

Sexual Development

The biology of sex interacts with complex environmental influences to produce a final phenotype. In the following discussions, we will be using the term *sex* to refer to biological sex. The term *gender* is usually applied in situations that involve social, learned, and personal aspects. The biological and experiential aspects of sex and gender should not be construed as an either/or type of discussion. As we saw in the case of nature and nurture, our biology and experience typically intertwine in such a manner that they only rarely can be compartmentalized in useful ways (see ● Figure 10.1).

The Genetics of Sex

In 355 BCE, Aristotle argued that the sex of a child was the result of the temperature of semen at the time of conception. Hot semen resulted in males, and cool semen resulted in females. Today, we understand that an individual's genetic sex begins with sex chromosomes inherited from two parents. Mothers provide an **X chromosome** to all their offspring; fathers determine the offspring's sex by providing either another X (producing a female) or a **Y chromosome** (producing a male). The initial receipt of an XX or an XY genotype begins a cascade of hormonal, structural, and behavioral events. These pivotal sex chromosomes, along with the other 22 pairs of human chromosomes, are illustrated in ● Figure 10.2. This view of the chromosomes is known as a **karyotype**, which is the profile of chromosome number and appearance in the nucleus of a cell as seen under a light microscope.

In the vast majority of cases, the transmission of the sex chromosomes to a child is uneventful. However, variations in sex chromosomes occur that can illuminate the contributions of genetic sex to the adult phenotype. Sex chromosomal abnormalities



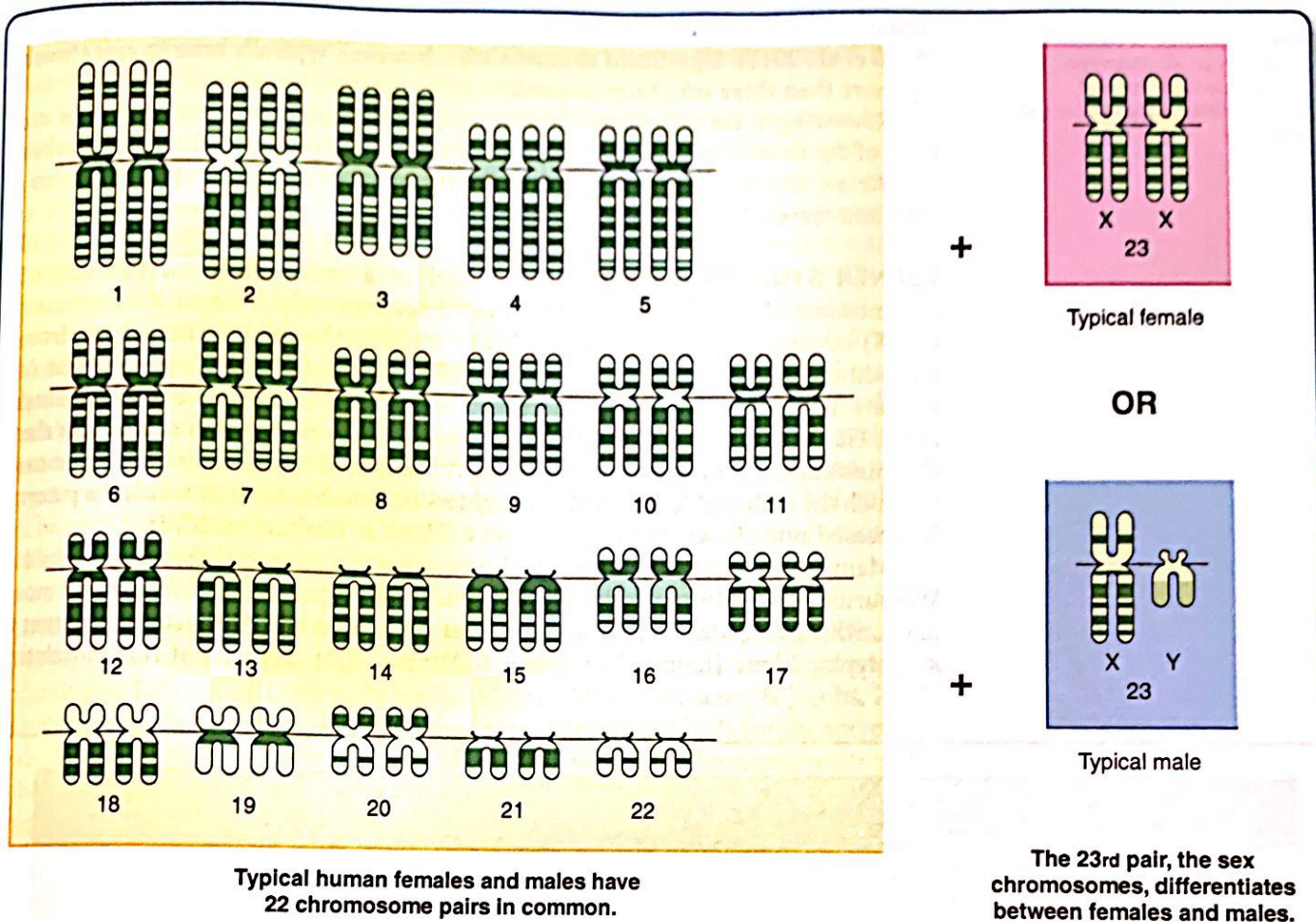
Reuters/Corbis

● **Figure 10.1** **David Reimer and the Nature and Nurture of Sex and Gender** On the advice of 1970s experts, who believed that socialization was more important than biology in the development of gender, David Reimer was raised as a girl following an accident during his circumcision. In contrast to the experts' claims, David never accepted a female role. By the age of 14, he chose to live as a male (above). He married and adopted his wife's children but, sadly, committed suicide in 2004.

X chromosome One of two types of sex chromosomes; individuals with two X chromosomes will usually develop into females.

Y chromosome One of two types of sex chromosomes; individuals with a Y chromosome will usually develop into males.

karyotype A profile of chromosome number and appearance in the nucleus of a cell as seen under a light microscope.



● **Figure 10.2** The Human Genome Twenty-three pairs of chromosomes are found in the nuclei of all human body cells except red blood cells (which have no DNA) and sperm and egg cells (which contain only one copy from each pair of chromosomes).

occur in about 1 out of every 426 children (Nielsen & Wohler, 1991). Most sex chromosome variations produce relatively mild differences, but others are more dramatic. One set of twins possessing the same exact karyotype had very different phenotypes. One twin was a phenotypical male and the other twin was a phenotypical female (Maeda, Ohno, Matsunobu, Yoshihara, & Yabe, 1991). The twins shared a mosaic karyotype of 45,X/46,XY/47,XYY, with the number indicating the number of chromosomes in a cell (46 is typical) and the X and Y indicating the presence of sex chromosomes within that number. Having a mosaic karyotype means that a single individual has cells with differing complements of chromosomes.

In comparison to genetic abnormalities such as Down syndrome, in which an individual has three full or partial copies of the 21st chromosome, abnormalities due to a third sex chromosome appear to have relatively mild effects (Bender, Linden, & Harmon, 2001). In many cases, the effects are so mild that individuals with sex chromosome abnormalities do not get diagnosed (Boyd, Loane, Garne, Khoshnood, & Dolk, 2011). In conclusions drawn from a study of more than 13,000 newborns over a 13-year period, Nielsen and Wohler (1991) found that none of the children with three sex chromosomes had intellectual disabilities and that all were in regular public school. There were no increases in criminal activity, mental disorders, or physical disorders relative to the population with typical sex chromosomes. IQ may be reduced approximately 10 to 20 points compared to siblings, but it remains within normal ranges in most cases (Boyd et al., 2011). Out of the possible combinations of three sex

Turner syndrome A condition caused by an XO genotype, characterized by frequent abnormalities of the ovaries and infertility.

chromosomes, females with an XXX genotype experience the largest reduction in IQ (Boyd et al., 2011). Significant abnormalities, however, typically arise in cases involving more than three sex chromosomes.

Reviewing these genetic variations can provide insight into the impact of each stage of the developmental process on the sexuality and gender of the mature individual. We are also reminded of the variability that extends beyond simple definitions of male and female.

TURNER SYNDROME We have no record of a viable organism that has a Y chromosome alone. However, when a child receives only a single X chromosome (45, X) instead of the usual pair (46, XX or 46, XY), the result is **Turner syndrome**, a condition first described by American endocrinologist Henry Turner in 1938 (see Figure 10.3). Turner syndrome occurs in about 1 out of 2,000 live births (Levitsky, Luria, Hayes, & Lin, 2015). It is possible to identify the parent who contributes the X chromosome in cases of Turner syndrome. A number of studies have shown that cases in which the maternal X is passed to daughters outnumber cases in which the paternal X is passed along by a factor of three to one (Hook & Warburton, 2014).

Many individuals with Turner syndrome show chromosomal mosaicism (Hook & Warburton, 2014). In particular, Turner syndrome frequently features cryptic mosaicism, which involves complex mosaics that do not necessarily become apparent in karyotyping alone (Iourov, Vorsanova, & Yurov, 2008). Because of this mosaicism,



● **Figure 10.3** **Turner Syndrome** Individuals with Turner syndrome have normal female external appearance and genitalia but are usually infertile due to abnormally developing ovaries. This condition is also associated with short stature, skin folds in the neck, and difficulty with spatial relations tasks.

outcomes among individuals with Turner syndrome can be quite variable. For the purposes of this discussion, we will examine the characteristics of classic cases of Turner syndrome rather than cases involving mosaicism.

Individuals with Turner syndrome have typical female external genitalia, but the ovaries can develop abnormally into what is known as "streak gonad" due to an increase in connective tissue. In most cases, the ovaries do not produce either eggs (ova) or normal levels of female hormones, leading to infertility. Outward physical appearance is relatively unaffected with two major exceptions. Women with Turner syndrome are relatively short, reaching an average height of 4' 8", due to the absence of one SHOX gene, which regulates long bone development (Levitsky et al., 2015). Some individuals show webbed neck deformity, which can be surgically corrected (Lou, Konofaos, & Wallace, 2016). Intelligence is normal, but specific deficits in spatial relationships and processing visual cues can occur. In one large sample, however, women with Turner syndrome had higher educational and occupational achievement levels than typically developing women (Gould, Bakalov, Tankersley, & Bondy, 2013). Human growth hormone, plastic surgery, female hormone replacement therapy, and assisted reproductive technologies can be used to address the issues of height, neck appearance, hormone production, and fertility, respectively.

