating tissue to the gonads.

**FIGURE 6.8** The genetic basis of sex determination

The presence or absence of the SRY gene determines whether a fetus will become male or female.
The standard sets of sex chromosomes are XX (female) and XY (male). When nonstandard sets occur, they generally arise during one of the two meiotic cell divisions that give rise to male or female gametes. The anomalies described below are some of the most common.

**Turner Syndrome**
People with Turner syndrome have either a single X chromosome (‘XO’) or a single X chromosome plus a truncated portion of a second X chromosome. In either case, they lack a Y chromosome and therefore develop as females. Turner syndrome occurs in approximately 1 in 4000 live births and in an even higher fraction of all conceptions. (Many XO conceptuses die early in development.)

Girls with Turner syndrome usually lack normal ovaries. The germ cells that migrate into the embryonic ovaries require two X chromosomes for their survival and development as oocytes; therefore, in XO embryos the germ cells die. This, in turn, causes the ovaries to regress, leaving nothing but connective tissue (‘streak ovaries’). Therefore many girls with Turner syndrome lack gonadal hormones, do not enter puberty, and are infertile. They usually have short stature, and they may have a variety of other physical traits, such as an unusually broad chest and loose skin around the neck (‘neck webbing’). Cardiovascular and kidney defects may also occur. Individuals with Turner syndrome are not intellectually disabled, but they tend to have a characteristic array of cognitive deficits, including problems with visuospatial tasks, memory, and attention (Ross et al., 2000). These cognitive deficits are thought to result in part from the brain’s lack of exposure to gonadal steroids. Nevertheless plenty of women with Turner syndrome have been very successful in life: These include geneticist Dr. Catherine Ward Melver, current president of the Turner Syndrome Society of the United States (see figure).

Turner syndrome can be treated with growth hormone and androgens to increase childhood growth and with estrogens to induce the development of breasts and other secondary sexual characteristics. Appropriate regimens of estrogens and progesterone can lead to regular menstruation, and women with Turner syndrome can sustain pregnancy with the aid of egg donation and hormonal support.

**Klinefelter Syndrome**
People with Klinefelter syndrome have a single Y chromosome and two or more X chromosomes (XXY or XXXY). They are male because they possess the SRY gene on the Y chromosome. Klinefelter syndrome affects about 1 in 1000 live births.

XXY boys are physically healthy but tend to exhibit some degree of learning disability, especially with respect to language skills (Rovet et al., 1996). On the other hand, some XXY men do well at the college level and beyond. The full Klinefelter syndrome becomes apparent at puberty. It is marked to a variable degree by the following traits: tallness, small testes, gynecomastia (breast development in men), feminine body contours, and sparse facial and body hair. Men with Klinefelter syndrome have low testosterone levels and, in consequence, high levels of luteinizing hormone (LH). Their sperm counts are usually too low for normal fertility. Men with Klinefelter syndrome also tend to have a low sex drive. Nevertheless, these men may be able to become biological fathers by means of special in vitro techniques. Some aspects of Klinefelter syndrome can be alleviated by long-term treatment with testosterone injections or implants.

**XYY Syndrome**
People with one X and two Y chromosomes develop as males but may have genital anomalies and low fertility and tend to have low intelligence. This syndrome is nearly as common as Klinefelter (about 1 in 1500 live births).

A study of XYY men identified by routine chromosomal analysis at birth found a significantly increased rate of criminal convictions and antisocial behavior compared with XY males in the same birth cohort. Most of this increase was accounted for by the XYY men’s lower intelligence, however, rather than being an independent consequence of the chromosomal anomaly (Gotz et al., 1999).

**Triple-X Syndrome**
Triple-X syndrome is a mild disorder affecting about 1 in 2000 live births. The affected individuals have the XXX pattern and develop as females. There are some cognitive deficits, especially in verbal skills (Rovet & Netley, 1983), and fertility is low, but many XXX women are so similar to XX women that they remain undiagnosed.
The genital ridges develop at about 4 weeks postconception. A week or so later, cells within the genital ridges of male embryos begin to activate the SRY gene. Presumably, some higher-level gene, present in both sexes, attempts to turn on the SRY gene, but this instruction is obeyed only in males because only males have a SRY gene to activate.

SRY is active in the genital ridges for only a brief period. During this time it switches off genes that would otherwise promote development of the genital ridges into ovaries. Its main role, however, is to switch on genes that cause development of the genital ridges into testes (FIGURE 6.9). The most important of these genes is named SOX9. SOX9 remains active for a long period, directing and maintaining testicular development.

In females, the absence of SRY allows the genital ridge to develop into ovaries. Several genes, with names such as WNT4, DAX1, FOXL2, and RSPO1, are actively involved in this process (Kousta et al., 2010). The sequence in which these genes function has not yet been worked out, but one of them, FOXL2, is of particular interest. Knocking out this gene in an otherwise normal adult female mouse causes her ovaries to transform themselves into testes (Uhlenhaut et al., 2009). This happens because (as shown in Figure 6.9) FOXL2 normally suppresses the activity of SOX9, so with FOXL2 knocked out SOX9 switches on and converts the ovarian tissue into testicular tissue.

What we learn from this is that sexual differentiation in both sexes involves not just the activity of genes that promote the development of gonads appropriate to that sex, but also the suppression of genes that would otherwise promote the development of gonads appropriate to the other sex. What’s more, the maintenance of maleness or femaleness is a lifelong process whose details remain to be worked out. Thus—to gaze into a crystal ball, so to speak—it may eventually become possible to help transgender people change sex at a much deeper biological level than can be achieved at present. This might be accomplished by manipulating gene expression in their gonads and other reproductive organs.

Very occasionally, both ovarian and testicular tissues develop in the same individual. This atypical development is discussed in BOX 6.2.

Sexual Development Involves Growth or Breakdown of Precursor Structures

To produce a male or female human being requires the differentiation of many parts of the body: not just the gonads, but also the reproductive tract, the genitals, breasts, and many other organs, including the brain. A variety of developmental processes participate in the sexual differentiation of these various organ systems. Some operate within a few weeks of conception; others are delayed until puberty.

Primordial germ cells migrate into the developing gonads

Although the gonads develop from the genital ridges under the influence of genes such as the genes listed earlier, the gametes themselves—the sperm and the ova—do not originate in the gonads at all. Rather, they are the descendants of a group of cells generated in a transitory extraembryonic region of the conceptus known as the yolk sac.
Intersexuality is a broad term encompassing a variety of conditions marked by ambiguous or incomplete sexual differentiation. Many pediatricians prefer the term disorders of sex development (Lee et al., 2006), but some affected individuals consider that term prejudicial. Gonadal intersexuality refers to a rare kind of intersexuality in which a single individual possesses both testicular and ovarian tissue.

Another, more frequently used term for this condition is true hermaphroditism. Hermaphrodite, in Greek mythology, was a male–female figure parented by the gods Hermes and Aphrodite (Figure A). As described in Chapter 2, hermaphrodites are common or even the rule in some nonmammalian species. The addition of the modifier “true” distinguishes this condition from pseudohermaphroditism or nongonadal intersexuality (see Boxes 6.3 through 6.5), in which the gonads are entirely of one sex but nongonadal structures are sexually ambiguous.

We dislike the term “true hermaphrodite” for two reasons. First, the word “true” reflects an outdated notion that the gonads are the only “true” arbiters of a person’s sex. Second, the term “hermaphrodite” wrongly suggests that gonadal intersexes resemble hermaphroditic animals—that is, that they are capable of taking both the maternal and the paternal roles in reproduction, or even of producing offspring without engaging in sex at all. They cannot do so—in fact, the majority of intersexed individuals are infertile. Thus, we prefer—and in this text will use—the term “gonadal intersexuality.”

Persons with gonadal intersexuality may possess one ovary and one testis; more commonly, one or both gonads contain both ovarian and testicular tissue (ovotestes; Figure B) (Krob et al., 1994). Generally, the testicular tissue is poorly developed, whereas the ovarian tissue appears normal. The internal reproductive tracts and external genitalia are highly variable, but female structures usually predominate, and individuals affected by gonadal intersexuality tend to look like and identify as women. Several such women have become pregnant and successfully delivered children, but only one instance of a gonadally intersexed person fathering a child has been reported.

How does gonadal intersexuality arise? The majority of affected individuals have two XX chromosomes—the normal female pattern—and the reason they develop testicular tissue is not known. In some of these cases it may be that one X chromosome carries an SRY gene that has been translocated from a Y chromosome: testicular tissue could then arise in parts of the embryo in which that X chromosome is active.

A substantial minority of gonadally intersexed people are chromosomal chimeras, possessing some cells or tissue with the XY (male) pattern and some with the XX (female) pattern. Such chimerism can occur if two separate conceptuses of differing chromosomal sex fuse early in development. Alternatively, two sperm (one X, one Y) may penetrate a single ovum, one fertilizing the ovum itself and the other fertilizing one of the polar bodies, which then fails to degenerate and therefore contributes its progeny to the conceptus.

intersexed Having a biological sex that is ambiguous or intermediate between male and female.
disorders of sex development An alternative term for intersexed conditions.
gonadal intersexuality The existence of ovarian and testicular tissue in the same individual. Also called true Hermaphroditism.
true Hermaphroditism Outdated term for gonadal intersexuality.
About 4 weeks after conception, these primordial germ cells migrate into the embryo and home in on the developing genital ridges. It appears that they are attracted by some chemical signal put out by the cells of the genital ridges, for if the ridges are transplanted to some other part of the embryo’s body, the primordial germ cells will migrate to the ridges in their unusual location.

Once they have integrated themselves into the gonads, the primordial germ cells (or their descendants) develop into either the stem cells that will give rise to sperm (if they are in a testis) or primary oocytes (if they are in an ovary). Apparently the Sertoli cells (in males) and granulosa cells (in females) play a key role in guiding the developmental pathway of the germ cells.

**Male and female reproductive tracts develop from different precursors**

At about 6 weeks postconception, when the gonads are beginning to differentiate as ovaries or testes, two separate ducts run from the region of each gonad to the exterior of the embryonic body at the site of the future external genitalia. One of these, the Wolffian duct, is the excretory duct for the mesonephros. Because the mesonephros ends up contributing its tissue to the gonads, the Wolffian duct is in direct contact with the gonad. The other duct, the Müllerian duct, runs next to the gonad but does not actually contact it. The Wolffian and Müllerian ducts are the precursors of the male and female reproductive tracts, respectively (**FIGURE 6.11**).

To repeat: Embryos of both sexes possess a pair of both kinds of ducts. Thus male embryos are programmed to get rid of their Müllerian ducts and promote the development of their Wolffian ducts, while female embryos are programmed to get rid of their Wolffian ducts and promote the development of their Müllerian ducts.

**Primordial germ cells** The cells that give rise to oocytes and to the progenitors of sperm.

**Wolffian duct** One of two bilateral ducts in the embryo that give rise to the male reproductive tract.

**Müllerian duct** One of two bilateral ducts in the embryo that give rise to the female reproductive tract.
anti-müllerian hormone (AMH)
A peptide hormone secreted by Sertoli cells of the testis that prevents the development of the female internal reproductive tract.

For females, this process is relatively straightforward, requiring no outside instructions in the form of hormones or other signals. Thus, as originally shown by Jost, the surgical removal of the gonads from an embryo of either sex is followed by the spontaneous degeneration of the Wolffian ducts and the spontaneous development of the Müllerian ducts into the oviducts, uterus, and the deeper part of the vagina. (By “spontaneous” we mean “without external instructions.” Of course, many genes have to function within the developing female reproductive tract to produce the normal end product.)

Male embryos, on the other hand, have to override this intrinsic developmental program. Jost’s experiments led him to conclude that two hormones secreted by the developing testis accomplish this. These hormones have since been identified. First, the Sertoli cells secrete a protein known as anti-müllerian hormone (AMH). AMH binds to receptors in the vicinity of the Müllerian ducts and causes the ducts to regress and thus prevent development of the structures that derive from them—the oviducts, the uterus, and the inner portion of the vagina. The secreted testosterone, however, has no effect. The Wolffian ducts therefore fail to develop into the male reproductive tract, and the precursors of the external genitalia follow the “default” pathway, becoming the typical female structures—the clitoris, labia, and outer portion of the vagina. Even though testosterone is converted into the more potent hormone DHT in these target tissues, DHT is also without effect because it, too, normally binds to androgen receptors.

Newborn children may be diagnosed as having AIS because of a shallow vagina or because the testes are palpable as lumps in the groin. (They cannot descend farther because of the absent scrotum.) Many complete AIS babies are not diagnosed, however, and grow, play, and identify as normal girls.

Most girls with AIS who are not diagnosed during childhood are diagnosed at puberty or soon after. They usually visit a gynecologist because of a lack of pubic and axillary hair and because they do not begin to menstruate (primary amenorrhea). Teenagers with AIS do not develop acne or the usual adult body odor, both of which are androgen-dependent. They do develop breasts.

Adults with complete AIS tend to be taller than unaffected XX women (Marcus et al., 2000), possibly on account of the growth-promoting genes on the Y chromosome. Nevertheless, complete AIS adults look like women (see figure) and generally identify as such.

Medical treatment of AIS may include gonadectomy (removal of the testes, which, like all undescended testes,
carry an increased risk of cancer after puberty) and estrogen replacement (to prevent osteoporosis). Women with AIS may elect to have surgical revision of the vagina to make it adequate for coitus. Another possibility is to deepen and widen the vagina with dilators, but this stretching can sometimes occur naturally with sexual activity (see Figure 16.9B). As with most intersexed conditions, however, the medical problems of AIS are often perceived as trivial compared with the psychological trauma that may arise from deception by parents and doctors, stigmatization, and inappropriate treatment (see Box 6.8).

Complete AIS can be mimicked by other genetic conditions in which sensitivity to testosterone is normal but the levels of this hormone are abnormally low during development. These conditions include insensitivity to luteinizing hormone (LH), which is caused by an absence of the LH receptor; this condition deprives the Leydig cells of their signal to secrete testosterone. A similar condition is caused by a deficiency in one of the enzymes involved in the synthesis of testosterone. Unlike people with complete AIS, people with these other conditions will respond to exogenous testosterone with masculinization—which is an undesirable effect, of course, if the person identifies as female.

Children with partial AIS vary greatly in appearance, depending on how complete their insensitivity to androgens is. Some children with partial AIS have normal or near-normal male genitalia and are reared as boys. Some degree of breast development is likely to occur at puberty, however, and infertility in adulthood is a possibility. Others have ambiguous or near-normal female genitalia; most of these children are reared as girls. The genital appearance in partial AIS is mimicked by several other conditions including congenital adrenal hyperplasia (see Box 6.4).

pseudohermaphroditism Outdated term for intersexed conditions involving structures other than the gonads.

androgen insensitivity syndrome (AIS) An intersexed condition caused by absent or nonfunctional androgen receptors.

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**raphe**  The midline ridge of the perineum.

**urogenital sinus**  The common opening of the urinary and genital systems in the embryo.

The region of the fusion itself becomes the perineum. (Even in adults, the line of fusion is visible as a midline ridge or scar known as the **raphe**, which can be seen most easily with the help of a hand mirror.)

During the fetal period, the region in front of the fusion point, which includes the opening of the **urogenital sinus**, gives rise to the external genital structures in both sexes. As with the internal reproductive tracts, the female external genitalia develop by default; that is, in the absence of hormonal or other external instructions. Removal of the ovaries, for example, does not affect the process. (However, the process can be affected by a genetic defect in one of the enzymes involved in the synthesis of corticosteroids; this condition is called congenital adrenal hyperplasia [**Box 6.4**]). The genital swellings develop into the labia majora. The urethral folds develop into the labia minora, the outer one-third or so of the vagina, and the crura (deep erectile structures) of the clitoris. The genital tubercle develops into the glans of the clitoris. Remnants of the cloacal membrane persist as the hymen.
Congenital adrenal hyperplasia (CAH) involves a genetic defect in one of the enzymes that are involved in the synthesis of corticosteroid hormones in the adrenal cortex. (Corticosteroids have functions unrelated to sex, but they are made from the same precursor molecules that give rise to the sex steroid hormones.) Because of this defect, the production of corticosteroids is greatly reduced. The brain and pituitary gland sense this deficit and try to stimulate the adrenal cortex into increased production. The result is excessive growth (hyperplasia) of the adrenal cortex and an overproduction of the precursor steroids, which are then converted into a variety of androgens. The clinical syndrome results both from the lack of corticosteroids—which causes serious metabolic problems in either sex—and from the excess of androgens. The effects of the excess androgens show themselves in XX individuals (chromosomal females) as partial masculinization during fetal and postnatal development. In spite of this partial masculinization, the great majority of XX CAH children are raised as girls.

CAH is a recessive trait. If both parents carry a single defective copy of the gene, each of their children (of either sex) has a 1 in 4 chance of inheriting two defective copies and therefore of developing CAH. About 1 in 16,000 live-born children have the classic form of CAH (Carlson et al., 1999), but a larger number have milder forms of the condition. Among Ashkenazic (Central European) Jews, for example, 1 in 27 children has a mild form of the condition (New & Wilson, 1999).

The adrenal cortex begins secreting corticosteroids at about 6 weeks after conception. In CAH-affected fetuses, the excess secretion of androgens begins at some variable time after that. If the fetus is a chromosomal male (XY), the extra androgens are of little significance because the testes secrete large amounts of androgens in any case, and the male differentiation of the genitalia proceeds normally. (After birth, when androgen levels normally drop, the excess androgens in CAH boys may cause too-rapid growth and early puberty.)

If the fetus is a chromosomal female (XX), however, problems arise during fetal life. Since AMH is absent, the Müllerian ducts develop in the usual way, so all XX CAH children have a female internal reproductive tract. If the androgen excess occurs early enough in development, it may rescue the Wolffian ducts, which then persist along with the Müllerian duct structures. More commonly, the effects of the excess androgens are seen slightly later in fetal development, during the differentiation of the external genitalia. Although the outcome is variable, the newborn baby’s genitalia typically look like female genitalia that have been shifted in the male direction (masculinized). In particular, high levels of prenatal androgens may cause enlargement of the clitoris, and the labia may be partially fused at the midline to form a scrotum-like structure (see figure). If the condition is left untreated, further masculinization may occur at puberty.

Usually, however, the condition is recognized at birth and is treated by lifelong administration of corticosteroids. The treatment supplies the missing hormones and, by doing so, stops the compensatory overproduction of androgens. The masculinized genitalia are often “corrected” surgically by, for example, removing, shortening, or “recessing” the large clitoris early in life. This policy has recently been challenged by some people with CAH and by advocates for the intersexed.