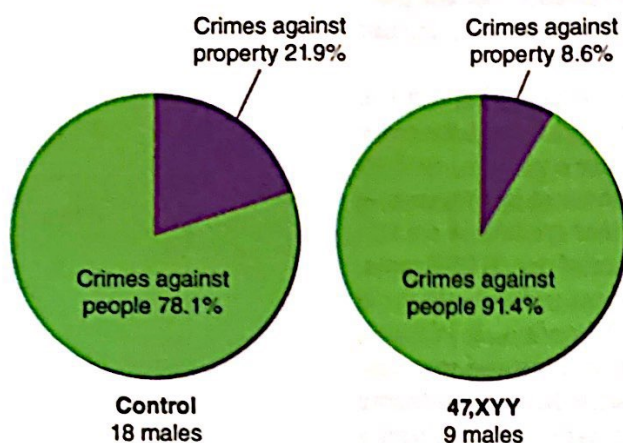
KLINEFELTER SYNDROME Klinefelter syndrome, first identified by Harry Klinefelter in 1942, is the most common genetic abnormality related to the sex chromosomes, occurring in 1.79 out of 1,000 male births (Morris, Alberman, Scott, & Jacobs, 2007). Klinefelter syndrome features a 47,XXY genotype. These individuals are phenotypically male, but they usually experience reduced fertility and require hormone treatment at puberty to promote the development of secondary male sex characteristics (facial hair, deeper voice, development of external genitalia) and to inhibit female characteristics such as breast development (Nielsen, Pelsen, & Sørensen, 1988). Other symptoms linked to having an extra X chromosome result from interference with the process of X-inactivation, in which one X chromosome in each female cell is randomly silenced (see Chapter 5).

Like Turner syndrome, Klinefelter syndrome is associated with normal intelligence that may be marked by mild cognitive difficulties and social awkwardness (Sørensen, 2007). In cases of Klinefelter syndrome, the cognitive difficulties usually take the form of delayed and reduced verbal skills. Left-handedness is more common among males with Klinefelter syndrome than in the general male population. These findings suggest that Klinefelter syndrome might affect brain lateralization or the localization of specific functions such as language in one hemisphere or the other (Ross et al., 2008).

47,YYY SYNDROME The existence of individuals with an 47,YYY genotype, also referred to as Jacob syndrome, was first reported by Sandberg, Koepf, Ishiara, and Hauschka (1961). This variation occurs in about 1 out of 1,000 male births. The physical and behavioral correlates of the condition are typically subtle and generally do not prompt the parents to seek a postnatal genetic analysis (Abramsky & Chapple, 1997). The boys appear to be physically within typical limits, although they tend to be somewhat taller and leaner, suffer from acne, and have a higher risk for minor physical abnormalities of the eye, elbow, and chest. Average IQ scores are slightly below the average of males with typical 46,XY genotypes (Linden, Bender, & Robinson, 1996). Language difficulties and autism spectrum disorder (ASD; see Chapter 16) are common in cases of 47,YYY (Lepage et al., 2014). Men with the 47,YYY genotype are fertile, but they are slightly more likely than typical men to produce sperm with sex chromosome abnormalities (Rives, Siméon, Milazzo, Barthélémy, & Macé, 2003).

The relationship between the 47,YYY genotype and a higher likelihood of antisocial behavior has been the subject of considerable debate (see ● Figure 10.4). An initial report suggested that YYY individuals were overrepresented in prisons

Klinefelter syndrome A condition in males caused by an XXY genotype, characterized by frequent problems with fertility, secondary sex characteristics, and verbal skills.



● **Figure 10.4** The 47,XYY Male Has Been Sensationalized

A series of novels by Kenneth Royce, later made into a television show in the 1970s, featured a main character, William "Spider" Scott, who had 47,XYY syndrome. According to the novels and the show, Scott must fight the "natural" criminal tendencies inherent in his genetic condition, which we know today is a considerable oversimplification of a complex situation.

(Casey, Segall, Street, & Blank, 1966). The popular press immediately embraced the hypothesis that an extra Y chromosome would produce a violent "super male." Men with 47,XYY do show a significantly higher rate of antisocial and criminal behavior than control participants (Stochholm, Bojesen, Jensen, Juul, & Gravholt, 2012). However, the majority of the criminal behavior of 47,XYY men involves property crimes rather than violent crimes (Milunsky, 2004). Further analysis suggested that criminal and antisocial behavior was more closely associated with lower intelligence than with an atypical genotype (Re & Birkhoff, 2015). In addition, compared to control populations, 47,XYY men had fewer partners, were less likely to become parents, had lower income, and were not as well educated (Stochholm, Juul, & Gravholt, 2012). These socioeconomic variables might contribute to higher rates of antisocial behavior as well.

LESSONS LEARNED FROM INDIVIDUALS WITH SEX CHROMOSOME ABNORMALITIES

Investigations of abnormal complements of sex chromosomes provide an interesting opportunity to observe the effects of the sex chromosomes on brain development.

Throughout the remainder of this chapter, we will emphasize the ability of sex hormones to shape the brain and cognition, but the sex chromosomes themselves have the ability to do this independent of their influence on sex hormones.

Consider the fact that each gene produces a protein, which means that we can see dose-dependent effects of a genotype on the resulting nervous system. A number of genes on the X chromosome escape X-inactivation (see Chapter 5), which means that the relevant genes of individuals with Turner syndrome would produce the least amount of proteins, typically developing individuals would produce moderate amounts, and individuals with three or more sex chromosomes would produce the most (Hong et al., 2014). Regions on the X chromosome that are under-expressed are correlated with visuospatial deficits, while over-expression is correlated with verbal deficits. These observations are consistent with the cognitive challenges faced by individuals with Turner syndrome and Klinefelter syndrome, respectively. In comparisons between individuals with Turner syndrome versus typically developing females and Klinefelter syndrome versus typically developing males, the member of each pair with the greater number of sex chromosomes demonstrated increased gray matter volume in the parieto-occipital region of the cortex accompanied by decreases in the temporo-insular area (Hong et al., 2014). Again, this pattern of cortical thickness is quite consistent with the characteristic cognitive challenges seen in Turner and Klinefelter syndromes. Individuals with 47,XYY showed patterns of brain structure that were more similar to males with Klinefelter syndrome than to typically developing males, again supporting a dose-dependent effect of extra sex chromosomes (Lepage et al., 2014).

gonads The internal organs, ovaries in females and testes in males, that produce reproductive cells (eggs and sperm) and secrete sex hormones.

external genitalia The external sexual organs, including the penis and scrotum in males and the labia, clitoris, and lower third of the vagina in females.

Three Stages of Prenatal Development

Development of male and female reproductive structures involves three distinct processes: the development of **gonads**, of internal organs, and of **external genitalia**. In the vast majority of cases, all three processes occur congruently to produce an unambiguous

male or female. In rare conditions known as **intersex**, elements of both male and female development occur in the same fetus.

THE DEVELOPMENT OF THE GONADS Up until the sixth gestational week, both male and female embryos have identical primordial gonads that have the capacity to develop into either **ovaries**, the female gonads, or **testes**, the male gonads.

At about six weeks gestation, a gene on the short arm of the Y chromosome, known as the **sex-determining region of the Y chromosome**, or **SRY**, is expressed in male embryos (Jager, Anvret, Hall, & Scherer, 1990). **Testis-determining factor**, the protein encoded by the **SRY** gene, switches on additional genes that cause the primordial gonads to develop into testes. In female embryos, which lack the **SRY** gene and its ability to produce testis-determining factor, alternate genes, including **Wnt4** (located on Chromosome 1) and **DAX1** (located on the X chromosome) guide the development of the primordial gonad into ovaries (Jeays-Ward, Dandonneau, & Swain, 2004). Chromosomally male mice genetically modified to lack the **SRY** gene develop ovaries, whereas female mice in which the **SRY** gene has been inserted develop testes (Goodfellow & Lovell-Badge, 1993).

DIFFERENTIATION OF THE INTERNAL ORGANS The differentiation of the internal organs, shown in •Figure 10.5, follows the development of the gonads. Until about the third gestational month in humans, both male and female embryos possess a male **Wolffian system** and a female **Müllerian system**. Advantages for this apparent duplication are not currently understood. In males, the Wolffian system will develop into the seminal vesicles, the vas deferens, and the prostate. In females, the Müllerian system will develop into the uterus, the upper portion of the vagina, and the fallopian tubes.

During the third gestational month, the male's relatively new testes begin to secrete two hormones, **testosterone** and **anti-Müllerian hormone**. Testosterone, one of several types of male hormone or **androgen**, promotes the development of the Wolffian system. Anti-Müllerian hormone initiates the degeneration of the Müllerian system. In the female fetus, no additional hormones are needed in this stage of development. Unlike the testes, the ovaries are not active during fetal development. In the absence of any androgens or anti-Müllerian hormone, the Müllerian system will develop in the typical female direction. In the absence of androgens, the Wolffian system regresses, although nonfunctional remnants can persist in adult females. No hormone analogous to the male anti-Müllerian hormone is needed to promote degeneration of the Wolffian system in females.

Androgen insensitivity syndrome (AIS) disrupts the normal development of the Wolffian system in males. In AIS, a defective gene produces abnormal androgen receptors (Gottlieb, Pinsky, Beitel, & Trifiro, 1999). As a result, the fetus's tissues are blind to the presence of androgens. Fetuses with AIS have an XY genotype and normal testes that remain undescended within the abdomen. The testes release androgens and anti-Müllerian hormone in a typical manner, but the lack of functional androgen receptors prevents the development of the Wolffian system. However, anti-Müllerian hormone still works normally, so the female Müllerian system also fails to develop. Because the Müllerian system is responsible for the upper two thirds of the vagina and the female internal organs, the result is a shallow vagina and no ovaries, fallopian tubes, or uterus. Although adult individuals with AIS are infertile, their external appearance is quite typically female.

AIS provides a clear view of the difference between chromosomal sex and **gender identity**, our sense of being male or female. Individuals with AIS are genetic males but typically have female appearance and female gender identities. Many marry and engage in typical female sexual behavior (Morris, 1953).

Complete AIS is unlikely to confer any advantages to female athletes, but as we saw in the case of sex chromosome abnormalities, outcomes can be highly variable.

intersex A condition in which elements of both male and female development occur in the same fetus.

ovaries Female gonads; the source of ova and sex hormones.

testes Male gonads; the source of sperm and sex hormones.

sex-determining region of the Y chromosome (SRY) A gene located on the short arm of the Y chromosome that encodes for testis-determining factor.

testis-determining factor A protein encoded by the **SRY** gene on the Y chromosome that turns the primordial gonads into testes.

Wolffian system The internal system that develops into seminal vesicles, vas deferens, and the prostate gland in males.

Müllerian system The internal system that develops into a uterus, fallopian tubes, and the upper two thirds of the vagina in the absence of anti-Müllerian hormone.