It has recently become possible to treat CAH prenatally. At-risk fetuses can be treated with a synthetic corticosteroid, and this may minimize or prevent masculinization of the external genitalia. This treatment is still experimental, however, and it raises ethical issues (Dreger et al., 2010).

An interesting aspect of CAH from a scientific standpoint concerns the possible effects of the prenatal androgen exposure on the fetus’s brain and its later psychosexual development. We will postpone our discussion of this issue to Chapter 7.

**congenital adrenal hyperplasia (CAH)** A congenital defect of hormonal metabolism in the adrenal gland, causing the gland to secrete excessive levels of androgens.

**recessive trait** An inherited trait that shows itself only when the responsible gene is present on both homologous chromosomes.
The development of the vagina from two different sources is reflected in its anatomical differences in adult women, alluded to in Chapter 3. The outer portion of the vagina, which develops from the urethral folds, is more muscular and more richly innervated than the inner portion, which develops from the Müllerian ducts.

In male fetuses, the presence of circulating testosterone, secreted by the testes, is required for the normal development of the male genitalia. As with the prostate gland, testosterone has to be converted to the more potent androgen DHT for full genital development. The conversion is performed by the enzyme 5α-reductase. (BOX 6.5 examines the atypical development that occurs as a result of 5α-reductase deficiency.) DHT binds to androgen receptors in the genital tissue and triggers several processes. The urethral folds fuse at the midline, forming the shaft of the penis and enclosing the urethra. (If this midline fusion fails to occur, a condition called hypospadias results, as discussed in BOX 6.6.) The genital swellings also fuse at the midline, forming the scrotum. The genital tubercle expands to form the glans of the penis. The prostate gland—and probably the homologous paraurethral glands in females—develops from the walls of the urogenital sinus, beneath the urethral folds.

Thus, we can define the following homologies: The male scrotum is homologous to the female labia majora, the shaft of the penis is homologous to the labia minora, and the glans of the penis is homologous to the glans of the clitoris. These homologies are approximate; some tissue from the urethral folds probably contributes to the deeper clitoral structures in women, for example.

**The gonads descend during development**

In fetuses of both sexes, the gonads move downward from their site of origin in the upper lumbar region of the embryo. By about 10 weeks postconception, they are positioned at the rim of the pelvis. In females, the ovaries remain in this position for the remainder of fetal life, but after birth they descend in the pelvis and end up on either side of the uterus.

In males, the movement of the testes is even greater. At 6 to 7 months postconception they descend into the pelvis, and shortly before birth they enter the scrotum. Key to this process are paired structures called gubernacula. Each gubernaculum is a fibrous band that attaches at one end to the testis and, at the other end, to the abdominal wall near the developing pubic bone. Because the gubernacula do not lengthen as the fetal body grows, they pull the testes farther and farther downward during fetal life. As the testes enter the scrotum, they draw various structures with them: the vas deferens, blood vessels, and nerves, as well as a portion of the peritoneal lining of the abdominal cavity (FIGURE 6.13). Collectively, these structures contribute to the...
The enzyme 5α-reductase, which is normally present in some androgen target tissues, such as the external genitalia, skin, and prostate gland, converts testosterone to the more potent androgen 5α-dihydrotestosterone, or DHT. Like congenital adrenal hyperplasia, 5α-reductase deficiency is an autosomal recessive trait that causes a form of intersexuality. For the most part it is very rare, but the condition tends to crop up in clusters in genetically isolated communities. The first and most thoroughly studied of these clusters is in the village of Salinas in the Dominican Republic. In 1974, Julianne Imperato-McGinley of Cornell University Medical College, along with several colleagues, reported that 24 XY individuals in the village had an intersexed condition caused by 5α-reductase deficiency (Imperato-McGinley et al., 1974).

Since the affected individuals are chromosomal males (XY), they develop testes. The testicular hormones, AMH and testosterone, as well as the receptors for these hormones, function normally. Therefore the affected fetuses develop the internal reproductive structures of males, and the female (Müllerian duct) structures regress. But the external genitalia do not fully develop in the male direction without the presence of DHT. Often they consist of labia-like structures instead of a scrotum, a urogenital sinus into which a blind vaginal pouch and the urethra open, and a phallus that resembles a clitoris more than a penis (Figure A). The testicles may be in the labia or in the inguinal canal. The prostate gland is present but small.

The affected individuals are raised as girls or, in communities that are familiar with the syndrome, as intersexed children. The increase in testosterone levels at puberty, however, is able to accomplish much of what was left undone earlier: the skin of the scrotum becomes pigmented and corrugated, the testes descend if they were in the inguinal canal, and the phallus enlarges to resemble a penis (Figure B). The rest of the body also changes in the male direction: There is a great increase in muscularity, the voice deepens, and there is no breast development. In effect, girls seem to grow into men. Only a few traits are completely DHT dependent and therefore do not appear in 5α-reductase-deficient individuals; these traits include acne and a receding hairline. Facial hair is sparse.

One of the most interesting and controversial aspects of the 5α-reductase story is how the affected individuals respond to their apparent change of sex at puberty. We will postpone our discussion of this matter, however, until Chapter 7. (Photographs courtesy of Julianne Imperato-McGinley.)
Hypospadias is a condition seen in males when the urethral folds fail to fully enclose the urethra (Kraft et al., 2010). The urethra then opens on the lower surface of the glans, close to the normal position (see figure); on the shaft of the penis; at the base of the penis; on the front of the scrotum; or even on the perineum behind the scrotum. The abnormal opening may be in addition to the regular opening at the tip of the penis or may replace it. Hypospadias is common: As many as 1 in 350 boys has hypospadias severe enough to require surgical repair (Aho et al., 2000), and far greater numbers have milder forms of the condition. In fact, German urologists examined the location of the urethral opening in 500 ”normal” men and found that only 55% of them had an opening in the supposedly ”normal” position at the very tip of the glans. In the other 45% the opening was located slightly behind the tip on the ventral surface of the glans, or at the level of the corona. Such positioning of the opening did not impair the men’s ability to discharge a single stream of urine, to engage in coitus, or to father children (Fichtner et al., 1995).

The cause of hypospadias in individual cases is not usually known. The condition is thought to result from a variety of endocrinological factors, such as deficits in testosterone synthesis or in the conversion of testosterone to DHT, or from exposure of the mother to steroidal drugs, especially progestins. A variety of techniques, comparable to those used in female-to-male sex reassignment surgery, are employed to repair severe hypospadias. Noting the benign effect of the mild forms of hypospadias, the German urologists questioned whether surgical repair is warranted when these forms are seen in newborns.

Micropenis means an unusually small penis—less than about 2 cm (0.8 inches) in stretched length—in a newborn male (Tsang, 2010). This condition, which affects about 2% of boys (depending on exact definitions), can arise from a wide variety of causes, and it is sometimes associated with hypospadias. The treatment of micropenis is controversial. In most cases the penis can be induced to grow larger with a few months’ treatment with testosterone, and there are also surgical techniques that can enlarge the penis in early childhood. Sometimes the penis is judged inadequate, and the child may be surgically reassigned as a girl. Whichever course is taken, dissatisfaction with the genitalia in adulthood is common (Wisniewski et al., 2001). Nevertheless, children with micropenis who are allowed to grow up as male generally develop into heterosexual men with a strong male identity, enjoy an active sex life, and are indistinguishable from other men in terms of their general mental health (Reilly & Woodhouse, 1989; Lee & Houk, 2004). Thus, the justification for sex reassignment in young children with micropenis has been questioned (Calikoglu, 1999).

When older boys are seen by pediatricians on account of a small penis, the real culprit is often obesity, which can cause an average-sized penis to become partially hidden in the pubic fat pad.

**Atypical Development: Hypospadias and Micropenis**

**Hypospadias** is an abnormal location of the urethral meatus on the underside of the glans, the shaft of the penis, or elsewhere.

**Micropenis** means a penis shorter than about 2 cm (0.8 inches) in stretched length at birth.
spermatic cord. Although the testes sit in sac-like spaces that are developmentally part of the abdominal cavity, the connection between these spaces and the pelvic cavity is usually sealed off after the testes descend. Thus, even though the cremaster muscle can pull the testes upward in the scrotal sac, the testes cannot move all the way back into the pelvis.

Because the Wolffian ducts are attached to the developing testes before the descent begins, the vasa deferentia (which form from the Wolffian ducts) are drawn out along the course of the descent. That is why the vasa deferentia of adult men take a route that seems unnecessarily circuitous, arching upward over the ureters before they turn downward and medially toward the prostate gland. The kidneys, by moving upward during development, contribute to this circuitous route.

In 2% to 5% of full-term newborn boys, one or both testicles have not yet arrived in the scrotum. In many of these boys, the tardy testicles arrive within a few weeks after birth, but if they are still no-shows at 3 months, the condition is considered pathological and is named cryptorchidism. About 1% of boys have this condition (Inan et al., 2008). Usually, the missing testicles have been held up somewhere along the path of their fetal descent—most commonly, in the inguinal canal. Cryptorchidism is associated with lowered fertility and with an increased risk of testicular cancer after puberty. Undescended testicles can often be surgically moved into the scrotum; this procedure is best done before 2 years of age (Lim et al., 2003). If the testicles are near their goal, they may be induced to complete their descent by treatment with gonadotropins or with gonadotropin-releasing hormone (GnRH). Correction of cryptorchidism improves the prospects for fertility but does not eliminate the increased risk of cancer. Once they are in the scrotum, however, the testes can be monitored by regular self-examination, thus increasing the likelihood that any cancer that does develop will be detected at an early stage.

**Hormones Influence the Sexual Differentiation of the Central Nervous System**

Like male and female bodies, male and female brains differ from each other. These differences contribute to sex differences in cognition, personality, and sexuality. We therefore turn our attention to these brain differences and ask how they arise.

**The CNS contains sexually dimorphic structures**

We described in Chapter 4 how parts of the central nervous system (CNS) differ in structure between the two sexes. The example we cited was Onuf’s nucleus in the sacral level of the spinal cord. (Recall from Chapter 4 that “nucleus,” in neuroanatomy, means a cluster of nerve cells, not the nucleus of a cell.) Onuf’s nucleus contains the cell bodies of the motor neurons that innervate some of the striated muscles of the pelvic floor, including those associated with the root of the penis. Onuf’s nucleus is larger, and contains more neurons, in men than in women. (See also Web Topic 6.3 Sexual Dimorphism Can Arise as an Indirect Effect of Hormonal Levels.)

The brain also contains sexually dimorphic cell groups. The most extensively studied of these is a cell group in the medial preoptic area, the frontmost portion of the hypothalamus. The medial preoptic area is involved (at least in laboratory animals) in the generation of sexual behavior typically shown by males (“male-typical” sexual behavior), such as mounting, intromission, and ejaculation, and it may be involved in higher-level traits, such as partner choice, as well. In some species, damage to this area in male animals results in the display of behavior patterns typically shown by males.
third interstitial nucleus of the anterior hypothalamus (INAH3) A sexually dimorphic cell group in the medial preoptic area of the human hypothalamus.

sexually dimorphic nucleus of the preoptic area (SDN-POA) A cell group in the medial preoptic area of the hypothalamus of rodents that is larger in males than in females.

Sexual dimorphism arises as a consequence of differing hormonal levels during a sensitive period

How do sex differences in the structure of the CNS arise during fetal development? The best-documented cause is the same as the main cause of sex differences in the rest of the body—the higher levels of circulating androgens in males than in females during development.

Roger Gorski and his colleagues at UCLA studied the development of a sexually dimorphic cell group in the rat’s hypothalamus named the sexually dimorphic nucleus of the preoptic area (SDN-POA) (Davis et al., 1995). This cell group may be equivalent to the human cell group INAH3 mentioned above. They found that female rats could be induced to develop a large (male-sized) SDN-POA by administration of testosterone and that male rats could be induced to develop a small (female-sized) SDN-POA females (Kindon et al., 1996; Paredes et al., 1998). Thus, the medial preoptic area may normally play a role in the active suppression of female-typical behavior.

Within the medial preoptic area is a cell group that is larger (on average, at least) in males than in females. In humans it has the name third interstitial nucleus of the anterior hypothalamus, or INAH3 (Allen et al., 1989; Byne, 1998) (FIGURE 6.14). It is the best-studied cell group out of a number of nuclei in the base of the brain that are larger in males than in females (Allen & Gorski, 1990). In Chapter 14 we’ll review evidence that the size of INAH3 in men is related to their sexual orientation.

The introduction of advanced imaging techniques has led to the discovery of numerous structural, functional, and chemical differences throughout the brains of men and women. In terms of structure, for example, the two cerebral hemispheres are about the same size in women, but in men the right hemisphere is usually slightly larger than the left (Savic & Lindstrom, 2008). In addition, several regions within the cerebral cortex are larger in volume (relative to the volume of the entire brain) in one sex or the other (Goldstein et al., 2001). As an example of a functional difference, a brain structure named the amygdala is involved in the encoding of emotionally laden experiences into memory, but men use the right amygdala for this task, while women use the left amygdala (Canli et al., 2002). And in the realm of chemistry, men’s brains produce serotonin—a neurotransmitter involved in the regulation of mood—at a higher rate than do women’s brains. In the case of another neurotransmitter, dopamine, it’s the other way around (Cosgrove et al., 2007). Such differences could underlie differences in the prevalence of certain mental disorders in the two sexes: Depression, for example, is twice as common in women, whereas alcoholism is twice as common in men (World Health Organization, 2011).
Sensitive period

A period of development during which the survival or growth of a biological system depends on the presence of some factor, such as a hormone.

by castration—that is, by removal of the rat’s own supply of testosterone. In either case, however, the manipulation had to be done during a restricted sensitive period of development (Figure 6.15). In rats, this period begins a few days before birth and ends soon after birth. Comparable treatments in adult rats have little or no effect on the size of the nucleus.

Gorski’s group found that about the same numbers of SDN-POA neurons are generated in both sexes. Thus, testosterone does not influence this initial step in the development of the sexually dimorphic nucleus. Rather, it influences the survival of SDN-POA neurons. Soon after they have begun to form the nucleus, SDN-POA neurons produce androgen receptors and, in fact, become dependent on the presence of testosterone for their survival. Thus, in females, whose testosterone levels are low, the majority of SDN-POA neurons die. These cells can be “rescued” not only by systemic administration of testosterone, but also by local injections of miniscule quantities of the same hormone into the hypothalamus itself. This finding supports the notion that androgens act directly on the SDN-POA neurons to promote their survival and development.

We have no direct evidence as to whether similar processes guide the sexual differentiation of INAH3 in humans. If they do, it’s likely that the sensitive period is well before birth, rather than around the time of birth, as with rats. That’s because humans, with their longer period of development in utero (9 months, versus 3 weeks for rats), are born at a much later stage of brain development.

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mounting  A male-typical sexual behavior: climbing onto the female to reach a position in which intromission is possible. (Used mostly for nonhuman animals.)

lordosis  In female rodents, an inverse arching of the back that exposes the vulva for intromission by a male.

activational effect  The influence of a sex hormone on the function of brain circuitry in adulthood.

organizational effect  The influence of a sex hormone on the development of brain circuitry.

**Early Hormonal Exposure Influences Later Sexual Behavior**

Hormone levels during development not only guide the development of anatomical differences between male and female brains; they also have some influence on an animal’s or person’s sexual behavior in adulthood. Of course, the evidence for this statement comes mostly from animal experiments, which we discuss first. It is impossible, both for ethical reasons and because of the prolonged time course of human development, to do equivalent experiments on humans. Still, as we will see later in this chapter and in subsequent chapters, there are enough clues from a variety of sources to conclude that the animal results are at least partially applicable to humans.

**Experiments on rodents show activational and organizational effects of androgens**

The key observations of animal sexual behavior were made by a group at the University of Texas, led by William Young, in the 1950s and 1960s (Phoenix et al., 1959). Young’s group studied mounting and lordosis, the mating behaviors typically shown by male and female rodents, respectively. When mounting, the male approaches the female from the rear and places his forequarters on her rump. Lordosis is the response to mounting shown by a receptive female. She bends her back into a U shape and deflects her tail, thus raising and exposing her vulva for intromission by the male (FIGURE 6.16). Female rodents rarely mount other animals, and male rodents rarely display lordosis in response to being mounted.

If an adult female rodent is injected with sufficient testosterone to produce male-like levels of the hormone in her blood, she will begin to mount receptive females. If an adult male is castrated, removing his source of testosterone, he will stop mounting. Thus, it is simply the level of testosterone in adulthood that determines whether a rodent mounts or not. This direct effect of a hormone on a behavior in adulthood is called an activational effect.

The situation with lordosis is quite different. If an adult male rat is castrated (by removal of his testosterone source) and treated with estrogens, thus mimicking a female hormonal environment, he will not show lordosis behavior. But if a male rat is castrated early in development and treated with estrogens when he is adult, he will display lordosis (FIGURE 6.17). Conversely, if a female rat is treated with testosterone early in development, she will not display lordosis in adulthood, no matter what hormones she is given. In other words, the levels of testosterone during development determine whether a rodent is capable of showing lordosis when exposed to estrogens in adulthood—high levels of testosterone prevent lordosis; low levels permit it. This is called an organizational effect because the levels of testosterone during development permanently affect the organization of the brain circuitry responsible for a given behavior.

The experiments just described were focused on the motor patterns shown by rodents during sex—mounting or lordosis. In other studies, the animal had to choose between a male and a female partner. This, then, was a test of what we might, in humans, call “sexual orientation.” It turns out that organizational effects of testosterone play an important role here: Female rats that were exposed to high levels of testosterone during development are shifted in their partner preference toward females (de Jonge et al., 1988), and males in which the synthesis or action of testosterone was blocked during development are shifted toward preferring male partners (Bakker et al., 1993). Similar effects have been described in a variety of other species.

For more information on the basis of organizational and activational effects, please see Web Topic 6.4 Organizational and Activational Effects of Hormones on the Brain.
**Primates have multiple sensitive periods**

How relevant is all this to human sexuality? One way of approaching this question is by extending the rodent research to primates. Researchers led by Robert Goy conducted a multiyear study of female macaque monkeys that had been treated with testosterone during fetal life. Goy’s group obtained results comparable to what had already been observed in rats and guinea pigs. Even before puberty, the effects of the prenatal testosterone exposure were obvious. Prepubescent monkeys engage in a lot of “play-sex,” in which one monkey mounts but does not penetrate another. Males take the mounting role more commonly than do females. Goy’s prenatally treated females also commonly took the mounting role in play-sex. This “masculinization” affected other traits besides play-sex behavior. For example, male prepubescent monkeys typically engage in more “play-fighting” or “rough-and-tumble play” than do females, but prenatal treatment with testosterone increased young female monkeys’ engagement in these activities (Goy et al., 1988; Wallen, 1996).