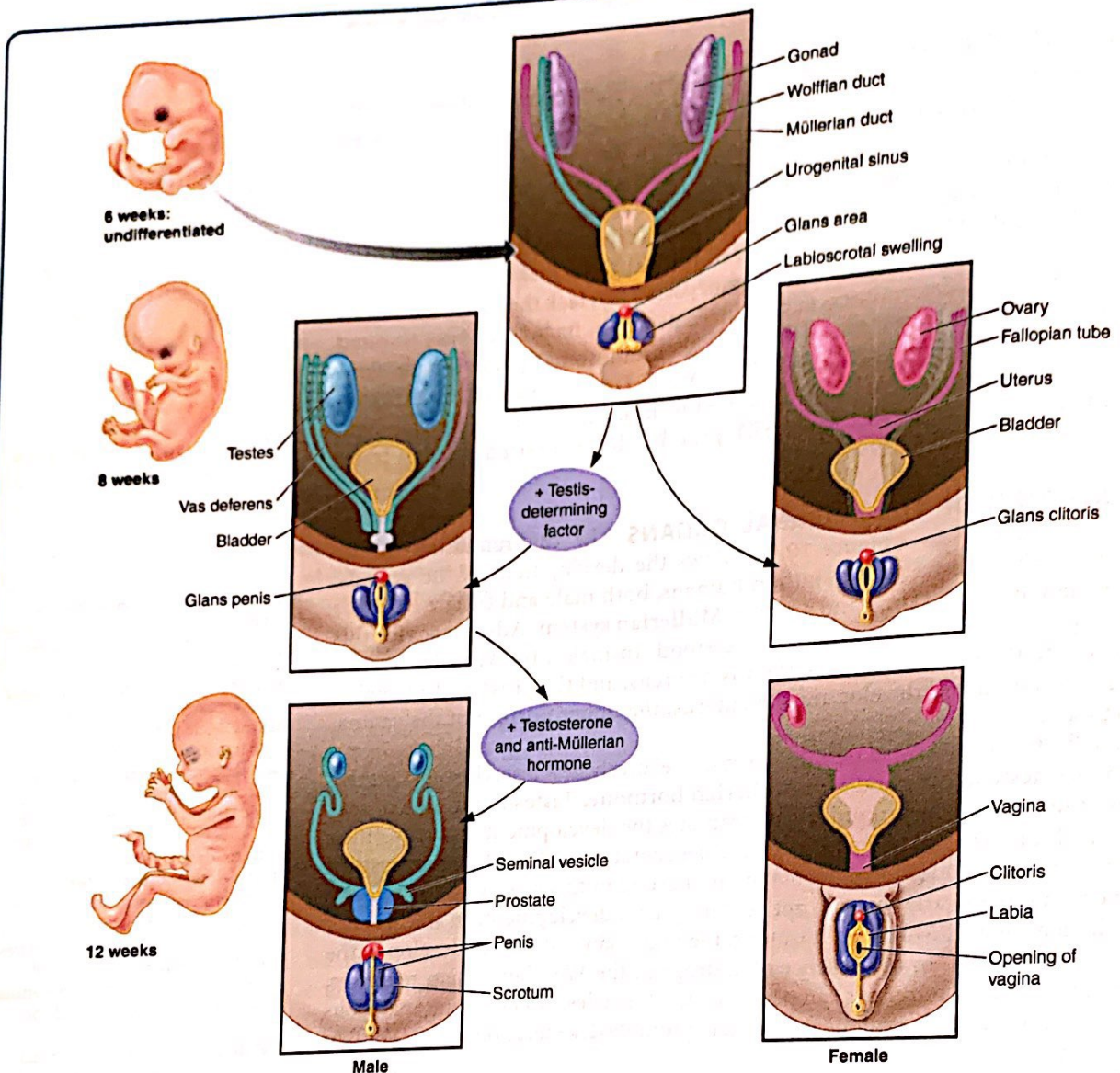
testosterone An androgen produced primarily in the testes.

anti-Müllerian hormone A hormone secreted by fetal testes that causes the degeneration of the Müllerian system.

androgen A steroid hormone that develops and maintains typically masculine characteristics.

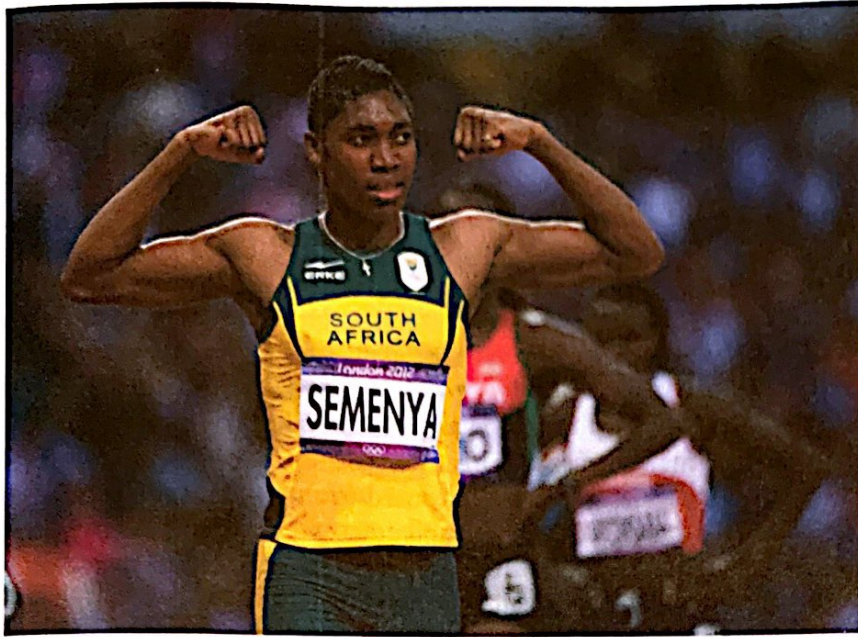
androgen insensitivity syndrome (AIS) A condition in which a genetic male fetus lacks functional androgen receptors, which leads to the development of female external genitalia and typically female gender identity and sexual behavior.

gender identity The sense of being male or female, independent of genetic sex or physical appearance.



● **Figure 10.5** Differentiation of Gonads and External Genitalia During the first six weeks after conception, the primordial gonads are undifferentiated. Subsequently, testis-determining factor encoded by the *SRY* gene on the Y chromosome will begin to turn the undifferentiated gonads into testes in males. The testes begin to release androgens, causing the external genitalia to develop into a penis and scrotum. Alternate genes guide the development of female gonads into ovaries. In the absence of androgens, the female external genitalia develop into clitoris, labia, and vagina.

Incomplete forms of AIS might be an advantage for women in sports due to the effects of androgens on muscle development and the oxygen carrying capacity of the blood (Wood & Stanton, 2012). Although AIS occurs in 1 out of 20,000 male births, it is estimated that 1 out of every 421 women competing at international levels of sport have a disorder of sex development (46,XY DSD), with the majority of these having AIS (Ferguson-Smith & Bavington, 2014). Historically, a number of female athletes with AIS were disqualified from competition on the basis of genetic testing, which in these cases, would produce an XY result. Most international sports organizations have now eliminated genetic testing. The current philosophy in sports is that a person identifying and living as a woman should compete as a woman.



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● **Figure 10.6** Androgen Insensitivity Syndrome (AIS) Castor Semenya of South Africa was forced to undergo “gender verification” after observers complained about her “masculine appearance.” Semenya’s situation remains appropriately private, but it is very likely that she has androgen insensitivity syndrome (AIS). Model Hanne Gaby Odiele has recently disclosed that she has AIS. This condition is believed to be more common among female athletes and fashion models than in the general population.

(see ● Figure 10.6). The International Olympic Committee (IOC) allows female-to-male transgender athletes to take part in men’s competitions without restriction. Male-to-female transgender athletes need to demonstrate testosterone levels below a cutoff point for one year prior to Olympic competition (International Olympic Committee [IOC], 2015). Keep in mind, however, that individuals with AIS are not considered to be transgender.

DEVELOPMENT OF THE EXTERNAL GENITALIA The development of the external genitalia, illustrated in Figure 10.5, follows the differentiation of the gonads during the sixth gestational week. The male external genitalia include the penis and scrotum. The female external genitalia include the labia, clitoris, and outer part of the vagina. The appearance of the external genitalia remains an important psychological “sign” of sex, and ambiguity of the genitalia at birth is a source of significant stress for parents (Wolfe-Christensen et al., 2012). Health care providers typically use the Prader scale shown in ● Figure 10.7 to assess the relative masculinization of the external genitalia.

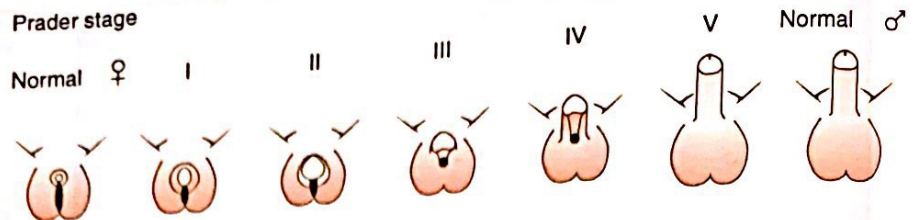
No hormonal activity is required to develop female external genitalia. However, hormonal stimulation is essential for the development of male external genitalia. A particular androgen, **5-alpha-dihydrotestosterone**, must be recognized by receptor sites for the male external genitalia to develop normally. A reaction between testosterone from the testes and the enzyme 5-alpha-reductase produces 5-alpha-dihydrotestosterone. We will see later in the chapter that the absence of 5-alpha-dihydrotestosterone leads the immature genitalia to develop in the direction of an ambiguous to female pattern.

If genetic females are exposed prenatally to excess androgens, their external genitalia become masculinized. **Congenital adrenal hyperplasia (CAH)** is a recessive heritable condition in which the fetus’s adrenal glands release elevated levels of androgens during the second trimester of pregnancy, which is also when sexual differentiation is well underway. Males with CAH show few observable effects related to sexual

5-alpha-dihydrotestosterone An androgen secreted by the testes that masculinizes the external genitalia.

congenital adrenal hyperplasia (CAH) A condition in which a fetus is exposed to higher-than-normal androgens, resulting in masculinization of external genitalia and some cognitive behaviors in affected females.

● **Figure 10.7** The Prader Scale The Prader scale is used to assess the relative masculinity of the external genitalia of newborns. Example IV shows a hypospadias, in which the urethra of the male is not properly positioned relative to the penis.



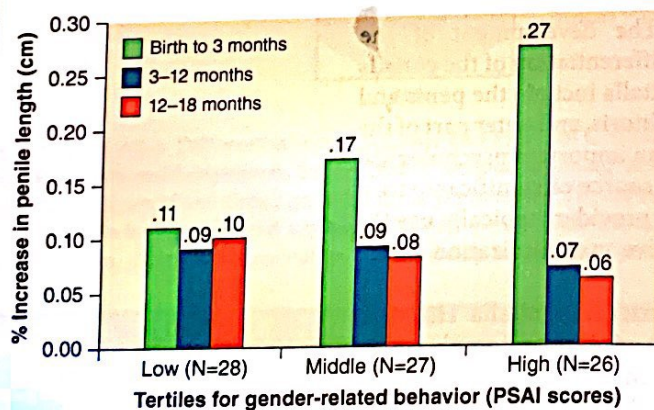
development, because male fetuses are already typically exposed to high levels of circulating androgens. Females with CAH are exposed to about half the amount of androgens of a typical male and are born with ambiguous external genitalia, like the middle images in Figure 10.7. The clitoris is enlarged, the labia look similar to a scrotum, and in some cases, there is no vaginal opening.

Females with CAH more frequently describe themselves as tomboys, engage in more male-interest play, and are more likely than other women to engage in bisexual and lesbian behavior (Hines, Brook, & Conway, 2004; Meyer-Bahlburg, Dolezal, Baker, & New, 2008; Money, Schwartz, & Lewis, 1984). However, it is important to remember that the majority of women with CAH are heterosexual, and that the majority of bisexual and lesbian women do not have CAH or other similar conditions.

Development at Mini-puberty

In addition to the prenatal release of androgens, males experience a second surge of androgen exposure between the ages of one and three months, diminishing by about the age of six months. This period is commonly referred to as a “mini-puberty.” The most obvious outcome of this exposure is an increase in the length of the baby’s penis.