After the treated females reached puberty, Goy’s group tested their adult sexual behavior (Pomerantz et al., 1986). They first removed the ovaries from the monkeys and gave them a series of testosterone injections, thus simulating the hormonal environment of a normal adult male monkey. The females who had been exposed to testosterone prenatally responded to this endocrinological sex reversal by showing male-typical sexual behavior, especially a style of mounting called the “footclasp mount,” in which the mounting animal raises itself on the feet or hind legs of the other animal (FIGURE 6.18). Such behavior was not shown by a comparison group of female monkeys that experienced normal prenatal development, even though they were subjected to the same endocrinological manipulation (ovary removal and testosterone treatment) in adulthood. Thus, it was organizational effects of the prenatal exposure to testosterone, in combination with activational effects of the testosterone treatment in adulthood, that caused Goy’s females to perform adult-style mounting.

Goy and his colleagues found that monkeys have not just a single “sensitive period,” but several. For example, testosterone treatment of females early in fetal life was most effective in promoting mounting behavior, but treatment later in fetal life was most effective in promoting rough-and-tumble play (Goy et al., 1988). It thus appears that the brain circuits mediating different kinds of sex-differentiated behaviors mature at different times and become sensitive to testosterone levels at different times. It is therefore possible, by precise timing of testosterone treatments,
not merely to dissociate a monkey’s behavior from its anatomy (in other words, producing a monkey with female genitalia but male-like sexual behavior), but it is also possible to dissociate one kind of sex-typical behavior from another (producing a female that participates in rough-and-tumble play but not in male-like play-sex behavior, for example).

We will defer our main discussion of the development of human sexual behavior until later chapters. We will make the case, however, that the observations on rodents and primates that we have just described are relevant to human sexual development.

Estrogens seem to play little role in prenatal sexual development. The ovaries do not produce significant quantities of sex steroids before birth. Estrogens are present in embryos and fetuses of both sexes—in particular, they reach the fetus from the mother’s circulation, and they are also manufactured by the placenta from androgens secreted by the testes (in males) or the adrenal gland (in both sexes). That these estrogens can influence fetal development to some degree is illustrated by the fact that some newborn infants have visible breast development and may even secrete milk (so-called witch’s milk) for a short time. In general, however, it seems that the fetus, and particularly its brain, is protected from the effects of external estrogens. These protective mechanisms include the chemical alteration of estrogens as they enter the fetal circulation and the existence of binding proteins that lower the levels of the free steroids. Furthermore, laboratory animals and humans that are insensitive to estrogens because of a congenital absence of estrogen receptors experience no obvious abnormalities of prenatal development (Korach et al., 1996). This stands in marked contrast to the situation of genetic males who lack androgen receptors: Their fetal development is radically affected (see Box 6.3).

**Other Y-Linked Genes Besides SRY Influence Development**

So far, we have attributed prenatal sexual differentiation almost entirely to the secretions of the developing testis—AMH and androgens—in males, and to the lack or low levels of comparable hormones in females. Because testis development is controlled by the gene SRY, this model places the responsibility for sexual differentiation on the presence (in males) or the absence (in females) of SRY, in line with the original hypothesis spelled out by Alfred Jost in the 1940s. But this model is probably incomplete. In particular, other genes on the Y chromosome besides SRY influence sexual development. Several Y-linked genes are involved in spermatogenesis (Affara & Mitchell, 2000). Thus, the rare XX individuals who are male by virtue of having a SRY gene that has jumped from a Y to an X chromosome during spermatogenesis, as described earlier, have defective spermatogenesis and are sterile because they lack these other Y-linked genes.

At least one gene on the Y chromosome increases stature, and a part of the reason that men are, on average, taller than women is the fact that they possess this gene (Salo et al., 1995). In fact, it has been reported that male conceptuses grow faster than female conceptuses even before implantation (and therefore long before the testis has begun to secrete hormones). Again, this difference is due to a gene on the Y chromosome that is different from SRY (Burgoyne et al., 1995).

Finally, studies on sex-reversed mice indicate that some differences in brain organization and behavior between male and female mice are influenced by genetic mechanisms that do not involve the SRY-testis-hormone cascade (Ngun et al., 2011). Thus, the “classical” mechanism postulated by Jost, while unquestionably of central importance in sexual differentiation, is not the entire story. The nonclassical mechanisms remain to be elucidated.
External Factors Influence Prenatal Sexual Development

Increasing evidence from animal studies suggests that environmental factors operating during pregnancy can affect the sexual development of fetuses. In rats, for example, subjecting a pregnant female to stress (such as forced immobilization or bright lights) or administering alcohol to her affects the later sexual behavior of her male offspring. In general, these males are partially “demasculinized” in their sexual behavior: They are less ready to approach and mount receptive females, and they ejaculate less often than untreated male rats (Ward et al., 1994). Also, anatomical and chemical changes in the brains of these prenatally stressed rats are consistent with demasculinization: The volume of the SDN-POA is reduced, and the levels of some neurotransmitters and related compounds are more similar to those typically found in females than in males (Anderson et al., 1986; Reznikov et al., 1999).

Although alcohol and stress can affect fetal development in humans, too, little evidence points to specific effects on sexual development. One external factor that can affect human sexual development is the administration of sex hormones or related drugs to pregnant women. Between 1938 and 1971, several million pregnant women in the United States were given the drug diethylstilbestrol (DES), a synthetic estrogen agonist. It was prescribed for women who were at increased risk of miscarriage and even for average-risk women. We now know that DES does not prevent miscarriage and in fact may make miscarriage more likely. Administration of the drug to pregnant women was halted when it was found that it caused serious health problems for some of the female children born to those women. About 1 in 1000 of these girls, when they reached young adulthood, developed a cancer of the cervix or vagina that is normally very rare in that age range (Herbst, 1999). Women exposed to DES in utero may also have an increased risk of breast cancer later in life (Palmer et al., 2002). Others have had fertility problems, and some have anatomical abnormalities of the reproductive tract. Males exposed to DES in utero have an increased risk of genitourinary malformations, but their fertility is not impaired (Wilcox et al., 1995a; Perez et al., 2005). The DES experience highlights the dangers of administering hormone-related drugs to pregnant women.

Biological and social factors interact postnatally

One of the most common misconceptions about genes and development is that genes run the whole show before birth, and the environment takes over after birth. We’ve just seen how the environment (meaning, in this case, the mother, as well as factors external to her) can influence prenatal development. Conversely, genes continue to play a major role in postnatal development. Still, it is true that there are far more opportunities for the environment to influence development once a fetus has left the protective cocoon of its mother’s uterus.

We will have much more to say about postnatal sexual development in later chapters, but we should mention here a couple of examples of ways in which environmental factors influence development during the period between birth and puberty. One such example concerns social isolation. A research group led by psychobiologist Marc Breedlove compared the effects of housing rats one to a cage and in groups from the time of weaning through adulthood (Cooke et al., 2000). They found that male rats raised in isolation were less likely than group-raised rats to respond, with a penile erection, to the presence of an estrous female or to achieve intromission with a female. The isolation also led to anatomical changes in brain organization.
Researchers led by Kim Wallen have conducted a multi-year study of the interaction of hormonal and social factors in the sexual development of rhesus monkeys and other nonhuman primates (Wallen, 1996, 2001). One example of their findings: Monkeys reared in same-sex peer groups show sexual behavior (during their juvenile life at least) different from that of monkeys raised in mixed-sex peer groups. In either type of rearing environment, males display more mounting behavior than do females—this difference results from their different prenatal hormonal exposure. But the sex difference in mounting behavior is much less marked among monkeys raised in same-sex groups than among those raised in mixed-sex groups. Apparently, exposure to female peers increases the propensity of male juveniles to mount other animals (of either sex), whereas exposure to male peers diminishes the propensity of female juveniles to mount other animals. Thus, prenatal hormone exposure does not rigidly predestine animals’ sexual behavior, but it generates a predisposition that can be modified by social circumstances.

**Puberty Marks Sexual Maturation**

During early infancy, the levels of circulating gonadotropins (LH and FSH) are high in both sexes. In girls, the presence of these hormones does not have major or consistent effects on the secretion of hormones by the ovaries, which remains very low throughout childhood. In infant boys, however, the gonadotropins spur the secretion of enough testosterone by the testes to bring circulating testosterone to adultlike levels (Andersson et al., 1998). The function, if any, of this brief postnatal testosterone surge is not known. By about 6 to 9 months of age, testosterone sinks back to very low levels and remains low until puberty, the time at which biological changes make an individual capable of sexual reproduction.

Although there are no marked differences in sex hormone levels between girls and boys throughout most of childhood, there are sex differences in personality and behavior. In part, these differences reflect the different androgen levels to which girls and boys were exposed during fetal life. We will discuss this topic further in Chapter 7.

**The pubertal growth spurt occurs earlier in girls than in boys**

The most obvious biological process during childhood is growth (FIGURE 6.19). The rate of growth decreases over time: At the age of 1 year a child is growing in height at a rate of 15 to 20 cm (6 to 8 inches) per year, but by shortly before puberty, growth has slowed to about 5 cm (2 inches) per year. Then comes the pubertal (puberty-associated) growth spurt, in which the growth rate rises briefly to a peak of about 10 cm (4 inches) per year.

The pubertal growth spurt results in a height gain of about 25 cm (10 inches) for girls and 28 cm (11 inches) for boys. About 2 years after the beginning of the growth spurt, however, growth in height finally ceases, as the growth zones in the long bones cease to function and they close (that is, they become solid bone). There is considerable individual variation in the timing of the pubertal growth spurt, but in the contemporary U.S. population it begins at an average age of about 11 (for girls) or 13 (for boys). The age difference allows for about 2 years
The first stage of breast development at puberty.

The spurt in height is not the only change in growth during puberty. The structure of the skeleton also changes, with girls developing wider hips and boys developing wider shoulders. Body composition also changes: By adulthood, men have 50% more bone and muscle mass than women, and women have twice as much body fat as men. Of course, these are very much statements about averages—there are plenty of muscular women and fat men. Genes influence variations in body composition among individuals of the same sex, and factors such as food availability and athletic training can greatly modify the effects of biological predispositions.

Puberty is marked by visible and invisible changes in the body

More directly relevant to sexuality are pubertal changes in the external genitalia, secondary sexual characteristics, internal reproductive tract, and gonads. In girls, the most noticeable change in the external genitalia is the growth of pubic hair (FIGURE 6.20), but, in addition, the labia majora and labia minora become more prominent, the vagina deepens, and the vaginal wall thickens. Axillary (armpit) hair appears a little later than pubic hair.

The most important secondary female sexual characteristic to appear at puberty is the breasts. Breast development goes through several stages (FIGURE 6.21). The breast first shows itself as a small mound—the breast bud—centered on the nipple. As breast development continues, both the nipple and the surrounding areola come to project forward from the breast, and the areola enlarges. With the completion of breast development, the areola lies flush with the breast once more, and only the nipple projects.

Inside a girl’s body, puberty is marked by a spurt of growth in the ovaries, uterus, and oviducts. The oviducts, which before puberty have a somewhat contorted course, become straighter. The cervix begins to produce the characteristic secretions of adult life. And in the ovaries, the recruitment of primordial follicles into the process of follicular maturation begins.

FIGURE 6.20  Typical development of pubic hair in girls at puberty

(A) Prepubertal state: No hair is visible. (B) Sparse, long, downy hair grows along labia. This stage occurs at about 8.8 years in African-Americans and about 10.5 years in white Americans, but with considerable variability. (C) Coarser, curly hair grows along labia. (D) Hair covers labia. (E) Hair spreads over mons veneris but not to the adult extent or density. (F) Hair forms adult-like “inverse triangle” and extends to inner surface of thighs; this final pattern varies considerably among women. (From van Wieringen et al., 1971.)

FIGURE 6.21  Typical development of breasts in girls at puberty

seen in side and frontal views. (A) Prepubertal appearance. (B) Breast bud stage: Nipple, areola, and nearby breast tissue form a small mound at about 8.9 years (for African-American girls) or about 10 years (for white American girls). (C) Further enlargement of areola and breast. (D) Nipple and areola project out from breast. (E) Adultlike stage: Areola is now flush with the breast; only the nipple projects forward. (From van Wieringen et al., 1971.)
Can a girl become pregnant before her first period?

Yes. If she ovulates on her first menstrual cycle (which doesn’t always happen), she can become pregnant before her first period, which would normally occur two weeks later. If she does become pregnant her first period won’t occur, but since she’s not expecting a period she might not discover the pregnancy for many weeks.

The most noteworthy event in a girl’s puberty is the onset of menstruation, called menarche (pronunciations vary—MEN-ar-kee is as good as any). Because menarche is an event rather than a process, and a highly memorable one at that for many women, it is commonly used to date female puberty, even though it occurs long after the beginning of puberty. In the contemporary U.S. population, the average age at menarche is 12 to 13 years, but the range of 11 to 17, or even 10 to 18, is considered normal. There are also ethnic differences within the U.S. population—the average age at menarche is 12.2 for African-American girls and 12.9 for white girls (Herman-Giddens et al., 1997).

There has been a historical trend toward earlier menarche in a number of Western countries (FIGURE 6.22). In mid-19th-century Europe, the average age at menarche may have been as high as 16 to 17, although there is some uncertainty about the accuracy of these records. In the United States at the beginning of the 20th century, it was about 14. Age at menarche decreased at an average rate of more than 1 month per decade during most of the 20th century (McDowell et al., 2007). This trend is continuing: According to a large Danish study, the average age of menarche dropped by nearly 3 months between 1991 and 2006, and the age of breast development dropped by a year over the same time span (Aksglaede et al., 2009).

The average timetable for the visible events of female puberty in the U.S. white population is roughly as follows: Breast development begins at 10, pubic hair appears at 10.5, and menarche occurs at 12.9. In the U.S. African-American population, pubic hair appears at an average age of 8.8, breast development begins at 8.9, and menarche is at 12.2 (Herman-Giddens et al., 1997). In both populations, the pubertal growth spurt peaks about 1 year before menarche.

Menstruation may be irregular for the first year or two after menarche. Furthermore, the initial menstrual cycles tend to be anovulatory. For this reason, a young woman may not be capable of becoming pregnant for a year or so after menarche. However, there is much variation in this respect, and the fact that a young woman has only recently begun to menstruate should not lead her to believe that she is incapable of conceiving.

For boys, an early sign of puberty is the enlargement of the testicles and scrotum, which begins at the age of 10 to 13 (FIGURE 6.23). Between 11 and 15, the penis grows in length and then in girth, and pubic hair appears. During the same period, the larynx (voice box) grows and the vocal cords thicken, leading to a deepening of the voice. The rate of pubertal growth peaks at about 14.

First ejaculation, which occurs at about age 13, may occur with masturbation or during sleep (a nocturnal emission). Initially, the semen may lack mature spermatozoa; in fact, a male can be infertile for a year or two after his first ejaculation. As with girls soon after menarche, however, there is no guarantee on this point.

Many boys experience transient development of breasts (adolescent gynecomastia) during mid-puberty: about half of all boys do so, according to one longitudinal study (Biro et al., 1990). These boys tend to have relatively low levels of free testosterone in their blood, but the precise hormonal mechanism of adolescent gynecomastia is not well understood. The enlarged breasts nearly always disappear without treatment.

Facial and axillary hair begins to appear about 2 years after the growth of pubic hair. Body hair may appear soon thereafter, especially on the chest, but its appearance is highly variable among individuals and among ethnic groups. Recession of the scalp hairline at the temples may occur soon after the
other events of puberty and does not necessarily presage male-pattern baldness.

One pubertal trait that afflicts many teens, especially boys, is acne. The key feature of acne is the blockage of sebaceous (oil-producing) glands associated with hair follicles—most commonly on the face, neck, or back. An excess production of oil and shedding of epidermal skin cells within the glands cause the blockage. The blocked glands become a breeding ground for a common skin bacterium, Propionibacterium acnes. The blocked gland is called a whitehead if it is below the skin, a blackhead if it reaches the surface, and a pustule or pimple if it becomes inflamed. Severe acne can lead to permanent scarring. The condition can be treated with topical (local) medications containing benzoyl peroxide, salicylic acid, or sulfur. Severe cases may be treated effectively with an oral drug, isotretinoin (Accutane), but this drug can have serious side effects, including fetal defects if taken by pregnant women.

What drives puberty?

So far, we have simply described the major phenomena associated with puberty. But what triggers and orchestrates these phenomena? Let’s start by looking at the proximate (immediate) causes, then track back to the earlier events that get puberty under way.

The proximate causes of most of the phenomena of puberty are, of course, hormones—in particular, androgens and estrogens, along with growth hormone. Although estrogen effects predominate in girls and androgen effects predominate in boys, both androgens and estrogens are needed in both sexes for normal completion of puberty.

Androgen levels rise steadily in both sexes during puberty but reach much higher final levels in men than in women. Androgens are responsible for muscle development, change of voice, and spermatogenesis (in combination with FSH), as well as the appearance of pubic and axillary hair in both sexes. In men, androgens are also responsible for the pubertal development of the external genitalia, prostate, seminal vesicles, sebaceous glands, and facial and body hair (and for male-pattern baldness), but full development of these characteristics requires the conversion of testosterone to the more potent androgen DHT in the target tissues (see Chapter 5). Testosterone also acts on the brain to promote the psychosexual development associated with puberty in both sexes.

Estrogens (in combination with growth hormone and progesterone) promote development of the breasts. Estrogens and progesterone (in combination with FSH and LH) trigger menarche. In males, estrogens are required for the normal functioning of the epididymis in concentrating sperm and are therefore necessary for male fertility. In both sexes, estrogens are responsible for an increase in bone density at puberty, as well as for the closure of the growth zones in the long bones at the end of the pubertal growth spurt. Thus, individuals who cannot manufacture estrogens or who lack estrogen receptors fail to stop growing at the end of puberty and may become exceptionally tall (Sharpe, 1997).

What drives the increase in circulating sex steroids during puberty? The initial rise in androgen levels, which triggers the appearance of pubic and axillary hair in both sexes, is due to an increase in androgen secretion by the adrenal glands. The subsequent main increase in sex steroids during puberty, however, is due to their secretion by the gonads.
This gonadal secretion is driven by an increase in the release of the gonadotropins LH and FSH.