As we will see elsewhere in this chapter, prenatal exposure to androgens has been linked to a number of behaviors, including toy choice and aggressiveness. Because the timing of the mini-puberty overlaps a period of known significant neural plasticity (see Chapter 5), researchers have asked if this androgen surge is also related to any behavioral outcomes. Concentrations of testosterone in the urine of male infants between one and six months of age predicted their gender-typical play behavior at age 14 months (Lamminmäki et al., 2012). If we wish to answer the question of whether mini-puberty affects later behavior, it is important to separate the results of pre- and postnatal androgen exposure, which are likely to be positively correlated. This distinction can be achieved by comparing anogenital distance (AGD) at birth, a sensitive marker of prenatal androgen exposure, and penile growth during mini-puberty. Both AGD and rate of penile growth independently predicted gender-typical play at ages three to four years (see ● Figure 10.8) (Pasterski et al., 2015). Thus, mini-puberty does appear to influence later behavioral outcomes.



● **Figure 10.8** Mini-puberty and Sex-Typed Play Gender-typical play behavior on the standardized Pre-school Activities Inventory (PSAI) is correlated not only with measures of prenatal exposure to androgens but also with penis growth in infancy, a measure of androgen activity during the mini-puberty stage. Boys with the greatest penis growth during the first three months of infancy were most likely to show gender-typical play behavior at ages three to four years.

Development at Puberty

The prenatal development of gonads, internal organs, and external genitalia, along with mini-puberty, are only part of the sexual development story. At puberty, additional hormonal events lead to maturation of the genitals and the development of **secondary sex characteristics**. Secondary sex characteristics include facial hair and a deeper voice for males and wider hips and breast development for females.

TYPICAL AGE AT PUBERTY As shown in • Figure 10.9, the average age of puberty has dropped dramatically over the past century and a half, from about 16 to about 12 years of age (Frisch, 1983; Herman-Giddings et al., 1997). Possible explanations for this drop in age at puberty include increased rates of childhood obesity (see Chapter 9). Accumulation of enough body fat to support reproduction might serve as a signal for puberty. When body fat is abnormally low, as in anorexia nervosa, puberty is delayed.

Exposure to compounds similar to female hormones in meat and dairy products, shampoo, plastics, and insecticides might also trigger earlier puberty. All edible tissues from animals contain a type of **estrogen**, or female hormone, called **estradiol**, so we can assume that humans who consume meat have always experienced some level of exposure to outside sources of sex hormones. However, many nations, including the United States, also permit the use of additional sex hormones to promote growth in livestock production. Consumption of treated meat can increase exposure to estrogens by nearly 40 percent (Aksglaede, Olsen, Sørensen, & Juul, 2008). Because children are especially sensitive to small amounts of hormone, increased exposure from external sources is cause for concern (Aksglaede et al., 2006).

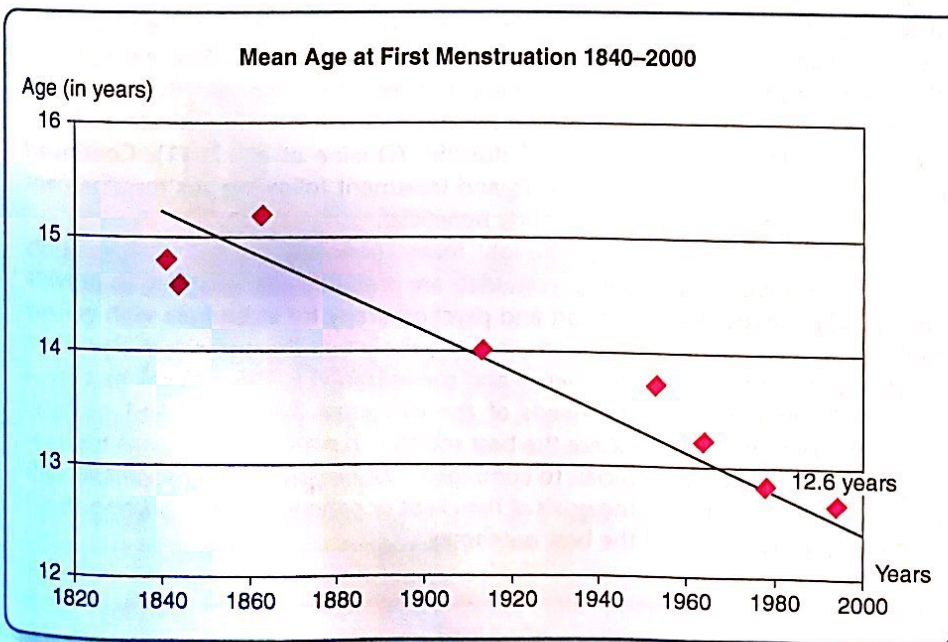
Exposure in utero to a number of endocrine disruptors, including phthalates, diethylstilbestrol (DES), and bisphenol A (BPA), might promote earlier puberty directly or by increasing obesity (Biro, Greenspan, & Galvez, 2012). Phthalates have been found to advance puberty in rats (Ge et al., 2007). Phthalate exposure also appears to reduce the likelihood that boys will play with “masculine” toys (Percy et al., 2016). Phthalates are released into air and fluid from plastic and cosmetic products and are found in measurable levels in most of the world’s human population (Sathyanarayana et al., 2008). Soy contains phytoestrogens, or estrogen-like substances, leading to concerns about the effects of consuming soy on children. Consumption of soy formula from birth is associated with epigenetic change resulting in decreased expression

secondary sex characteristics

Characteristics related to sex that appear at puberty, including deepening voice and facial hair growth in males and widening hips and breast development in females.

estrogen A steroid hormone that develops and maintains typically female characteristics.

estradiol An estrogen hormone synthesized primarily in the ovaries.



• **Figure 10.9** Female Age at Puberty Since 1840, the average age of puberty has dropped from nearly 16 years to around 12 years (Ducros, 1978). Among the possible explanations for this drop are increased rates of obesity and exposure to estrogen-like chemicals from foods, plastics, and insecticides.

gonadotropin-releasing hormone (GnRH) A hormone released by the hypothalamus that stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary gland.

follicle-stimulating hormone (FSH) A hormone released by the anterior pituitary that stimulates the development of eggs in the ovaries and sperm in the testes.

luteinizing hormone (LH) A hormone released by the anterior pituitary that signals the male testes to produce testosterone and that regulates the menstrual cycle in females.

of an estrogen-responsive gene (Harlid, Adgent, Jefferson, Panduri, Umbach, Xu, Stallings, et al., 2017). Use of soy formula has been linked to altered age at menarche (the onset of menstruation) and increased risk of uterine fibroids and endometriosis (Harlid et al., 2017).

HORMONE CHANGES AT PUBERTY At the onset of puberty, **gonadotropin-releasing hormone (GnRH)** is released by the hypothalamus. This hormone initiates the release of two hormones by the anterior pituitary gland, **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. Both males and females release these same hormones, but with different effects. In response to stimulation by FSH and LH, the testes begin to produce additional testosterone, and the ovaries produce estradiol. The testes also produce small amounts of estrogens, including estradiol, and the ovaries produce small amounts of androgens, including testosterone.

In males, this burst of additional androgens stimulates muscular development, maturity of the external genitalia, facial hair, and enlargement of the larynx, which leads to a deeper voice. In conjunction with LH and FSH, testosterone begins to regulate the production of sperm. Testosterone also affects a male's hairline and can result in baldness later in adulthood. In females, estradiol produces breast growth, maturity of the external genitalia, maturity of the uterus, and changes in fat distribution and quantity. LH and FSH regulate the menstrual cycle. In both sexes, estradiol slows down skeletal growth. Individuals who experience early sexual maturation reach their adult heights at earlier ages than their later-developing peers.

Behavioral Neuroscience GOES TO WORK

HOW DO THERAPISTS TREAT GENDER DYSPHORIA?

Gender dysphoria is defined as the "distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender" (APA, 2013, p. 451). This term replaced the earlier term *gender identity disorder* used by psychiatrists and psychologists (APA, 2000). The change in terms resulted from a recognition that it is not the identity that is the problem requiring treatment, but rather the distress caused by the individual's perceptions of his or her situation.

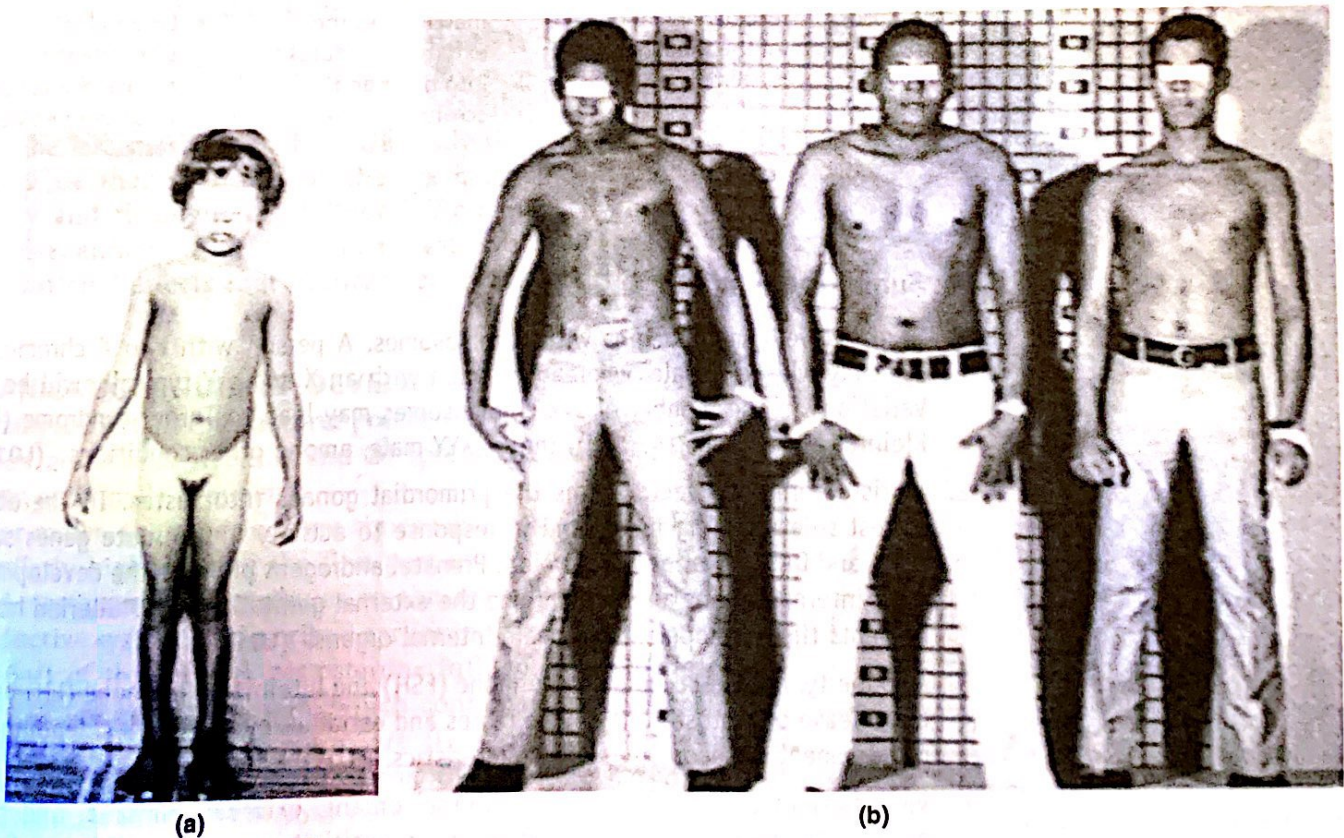
The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (APA, 2013) specifies criteria for diagnosis but does not make recommendations for treatment. In response to that lack, the authoring organization, the American Psychiatric Association, has begun work on treatment guidelines (Byne et al., 2012). The guidelines cover different age groups in detail, in recognition that gender dysphoria can be very different in a young child, an adolescent, and an adult. In the meantime, the American Psychological Association has published a different set of guidelines for psychological practice with transgender and gender nonconforming people (American Psychological Association [APA], 2015).