Gonadotropin secretion is triggered, in turn, by an increase in the secretion of GnRH by the hypothalamus. This increase is a key event during puberty (FIGURE 6.24). The rest of the body seems to be primed from early childhood to heed the call of GnRH (BOX 6.7); only the lack of GnRH prevents puberty from taking place at 2 or 3 years of age. Thus, we would like to know why GnRH secretion increases when it does, rather than earlier or later.

The body may signal its readiness for puberty to the brain

One theoretical possibility is that the hypothalamus possesses an internal clock that counts off the years since birth. That seems not to be the case, however. Instead, it has been suggested that GnRH secretion increases when the body has reached a certain critical weight, weight-to-height ratio, or body fat ratio (the proportion of body weight that is due to fat). The timing of puberty correlates better with body weight than with chronological age. In girls, the pubertal growth spurt begins at an average weight of 30 kg (66 lb). In boys, puberty seems to be triggered at a higher body weight than in girls: about 55 kg (121 lb).

Menarche occurs at an average weight of 47 kg (103 lb) in Western countries but at a significantly lower weight in some developing countries, such as India (Rao et al., 1998). In any given culture, somewhat obese girls tend to experience menarche earlier than thin girls, and very thin girls may not experience menarche at all (primary amenorrhea). Furthermore, if women lose most of their body fat after puberty—as can happen during famines, as a consequence of eating disorders such as anorexia nervosa, or even as a result of extreme athletic activity—their menstrual cycles may cease (secondary amenorrhea).

How might the brain know when the body has reached a certain weight or composition? One hypothesis involves the hormone leptin, a peptide hormone that is secreted by fat cells (Rogol, 2010). In general, leptin levels in the blood provide an indication of how much fat the body has accumulated. It would make sense if a puberty-inducing signal were derived from fat cells, especially in girls, because a girl should not become reproductively mature until she has accumulated the energy stores necessary to sustain pregnancy. Supporting the idea that leptin helps trigger puberty is the finding that children suffering from a mutation in the gene for the leptin receptor do not enter puberty (Clement et al., 1998).

Leptin does not directly activate the GnRH-secreting cells of the hypothalamus, however. Rather, leptin, along with other chemical and neural signals, appears to stimulate a group of hypothalamic neurons that manufacture and secrete a signaling molecule named kisspeptin (Kauffman, 2010). Kisspeptin stimulates the GnRH neurons to secrete GnRH, and the rare individuals who lack the receptor for kisspeptin—like those who lack the receptor for leptin—fail to enter puberty.

In summary, puberty is the end result of a long chain of chemical signals: body fat → leptin → kisspeptin → GnRH → gonadotropins → gonadal steroids → target tissues. Why so complicated? Probably because it allows for multiple internal and environmental factors to influence the process, including feedback signals from the target tissues and the gonads.

Primary amenorrhea  Failure to commence menstruation at puberty.
Secondary amenorrhea  Absence of menstruation in a woman who has previously menstruated normally.
Leptin  A hormone secreted by fat cells that may play a role in triggering puberty.
Kisspeptin  A hormone produced in the hypothalamus that is involved in the initiation of puberty.

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Puberty has traditionally been considered **precocious** if the appearance of pubic hair or breasts, or enlargement of the testicles, begins before age 8 (in girls) or age 9 (in boys) (see figure). These criteria are no longer realistic, for girls in the United States at least, because about 10% of white girls, 15% of Hispanic girls, and 23% of African-American girls have breast development at age 7 (Biro et al., 2010). (Asian-American girls develop on about the same schedule as white girls.) Current guidelines therefore recommend that girls be evaluated for precocious puberty if they have pubic hair or breast development before age 7 (white girls and Asian-American girls) or before age 6 (black girls) (Muir, 2006). Slightly older girls (e.g., age 8) should be evaluated only if special circumstances apply, such as an unduly rapid progression through the stages of puberty.

The cause of most cases of precocious puberty cannot be determined. In medical jargon, such cases are called **idiopathic**. A few cases, however, are caused by tumors at or near the base of the brain. Puberty may also be triggered by disorders affecting the gonads.

Precocious puberty can adversely affect a child’s final height. Affected children may initially grow faster than normal, but once the pubertal growth spurt ends, they are likely to be overtaken and left behind by their peers. The earlier puberty begins, the shorter the individual is likely to be in adulthood. Girls who enter puberty at the low end of the normal range (say, at 7 or 8 years of age) suffer little, if any, loss of adult height because their early entry into puberty is partially compensated by an increased duration of the pubertal growth spurt (Shangold et al., 1989). This is partly why the recent guidelines for precocious puberty exclude these girls.

The early sexual maturity that goes along with precocious puberty may cause psychological and social problems for the affected children, especially for girls (Dorn, 2007). These girls tend to have poor self-esteem on account of the physical differences between them and their peers. They may become targets for sexual advances that they cannot easily repel, and they themselves may develop sexual feelings that they don’t know how to cope with. Problems such as alcohol and substance abuse, disruptive behavior, and suicidality are commoner among children who enter puberty early than among other children.

Most cases of precocious puberty can be treated with a GnRH analog such as leuprolide (Lupron). You might think that this would be exactly the wrong drug to give, since GnRH normally triggers puberty. GnRH’s normal action depends on its pulsatile secretion, however. If a GnRH analog is administered in the form of monthly depot injections, which maintain constant high levels in the blood, it suppresses the secretion of pituitary gonadotropins and hence the secretion of the gonadal steroids. Growth hormone is sometimes also administered. Although the use of these drugs has been somewhat controversial, they now appear to be quite safe and effective.

Puberty is considered **delayed** if the early signs of puberty do not appear by age 13 (sometimes 14) in girls, or by age 14 in boys. (A boy whose voice changes at age 16, as was the case with Canadian pop idol Justin Bieber, is near the upper end of the normal range.) Delayed puberty is more common in boys than in girls; it is usually idiopathic, in which case puberty eventually starts spontaneously. It is sometimes possible to “kick-start” the process with a short course of testosterone treatment. Brain tumors can also cause delayed puberty.

**precocious puberty** Puberty that begins early enough to be considered a medical problem.

**idiopathic** Lacking an identifiable cause.

**delayed puberty** Failure of onset of puberty by some criterion age, usually 13 or 14 in girls and 14 in boys.

**Dietary changes may be the reason puberty is beginning earlier**

With these insights into the mechanisms that trigger puberty, can we understand why puberty has been occurring at ever-younger ages over the last century or so, as described above? The leading hypothesis is that a progressive
change in diet over this period has allowed children to reach a body weight that triggers puberty at earlier and earlier ages. In particular, the introduction of cheap, calorie-dense manufactured foods has allowed children not merely to grow faster but also, often, to become overweight or even obese. These changes could be a large part of the reason for the changing age of puberty, but they may not be the entire reason; for one thing, body weight, though a better indicator than chronological age, is still far from being a precise predictor of the time of puberty. Also, even children of average weight seem to be entering puberty earlier than their predecessors.

Another hypothesis suggests that endocrine disruptors (hormone-like pollutants in the environment; see Box 5.5) are causing children to enter puberty early (Roy et al., 2009). Some studies have reported that children who experience precocious puberty have unusually high levels of such pollutants in their blood. Still, the idea that endocrine disruptors are contributing to the decreasing age of puberty in the general population is far from proven.

Sex hormones may have organizational effects at puberty

Earlier, we drew a distinction between prenatal organizational effects of sex hormones on brain development, which are conceived of as permanent differences in brain structure, and activational effects in adult life, which control the function of these sex-differentiated systems in a reversible fashion. While there is no reason to doubt the relevance of this distinction, evidence is also accumulating that puberty may be marked by a second phase of organizational effects.

The evidence comes mainly from brain imaging studies, which have shown that the structures of boys’ and girls’ brains diverge from each other during puberty. In Chapter 1, we described one such study, which described how certain regions of the cerebral cortex become better developed in one sex or the other during this period (Raznahan et al., 2010). Notably, individual differences in brain sensitivity to testosterone (caused by genetic differences in the androgen receptor) had a strong influence on this process of sexual differentiation, suggesting that testosterone is an important driver of the process.

In another study, German researchers examined brain structure in boys and girls aged 8 to 16 and also measured the children’s blood levels of testosterone and estrogen (Neufang et al., 2008). They found that both testosterone and estrogen levels influenced the development of sexually dimorphic brain structures, with testosterone appearing to drive male-typical development of certain structures and estrogen appearing to drive female-typical development of other structures (Figure 6.25). These emerging sex differences are likely to be of functional significance: For example, estrogen drives the growth of an area of the cerebral cortex known as the parahippocampal gyrus that is involved in memory processing (labeled red in the figure), and women outperform men in a variety of memory-related tasks.

The results of these imaging studies suggest that sexual differentiation of children’s brains at puberty goes far beyond a mere functional “switch-on,” such as is implied by the term “activational effect.” Studies in rats indicate that, during puberty, gonadal steroids actually promote the addition of new neurons to some sexually dimorphic nuclei (Ahmed et al., 2008). Thus, it is as if the prenatal process of sexual differentiation is put into temporary abeyance during childhood and then goes to completion when testosterone and estrogen levels rise at puberty. Much more work needs to be done before we can fully understand this process.

**FIGURE 6.25** MRI slice through the human brain, showing some of the regions whose size is affected by sex hormone levels at puberty. Green = enlarged by high testosterone; blue = diminished by high testosterone; red = enlarged by high estrogen. (From Neufang et al., 2009.)
Intersexuality Raises Complex Social and Ethical Issues

We describe a variety of intersex conditions from a biomedical perspective in Boxes 6.1 through 6.7. Certainly, intersexuality has medical aspects. Some children with ambiguous genitalia need medical or surgical treatment to save their lives or to correct conditions that greatly interfere with urination, coitus, and the like. Some intersexed people may request surgical treatment to bring their genital anatomy into conformity to the sex with which they identify.

Intersexed people often have nightmarish experiences with the medical profession, however, beginning in early childhood (Box 6.8). Often, they become so alienated that they stay clear of doctors during adulthood, possibly missing out on medical or psychotherapeutic treatments that could benefit them. Psychological distress and self-harming behaviors are significantly more common among intersexed persons than among other people (Schutzmann et al., 2009).

Personal Points of View

BOX 6.8

My Life With Androgen Insensitivity Syndrome

Katie Baratz Dalke, who has androgen insensitivity syndrome (AIS), recently graduated from the University of Pennsylvania School of Medicine. She wrote the following essay for this edition of *Human Sexuality* in order to give you some idea of the personal experience of living with a disorder of sex development.

*By all accounts, I was a perfectly healthy and normal baby girl, thriving under the love and attention of my family and constantly seeking opportunities to sing, dance, and try on my mother’s dresses and jewelry—the more sparkles, the better!*

*My family’s world changed forever when I was 6. That year, I collapsed in the shower with a painful lump in my groin. Convinced I had a hernia, my parents, both doctors, took me to the hospital. But when surgeons operated, they found a testicle that had started descending. Tests soon showed that instead of the typical XX chromosomes found in girls, I had the XY chromosomal complement of boys.*

*The doctor told my stunned parents that I had Complete Androgen Insensitivity Syndrome. He assured them that I would grow up normally, fall in love, and have a family through adoption, but they shouldn’t tell me that I had XY chromosomes and testes.*

*My parents did decide to tell me, but gradually. As a young girl, they showed me an anatomy book and told me that the uterus was the nest inside a woman where the baby grew. I didn’t have one, but I could adopt a baby that would grow in my heart and be part of my family. I learned about periods and knew I wouldn’t get them. Although I was sad that I wouldn’t be able to become pregnant and*
The Accord Alliance (See Web Resources at the end of this chapter) is devoted to promoting the medical and psychological health of people with intersexed conditions. The Alliance (which prefers the term “disorders of sex development”) works to establish a climate of greater openness with regard to intersexed conditions, with the hope of breaking down the taboos that surrounds them.

There is some controversy, even among intersexed people, as to whether, when, and what kind of surgery should be done on children with intersexed genitals. Because the ultimate gender identity of a young intersexed child cannot be confidently predicted, the ideal strategy may be to wait until the child is old enough to make a meaningful choice on his or her own. This is not always possible, however, for a variety of medical and social reasons. Understandably enough, parents often demand surgery to “normalize” their child, but they cannot know what will feel normal to the child as it grows up.

The medical community is becoming aware of the need to provide greater support for intersexed people, especially at adolescence, when many medical and psychosocial problems may arise (Wisniewski & Migeon, 2002).

felt different from my girl friends, I thought that was it—until I turned 16.

That year, my sister came home from school with a biology project. Everyone in her class was assigned a condition to research, and she randomly drew AIS. “Mom and Dad, it sounds a lot like Katie,” she said at dinner one night. “And there’s a woman with Mom’s name on the support group website.” My parents looked at each other. They’d wanted to wait until I was 18, but there was no going back now. They told me and my brother and sister everything. My dad finished up by saying, “You’re still our girl.”

I was devastated and angry, feeling betrayed by my parents and my own body. Looking back, I know those emotions came from a fear of what was wrong with me, plus the eternal conflict of adolescence: someone else deciding what’s best for you.

High school was grim. I went through puberty very late, and was taller and thinner than most of the boys all the way through senior year. I had horrible insomnia and tons of anxiety that sometimes veered into depression. I felt as if all of my girl friends were living a life I couldn’t access, one marked by the common experiences of periods, dating, and an effortless transition to womanhood. I, on the other hand, had to take estrogen pills to develop a womanly figure, and I had to use a vaginal dilator for 30 minutes a day so that I could comfortably have sex.

College was better. I found a therapist I loved and began to feel recognized by my classmates for my talents and interests rather than my body. I started to tell my story to friends and a few boyfriends, who were constantly supportive, encouraging, and loving.

Speaking of love... in my senior year, I met Sam, a runner and English major with a romantic streak. We started talking, and before I knew it, he was courting me with chocolate-covered strawberries and Marilyn Monroe movies. Shortly after we began dating, I knew that it was time to tell him about my AIS. He listened patiently and assured me that nothing about my genes or gonads changed the way he felt about me.

Four years later, we were married on an unseasonably warm New Year’s Eve, surrounded by our friends, family, and yes, lots of sparkles. We are beginning our lives together and planning to adopt our children, although I still feel pangs of sadness when I think about how much I’d like to be able to have children biologically.

I’m also really involved in the AIS community. It feels incredible to help others with the pain I went through—it was only after finding the AIS Support Group, the summer before college, that I realized AIS could be part of my life without dominating it, and that the loneliness I’d felt abated.

Ultimately, I want to be an advocate for people like me. It’s hard to convince doctors to change how they handle such cases if you’re not their peer, so I recently graduated from medical school with a masters in Bioethics and am beginning a residency in Psychiatry. As a psychiatrist, I hope to help people cope with having conditions like AIS, and to help doctors find the best way to treat them.
The male and female internal reproductive tracts develop from different precursors—the Wolffian and Müllerian ducts. In XY embryos (normal males), the testes secrete testosterone and its conversion to 5α-dihydrotestosterone (DHT). In genetically female fetuses that are exposed to or that cannot convert testosterone to DHT (5α-reductase deficiency), the external genitalia will be sex-atypical to a variable degree.

Both ovaries and testes descend from their original lumbar position during fetal life. The ovaries descend into the pelvis, on either side of the uterus. The testes descend into the pelvis and then through the developing inguinal canal into the scrotum. If the testes fail to descend by 3 months after birth, spermatogenesis may be impaired.

Exposure to sex hormones during fetal life is directly or indirectly responsible for the sexual differentiation of the central nervous system. These hormones cause the development of sexually dimorphic structures and circuits and, by doing so (at least in experimental animals), influence the kinds of sexual behaviors that are exhibited in adulthood. The effects of hormones on behavior are thought to occur in two main phases: organizational effects during prenatal brain development and activational (triggering) effects in adulthood.

External factors also influence prenatal sexual development. These factors may include drugs such as synthetic sex hormones. After birth, social factors further influence the development of the brain and adult sexual behavior, to judge from experimental studies in nonhuman primates.

Puberty is the biological transition from childhood to sexual maturity. It is marked by further development of the reproductive tracts and external genitalia, the appearance of secondary sexual characteristics (e.g., breasts or facial hair), signs of functional sexual maturity (i.e., onset of menstruation or ejaculation), and a growth spurt followed by cessation of growth. In the United States, puberty begins earlier in girls than in boys, and earlier in African-American girls than in white American girls. Precocious puberty (defined as puberty beginning before age 7 in girls or age 9 in boys) and delayed puberty can usually be treated medically, if necessary.

Puberty is caused by a rise in the circulating levels of adrenal and gonadal sex steroids and growth hormone. Gonadal secretion is triggered by a rise in pituitary gonadotropins, which, in turn, is triggered by the onset of secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. It is thought that the prime trigger for puberty is the attainment of a critical body weight, weight-to-height ratio, or body fat index. The body may communicate this information to the hypothalamus by means of the hormone leptin.

In Western countries, puberty has been starting at progressively younger ages over the last 150 years. The most likely reason is a progressive change in nutritional practices, which have led to more rapid weight gain during childhood.
Discussion Questions

1. Imagine that you have just become the proud parent of a newborn baby. Everything has gone perfectly until the nurse–midwife and pediatrician tell you that the baby’s genitals are unusual: They have some characteristics of females and some of males. Would this child be stigmatized and disadvantaged? How? Consider what you and your partner would do and why.

2. If you or your partner was pregnant and learned that you would have a baby with Turner or Klinefelter syndrome, what would you decide to do about it? What would be the disadvantages of such abnormalities for your child? Argue the reasons for your choice.

3. Puberty is occurring earlier than in the past. Do you think that this creates a social problem? What age of entry into puberty do you think should be considered unacceptably early and a justification for treatment? Do you think it would be a good idea to try to increase the average age of puberty by, for example, restricting children’s diets?

Web Resources

Accord Alliance (concerned with disorders of sex development/intersexuality) www.accordalliance.org
Androgen Insensitivity Syndrome Support Group www.aissg.org
Bodies Like Ours (support and information for people with atypical genitals) www.bodieslikeours.org/forums
Congenital Adrenal Hyperplasia Education and Support (CARES) Foundation www.caresfoundation.org
Klinefelter Syndrome Information and Support www.klinefeltersyndrome.org
Turner Syndrome Society of the United States www.turnersyndrome.org

Recommended Reading


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