In general, the guidelines for treatment call for appropriate diagnosis of gender concerns, evaluation of any coexisting psychological problems, psychotherapy to address discrimination and stereotyping, provision of complete education for the individual regarding medical and psychological options, evaluation for possible hormonal or surgical treatment, and education of family members and the community. Sex reassignment might alleviate the feelings of gender dysphoria, but this procedure also increases risk for suicide and psychological disorder (Dhejne et al., 2011). Continued monitoring and treatment following sex reassignment is frequently beneficial.

Although many generally trained psychologists and psychiatrists are probably well prepared to provide support and psychotherapy for individuals with gender dysphoria, it is also likely that therapists with significant experience and specialization in this area will best serve the needs of the individual. Evidence-based practice, where the best scientific research forms a basis for a clinician to combine his or her professional expertise with the goals of the client or patient, could help bring about the best outcomes.

We have previously reviewed atypical cases in which the first two organizing steps, involving the development of gonads and internal sex organs, were affected. A rare condition known as **5-alpha-reductase deficiency** affects the last step, the maturation of the male external genitalia. This condition, first observed in an extended family group living in the Dominican Republic, affects a male's ability to produce the enzyme 5-alpha-reductase. This enzyme converts testosterone into the more potent 5-alpha-dihydrotestosterone. As we saw previously, 5-alpha-dihydrotestosterone is responsible for the masculinization of the external genitalia in the fetus. Without sufficient 5-alpha-reductase, individuals are born with ambiguous external genitalia and may be raised as females. Development of male internal sexual structures is not affected by this condition because this process is governed by unconverted testosterone, which is normal in these cases. At puberty, increased levels of testosterone activate the development of secondary sex characteristics in a typical manner. In a surprising turn of events, about 60 percent of the children with this condition who have been raised as girls develop normal male external genitalia and take on a male gender role (Cohen-Kettenis, 2005; Imperato-McGinley, Guerrero, Gautier, & Peterson, 1974; Imperato-McGinley, Peterson, Gautier, & Sturla, 1979). (see ● Figure 10.10). In the Dominican Republic, these children are referred to as the "guevedoces," or "eggs (testes) at 12." With today's improved access to genetic testing, individuals can be assessed in infancy, usually leading to male sex assignment (Bertelloni et al., 2016).

5-alpha-reductase deficiency A rare condition in which a child is born with ambiguous genitalia but develops male secondary sex characteristics at puberty.



● **Figure 10.10 5-Alpha-Reductase Deficiency Changes External Appearance at Puberty** (a) Individuals born with 5-alpha-reductase deficiency are born with ambiguous external genitalia and are usually raised as girls. This child is 8 years old. (b) At puberty, unconverted testosterone, which is unaffected by the syndrome, produces male secondary sex characteristics. The male on the right is the typically developing brother of the male on the left, and the males on the left and in the center have 5-alpha-reductase deficiency.

From Peterson, R. E., J. Imperato-McGinley, T. Gautier and E. Sturla, "Male pseudohermaphroditism due to steroid 5-alpha-reductase deficiency," *American Journal of Medicine*, 62, 174, Figs. 3 and 7.

INTERIM SUMMARY 10.1**Summary Table: Steps in Sexual Development**

Chromosomes (determined at conception)	Gonads (Gestational weeks 6–8)	Internal Structures (Gestational weeks 9–12)	External Structures (Gestational weeks 6–12)	Puberty (8–16 years)
XX	- By 6 weeks, primordial gonads have developed but are undifferentiated relative to sex. - Alternate genes (not SRY) guide the development of the primordial gonads into ovaries.	- Müllerian system develops in the absence of androgens and anti-Müllerian hormone. - Primitive, nonfunctional Wolffian system is retained.	- In the absence of androgens such as testosterone, female external structures develop. - Female structures include labia, clitoris, and outer vagina.	- Gonadotropin-releasing hormone (GnRH) stimulates the release of LH and FSH by the pituitary. - LH and FSH signal the ovaries to begin releasing estradiol.
XY	- At gestational week 6, primordial gonads are developed but are undifferentiated. - At gestational week 8, testes-determining factor encoded by the SRY gene on the Y chromosome stimulates the development of primordial gonads into testes.	- Testosterone stimulates development of the Wolffian system. - Anti-Müllerian hormone stimulates the degeneration of the Müllerian system.	5-alpha-reductase converts testosterone to 5-alpha-dihydrotestosterone. 5-alpha-dihydrotestosterone masculinizes the external structures into penis and scrotum.	- Gonadotropin-releasing hormone (GnRH) stimulates the release of LH and FSH by the pituitary. - LH and FSH stimulate the release of additional testosterone by the testes.

Summary Points

- Sexual development begins with chromosomes. A person with two X chromosomes typically will be female, whereas a person with an X and a Y typically will be male. Variations in the number of sex chromosomes may lead to Turner syndrome (45,X), Klinefelter syndrome (47,XXY), the 47,XYY male, among other conditions. (LO1)
- Testis-determining factor turns the primordial gonads into testes. In the absence of testis-determining factor and in response to activity in alternate genes such as Wnt4 and DAX1, ovaries will develop. Prenatal androgens promote the development of male internal organs and masculinize the external genitalia. Anti-Müllerian hormone prevents the development of female internal organs. (LO1)
- At puberty, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) promote the release of testosterone by the testes and estradiol by the ovaries, leading to the development of secondary sex characteristics. (LO1)
- Variations in the development of internal organs, external genitalia, and secondary sex characteristics occur in androgen insensitivity syndrome, congenital adrenal hyperplasia, and 5-alpha-reductase deficiency. (LO1)

Review Questions

- What processes must occur to develop male and female gonads, internal organs, and external genitalia?
- What different pathways can occur in sexual development?

organization The permanent effects of sex hormones on body structures.

activation Reversible effects of sex hormones on body structures and functions.

Sex Differences in Hormones, Brain Structure, and Behavior

The cascade of events begun by the actions of genes on the X and Y chromosomes is only the beginning of the story of sex and gender. Continued expression of genes on both X and Y chromosomes, especially in the brain, hormone effects, and epigenetics continue to push the individual in one of many possible directions.

The Organizing Role of Sex Hormones

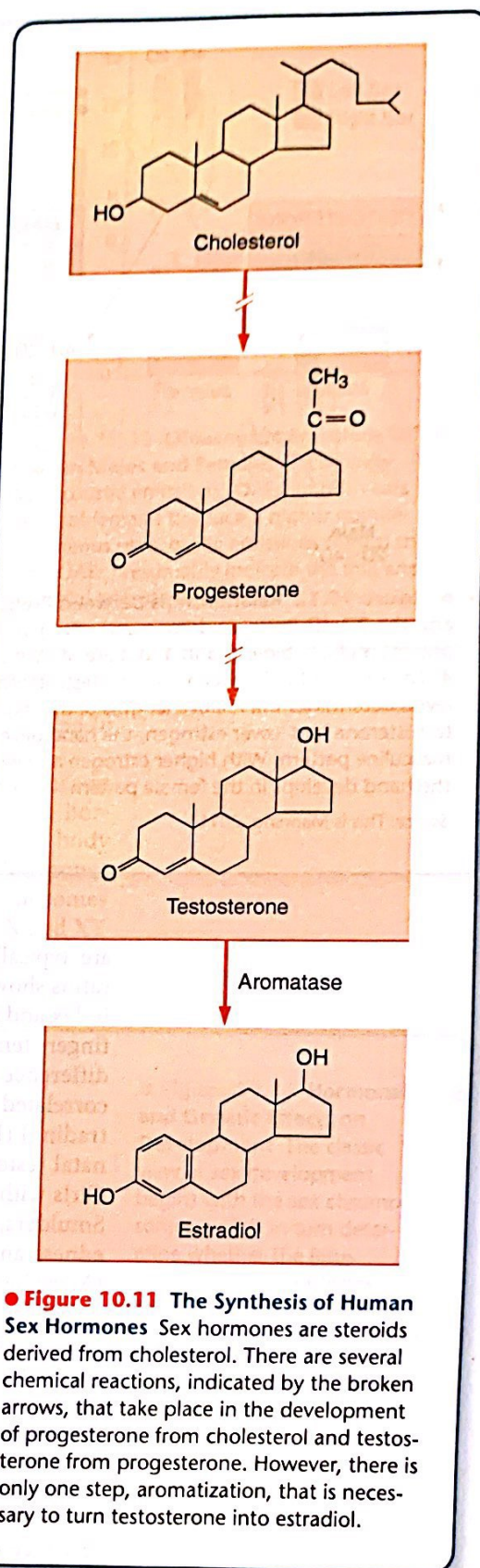
Sex hormones are classified as steroids, chemicals that are synthesized from cholesterol in the gonads and in lesser amounts in the adrenal glands, brain, bone, and fat cells. The chemical structure of cholesterol and the synthesis of the major sex hormones are illustrated in • Figure 10.11. Males and females both produce androgens and estrogens, but in different amounts. Adult females produce about 10 percent of the amount of androgens produced by adult males.

Sex hormones play both organizational and activating roles in development. In prenatal and early postnatal development, sex hormones organize circuits in the brain that differ according to sex. A classic view of **organization** assumes that this process produces permanent changes in biological structures. While this may be true much of the time, the fact that many hormonal organizing effects are based on epigenetics raises the possibility that these changes might be less permanent than originally thought. The organized circuits are then activated by the sex hormones at the onset of puberty and throughout adulthood. **Activation** by hormones is reversible, although the effects of activation are constrained by the organizational effects that occurred earlier (McCarthy & Arnold, 2011).

ORGANIZATION DURING DEVELOPMENT Sex hormones play especially important roles at three points in early human development: between gestational weeks 6 and 24 (prenatal development), mini-puberty, and finally at puberty.

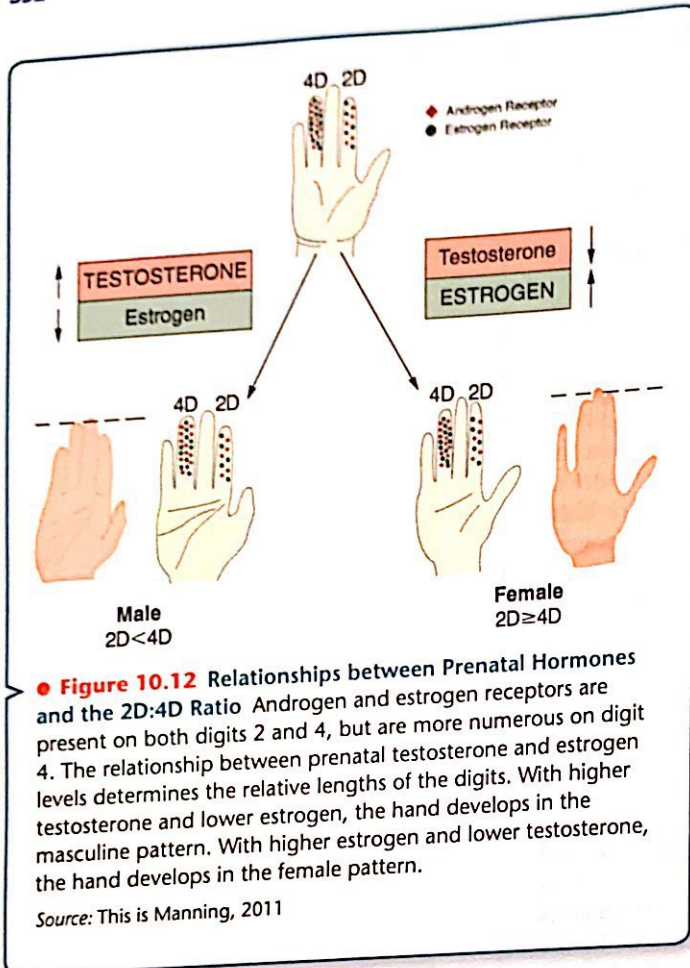
For males, these periods are times when testosterone levels are particularly high. During the first part of the prenatal organizing period, testosterone contributes to the development of the male reproductive system, as described earlier in this chapter. During the latter part of this period, testosterone influences both the reproductive systems and the brain, which contains androgen receptors (Hines, 2010). Estrogen receptors are also expressed in the prenatal brain. Estradiol plays a critical role in sexual development and also influences apoptosis in both sexes (Wilson, Westberry, & Trout, 2011). As we will see later in this chapter, certain parts of the human brain are **sexually dimorphic**, or differ between males and females in structure and volume. These differences are likely the result of different prenatal hormonal environments. Gray matter volume in cortical areas known to be sexually dimorphic is consistent with individual variations in fetal testosterone levels (Lombardo et al., 2012).

In the absence of influence by substantial amounts of prenatal testosterone, the female brain will continue to develop by default in a female direction. As we saw earlier, the vast majority of genetic males with AIS, who are insensitive



• **Figure 10.11** The Synthesis of Human Sex Hormones Sex hormones are steroids derived from cholesterol. There are several chemical reactions, indicated by the broken arrows, that take place in the development of progesterone from cholesterol and testosterone from progesterone. However, there is only one step, aromatization, that is necessary to turn testosterone into estradiol.

Sexually dimorphic Structurally different in males and females



to circulating testosterone, cannot be distinguished from typical girls and women in terms of outward appearance, gender identity, or behavior. In contrast, females with CAH and children of women who are prescribed androgens for medical reasons during pregnancy demonstrate more male-typical behaviors than unaffected females, while children of women who use anti-androgen medications during pregnancy show less male-typical behaviors (Hines, 2010).

MARKERS OF PRENATAL HORMONE ENVIRONMENTS Ethical constraints certainly preclude the artificial manipulation of the prenatal hormonal environment in humans. To investigate the possible influences of the prenatal hormonal environment on outcomes in typical individuals, researchers have attempted to identify biomarkers that are correlated with prenatal exposure to hormones. For example, testosterone levels in both maternal blood and in amniotic fluid are correlated with sex-typical behavior in offspring (Auyeung et al., 2009).

One possible biomarker for the prenatal hormonal environment is the relative length of the digits (fingers) of the hand, and in particular, the relationship between the length of the index finger (2D, because the thumb is 1D) and the ring finger (4D). Dividing the length of 2D by the length of 4D provides the 2D:4D ratio, which is determined by the prenatal ratio of testosterone to estrogens (Manning, 2011; Zheng & Cohn, 2011) (see • Figure 10.12).

Male 2D:4D ratios, particularly in the right hand, are typically smaller than female 2D:4D ratios, although the distributions of the ratios show wide areas of overlap (Wong & Hines, 2016). This means that the female index and ring fingers are similar in length (ratio approaching 1.0), while male index fingers tend to be shorter than ring fingers (ratio of about .955). The 2D:4D ratio sex difference occurs in other mammals as well as humans. The 2D:4D ratio is negatively correlated with sports ability and competitive ability in general (such as financial trading) (Hsu et al., 2015; Manning, 2011). In other words, evidence of higher prenatal testosterone predicts better sports performance and more competitive ability. Girls with lower 2D:4D ratios are more likely to be labeled as “tomboys” (Atkinson, Smulders, & Wallenberg, 2017). Having a low 2D:4D ratio is also linked to left-handedness and autism spectrum disorder, and it predicts some sex-dependent diseases (Manning, 2011).

Prenatal androgen exposure also affects anogenital distance, or the distance between the anus and genitalia. This distance is twice as large in males at birth compared to females, and is correlated with prenatal testosterone levels in both humans and rodents (Wong & Hines, 2016). Anogenital distance at birth predicts the extent of later gender-related behavior in males, but not in females (Pasterski et al., 2015).

Another potential marker for prenatal hormonal exposure occurs in the inner ear, where you might think sex differences are unlikely. The cochlea of the inner ear (see Chapter 7) is capable of producing its own sounds, known as **otoacoustic emissions**. As shown in • Figure 10.13, females produce louder and more frequent otoacoustic emissions (McFadden, 1993). These differences appear early in life and are possibly due to the amount of prenatal testosterone exposure experienced by

otoacoustic emissions Sounds emitted by the cochlea of the inner ear that show sex differences.

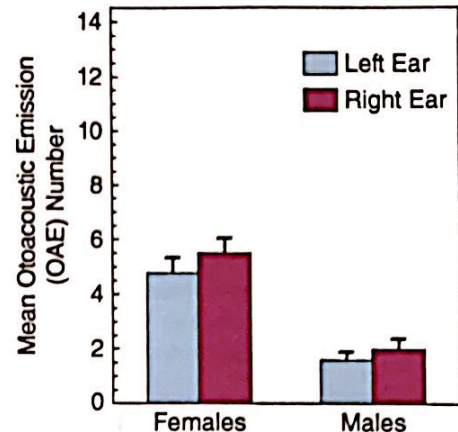
an individual (McFadden, 2011). Like the digit ratios, sex differences in otoacoustic emissions also occur in other mammals. Experimental manipulation of prenatal testosterone in sheep produced differences in otoacoustic emissions consistent with these signals serving as a biomarker for prenatal testosterone exposure (McFadden, Pasanen, Valero, Roberts, & Lee, 2009).

What can we learn about sex and gender from studies about finger length, anogenital distance, and sounds from the inner ear? As we will see in a later section, variations in these patterns not only differentiate between males and females but also contribute to our understanding of sexual orientation.

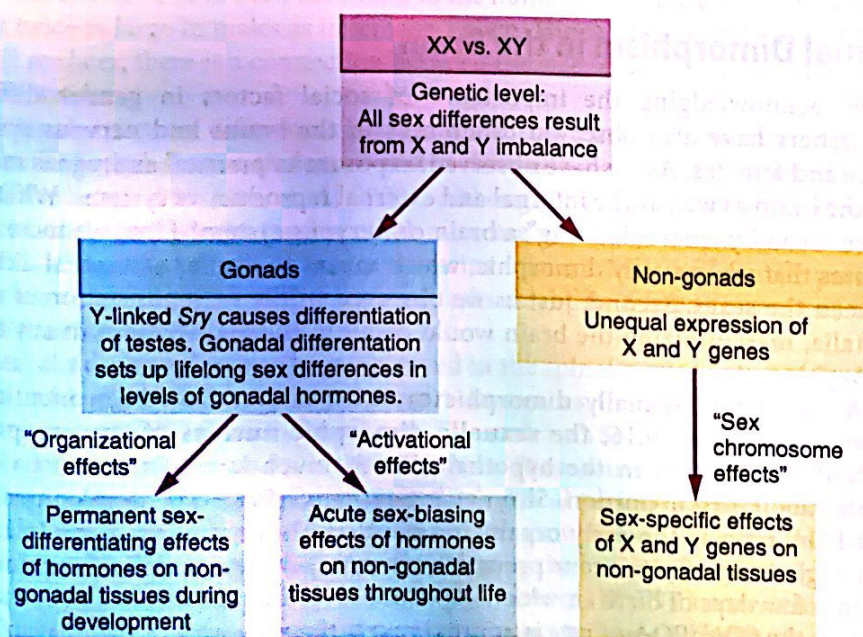
The Organizing Role of Sex Chromosome Genes

Although developmental neuroscientists often focus on the hormonal influences discussed above, this isn't the whole story (see • Figure 10.14). Long before the embryo is producing any sex hormones, genes on the sex chromosomes are producing proteins that influence neural structure and function (Arnold & McCarthy, 2016). Recognition of the contributions of sex chromosomes to brain and behavior is essential for understanding sex differences in diseases and disorders that affect one sex more than the other, such as autism (more common in males) and multiple sclerosis (more common in females).

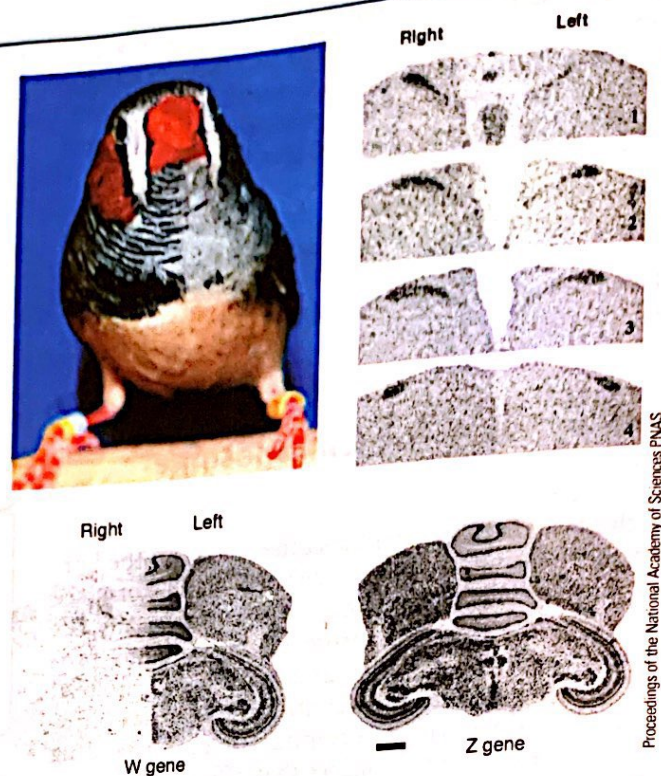
Outside of the gonads, sex chromosome effects interact with sex hormones in complex ways to produce phenotypes (see • Figure 10.15). In rodents, male hormones act to increase body weight, whereas male sex chromosomes decrease body weight (Arnold & McCarthy, 2016). In other words, chromosomes and hormones can produce compensatory effects. In other cases, hormones and chromosomes could produce synergistic effects, producing greater differences between XX and XY containing cells.



• **Figure 10.13** Otoacoustic Emissions Differ between Males and Females Recordings of otoacoustic emissions (OAEs) in both ears show that females produce a higher number of spontaneous otoacoustic emissions (OAEs) than males. OAEs presumably indicate the influence of prenatal testosterone levels.



• **Figure 10.14** Hormonal and Genetic Effects on Development The classic view of sex development begins with the sex chromosomes, which in turn determine whether the fetus develops ovaries or testes. Production of sex hormones by the gonads produces either permanent "organizing" influences or more reversible "activating effects" on cells, including those in the brain. Simultaneously, protein products of genes located on the X and Y chromosomes also influence many types of cells, often interacting with hormonal effects in complex ways.



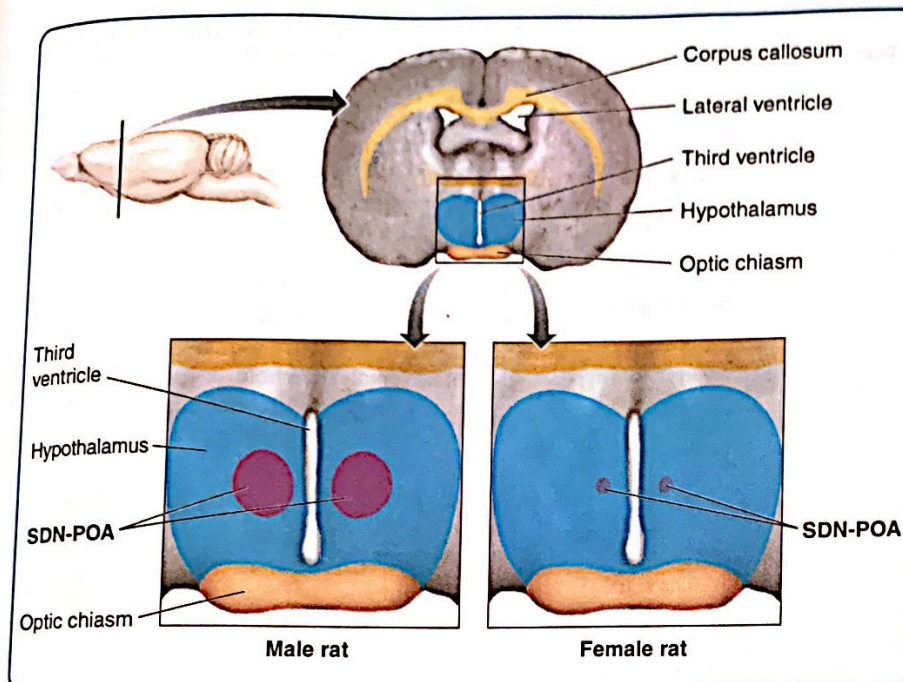
● **Figure 10.15** A Rare Gynandromorph Zebra Finch The gynandromorph zebra finch literally has a male side, complete with male plumage and a testis, and a female side, featuring female plumage and an ovary. In the upper right, the bird's song control nucleus, stained dark, is larger on the right, male side than on the left, female side. In the lower left image, the W gene (found only in bird females) is expressed only on the left side of the brain. In the lower right image, the Z gene is expressed more on the male side. Male birds typically have a ZZ genotype while female birds typically have a ZW genotype. The differences observed reflect the importance of genetic sex independent of hormonal effects.

Sexual Dimorphism in the Brain

While acknowledging the importance of social factors in gender differences, researchers have also observed differences in the brains and nervous systems of males and females. As we have observed, exposure to prenatal androgens masculinizes the brain as well as the internal and external reproductive systems. What exactly do we mean by "masculinizing" a brain or nervous system? First, we must identify features that are sexually dimorphic, which means to display structural differences between the sexes. Second, just as we observed in the masculinization of external genitalia, masculinizing the brain would result in the male pattern in any sexually dimorphic feature.

A number of sexually dimorphic brain structures have been identified. As shown in ●Figure 10.16, the **sexually dimorphic nucleus of the preoptic area (SDN-POA)**, located in the hypothalamus, is much larger in male rats than in female rats (Gorski, Gordon, Shryne, & Southam, 1978). The development of the SDN-POA reflects the early organizing effects of hormone exposure. In humans, most organizing effects occur prenatally. In rats, however, a critical window exists within a few days of birth in which exposure to androgens masculinizes the brain. At birth, the SDN-POA of rats is approximately the same size in males and females. Normally, the SDN-POA of the male begins to grow rapidly during the newborn

sexually dimorphic nucleus of the preoptic area (SDN-POA) A nucleus in the preoptic area of the hypothalamus that is larger in male rats than in female rats.



● **Figure 10.16** The SDN-POA of the Hypothalamus Is Sexually Dimorphic The SDN-POA, which is believed to be involved with sexual behavior, is much larger in male rats than in female rats. This difference probably results from the male rats' exposure to androgens shortly after birth.

period. If a newborn male rat is castrated, its SDN-POA is much smaller than normal. If a newborn female rat is injected with testosterone, its SDN-POA will be much larger than normal. Castration or injection of older animals does not change the size of the SDN-POA, indicating that this structure responds to early hormonal organization (Gorski, 1980). The precise function of the SDN-POA is not currently well understood, although lesions in this area of the hypothalamus generally reduce male sexual behavior (De Jonge et al., 1989).

The human equivalent of SDN-POA consists of a cluster of neurons in the preoptic area of the human hypothalamus known as the **interstitial nuclei of the anterior hypothalamus**, or INAH-1 (Bao & Swaab, 2011). Three additional clusters, INAH-2, INAH-3, and INAH-4, have been identified in the human brain. INAH-2 and INAH-3 are about twice as large in males as in females (Allen, Hines, Shryne, & Gorski, 1989). As we will see later, there is a connection between the size of these nuclei and a male's sexual orientation.

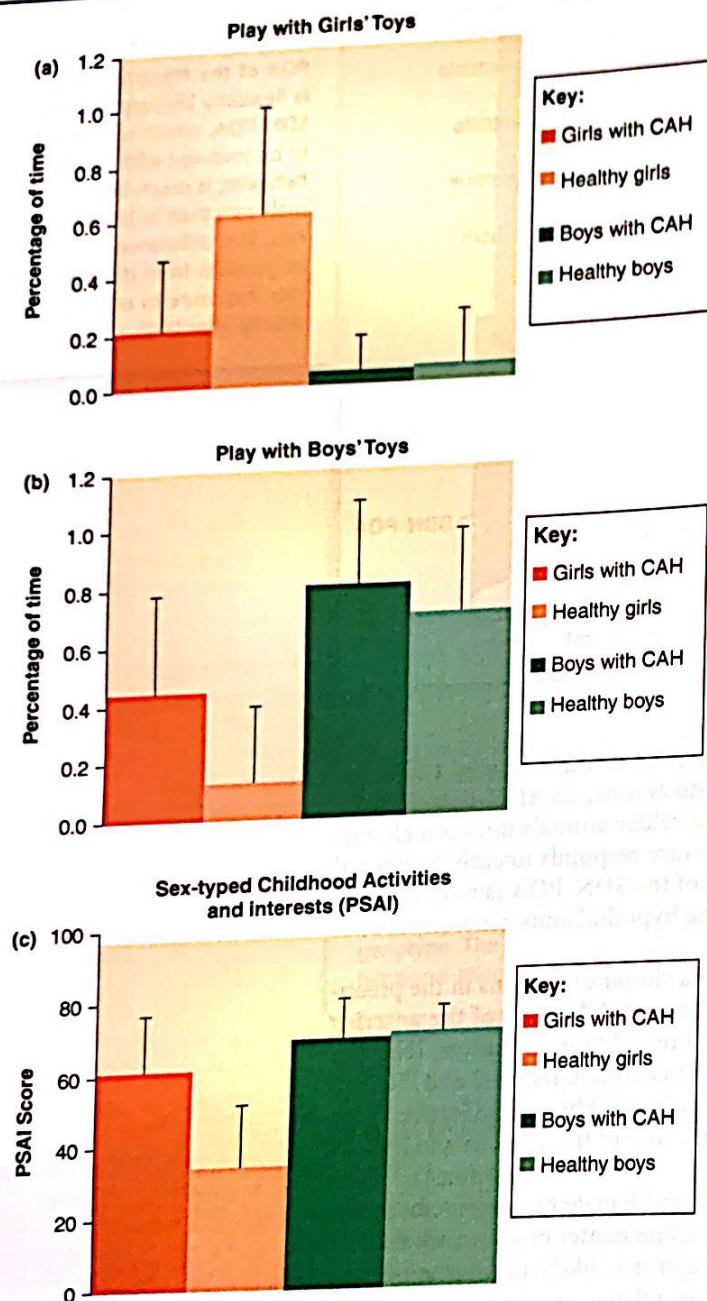
Additional structural differences between male and female brains have been discovered in the hypothalamus, thalamus, and in the white matter of the cerebral hemispheres (Breedlove, 1992; Hsu et al., 2008). Although it is likely that some of these differences, such as those in the hypothalamus, are related to sexual behavior, the significance of many of these differences remains unclear. Male and female patterns of performance on cognitive and emotional tasks might be related to some of these observed structural differences.

Sexual dimorphism has also been observed in the spinal cords of mammals. Male rats have more motor neurons in a structure known as the **spinal nucleus of the bulbocavernosus (SNB)** than do female rats. The male rat's SNB motor neurons innervate the bulbocavernosus muscles of the rat's penis. These muscles, or their equivalent, are missing in adult female rats. Prior to the rats' critical period of masculinization at birth, males and females both possess these muscles and about the same number of SNB cells (Rand & Breedlove, 1987). However, during the critical period, the low levels of androgens in female rats cause the muscles and most of the SNB neurons to die.

Sex differences in rates of neurogenesis and apoptosis (see Chapter 5) probably account for findings of different volumes in particular parts of the brain. Differences

interstitial nuclei of the anterior hypothalamus A collection of four small nuclei in the anterior hypothalamus, two of which (INAH-2 and INAH-3) appear to be sexually dimorphic. The size of INAH-3 might be associated with male sexual orientation.

spinal nucleus of the bulbocavernosus (SNB) Motor neurons in the spinal cord that innervate the male rat's bulbocavernosus muscles in the penis.



● **Figure 10.17 Prenatal Androgen Exposure and Play Behavior**

Typically developing boys are exposed prenatally to about 2.5 times the amount of androgens as typically developing girls. Girls with CAH are exposed to about half the amount of prenatal androgens as typically developing boys or about 25 percent more than typically developing girls. Boys with CAH are exposed to higher levels of androgens than typically developing boys, but because prenatal androgens are very high in both cases, this seems to have little behavioral effect. Time spent with girls' toys (a) is lower in girls with CAH than typically developing girls, but both are much higher than boys. Time spent with boys' toys (b) is higher in girls with CAH and typically developing unaffected girls, but is still lower than in boys. The PSAI score (c) results from subtracting scores for girl-typical items from boy-typical items on a 24-item, standardized measure. Higher scores reflect more male-typical behavior.

Source: Hines (2010)

in structures such as SDN-POA that are involved with reproduction appear more likely to occur due to different rates of cell death, while differences in structures such as the hippocampus and amygdala are more likely to result from different rates of neurogenesis (Arnold & McCarthy, 2016).

The brain is not just sexually dimorphic in terms of the volume of many structures but also in terms of synaptic density. For example, preoptic area neurons in male rodents have twice as many synaptic inputs than females (Arnold & McCarthy, 2016), which might affect the animals' responses to stimuli such as the odor of a potential mate.

Sex Differences in Behavior and Cognition

Undeniably, socialization plays a significant role in shaping male and female behavior, but recognizing the contributions of biology and the intricate interactions between biology and socialization enriches rather than diminishes our understanding of sex and gender.

PLAY BEHAVIOR Toy stores epitomize either/or thinking about males and females. Male-typical toys include cars, trucks, and guns and the color blue while female-typical toys include dolls, tea sets, and cosmetics and the color pink. Neutral toys do exist, such as books, puzzles, and crayons. While socialization clearly plays a role in a child's choice of toy, what do we know about biological contributions to play behavior?

Returning to the example of CAH females, who experience unusually high levels of prenatal androgens, provides interesting insights into the effects of biology on toy choice. Parents act as key socializing agents early in childhood; but parents of CAH daughters seem to be even more determined than parents of typically developing girls to socialize their daughters in a feminine pattern. Having been told that their daughters are likely to demonstrate some sex-atypical behaviors, parents who desire nothing but typical outcomes will attempt to compensate. Despite these efforts, toy choices by girls with CAH are significantly more likely to be in the masculine direction than in the feminine direction (Hines, 2010) (see ● Figure 10.17). In a similar fashion,



MCT/Getty Images



MCT/Getty Images

● **Figure 10.18** Sex-Typical Toy Preferences in Monkeys Young vervet monkeys show preferences for sex-typical toys in the absence of any human-like gender socialization.

androgen exposure as measured in maternal blood or amniotic fluid is predictive of masculine toy interest in typically developing girls (Hines, 2010). Because the parents of this latter set of girls have no information about their daughters' prenatal hormone state, it is highly unlikely that differences in socialization could account for these results.

Children begin to prefer sex-typed toys between the ages of 12 and 18 months. At these same ages, children are unable to match sex-typed toys (vehicles and dolls) with male or female faces or voices, suggesting that they have not yet been socialized to think of toys as "male" or "female" (Serbin, Poulin-Dubois, Colburne, Sen, & Eichstedt, 2001). Socialization is even less likely to play a role in the toy choices of monkeys (see ● Figure 10.18). Young male monkeys spend more time with wheeled toys and balls, whereas young female monkeys prefer dolls, plush animals, and pots (Alexander & Hines, 2002; Hassett, Siebert, & Wallen, 2008; Swan et al., 2010).

GENDER IDENTITY Gender identity is defined as a person's self-concept as male or female and is usually viewed as the end product of years of socialization. In **transsexuality**, a person's gender identity is inconsistent with his or her biological sex and can be resolved with sex-reassignment surgery and hormonal treatment. Information about the contribution of social factors in the development of transsexuality is sparse. Research on the biological correlates of transsexuality might illuminate general principles of gender identity as a whole.

Transsexuality in biological females is rare, occurring in approximately .005 percent of women (Dessens, Slijper, & Drop, 2005). In contrast, approximately 3 percent of women with CAH, raised as girls, express a wish to live as men, a rate that is 600 times greater than in the general public. An additional 5 percent of CAH women express a

transsexuality Having a gender identity that is inconsistent with biological sex.

general dissatisfaction with the female role (Bao & Swaab, 2011). Keep in mind that this still means that the vast majority of women with CAH (92 percent) are satisfied with their female gender identity.

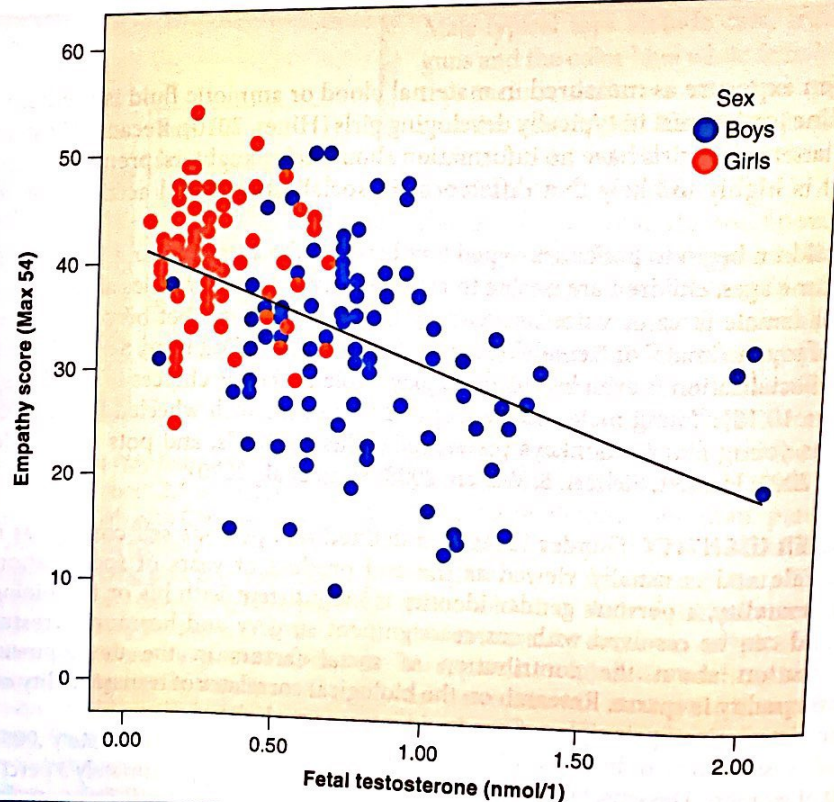
Transsexuality might occur due to the prenatal timing of hormone influences on the reproductive systems and on the brain, with influences on the reproductive systems occurring first. If these two processes are separable due to different timing, the systems might not develop congruently (Bao & Swaab, 2011). In a sample of male-to-female transsexual individuals, two brain structures known to be sexually dimorphic (the central nucleus of the bed nucleus of the stria terminalis [BSTc] and INAH-3) were found to show the typical "female" pattern of volume. In a single case of a female-to-male transsexual individual, BSTc and INAH-3 both conformed to the "male" pattern. Complicating this analysis, however, is the fact that BSTc typically does not show sexual dimorphism before puberty, while many transsexual individuals express strong gender dissatisfaction at younger ages.

Results from examinations of brain structure volume in adolescents with gender dysphoria (GD), or individuals who experience distress due to their sex and gender, show that GD youth are much more similar to those sharing their birth sex than with others sharing their preferred gender (Hoekzema et al., 2015). However, subtle differences were found in GD youth in sexually dimorphic structures that could indicate at least some level of atypical differentiation.

PERSONALITY Early organization of the nervous system might influence later development across a number of sophisticated behavioral domains, while interacting, of course, with socialization at each step of the way.

In general, large numbers of studies have pointed to higher empathy in females and higher levels of physical aggression in males (see ● Figure 10.19). Consistent with

● **Figure 10.19** Fetal Testosterone and Empathy
Levels of fetal testosterone are negatively correlated with children's scores on a standardized test of empathy.



the patterns we have already observed, females with CAH show decreased empathy and increased physical aggression relative to typically developing girls (Hines, 2010). Both boys and girls with high amniotic fluid levels of testosterone or prenatal exposure to androgen medications taken by their mothers show reduced empathy and higher levels of physical aggression. It is important to note that not all personality dimensions that show reliable differences between males and females, such as assertiveness, are related to prenatal testosterone exposure.

COGNITION In a large body of research data, males (both human and nonhuman) have been shown to have a slight advantage in visuospatial tasks (Kimura, 1992), whereas females have a slight advantage in verbal tasks and episodic memory, or memory for events in a personal timeline (see Chapter 13; Herlitz, Dekhtyar, Asperholm, & Weber, 2016). Research results investigating these trends within CAH females are mixed, suggesting that the organizing role of prenatal hormones plays less of a part here than in the previously discussed behavioral domains.

The male advantage in visuospatial skills appears early in life. However, visuospatial skills are correlated with current, not necessarily prenatal, testosterone levels in both men and women. Older men receiving testosterone supplements improved their performance on spatial tasks (Janowsky, Oviatt, & Orwoll, 1994). On tests of mental figure rotations, such as the sample shown in **Figure 10.20**, women received their best scores when testosterone levels were high and their worst scores when estrogen levels were high (Kimura & Hampson, 1994). In contrast to performance on spatial tasks, verbal fluency and manual dexterity in women appear to be correlated with higher levels of estrogens. Surprisingly, men who received testosterone supplements improved their scores on verbal fluency tests by a factor of 20 percent (O'Connor, Archer, Hair, & Wu, 2001). This suggests that the activating effects of current sex hormone levels interact with existing systems in complex ways. Testosterone boosts spatial performance in both men and women, while verbal performance was enhanced by testosterone in men and by estrogens in women.

In one interesting exploration of the relationship of adult hormone levels to cognitive performance, female-to-male and male-to-female transsexuals were evaluated before and after cross-sex hormonal treatment (Sommer et al., 2008). Using fMRI, both groups showed correlations between their estradiol levels with activation in language centers and their testosterone levels with brain activation during mental rotation tasks.

PSYCHOLOGICAL DISORDERS As we will see in Chapter 16, a number of psychological disorders show big differences in prevalence rates for men and women. Two thirds of adults with major depressive disorder are female, while the vast majority of individuals with autism spectrum disorder, attention deficit hyperactivity disorder, and Tourette syndrome are male. The extent to which the biological differences discussed so far contribute to these patterns is currently under active investigation.

Sexual Orientation

While the previous discussion of male and female prenatal hormonal environments, brain structure, and behavior is interesting in its own right, it also forms the foundation for understanding the biological correlates of sexual orientation.

Sexual orientation refers to a stable pattern of attraction to members of a particular sex. Approximately 1.8 percent of adult males and 1.5 percent of adult females identify themselves as gay or lesbian, and 0.4 percent of men and 0.9 percent of

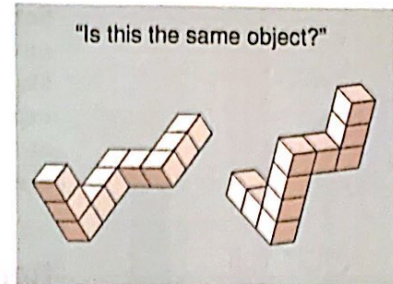


Figure Rotation

● **Figure 10.20 Gender Influences Cognition** Women generally have a slight advantage in verbal tasks such as naming objects that have the same color and listing words that begin with a particular letter. Men have a slight advantage in visuospatial tasks, such as this figure rotation task. When asked whether the two shapes are the same, males respond somewhat faster than females.

sexual orientation A stable pattern of attraction to members of a particular sex.

women describe themselves as bisexual (Ward, Dahlhamer, Galinsky, & Joestl, 2014). Sexual orientation is not synonymous with sexual behavior. Many people engage in same-sex behavior and fantasy while maintaining a strong heterosexual orientation. Stoller and Herdt (1985) described a tribal culture in which all adolescent males are expected to engage in same-sex behavior until they are married to women. In spite of this prior sexual experience, the sexual orientation of these males as adults was overwhelmingly heterosexual.

Hormones and Sexual Orientation

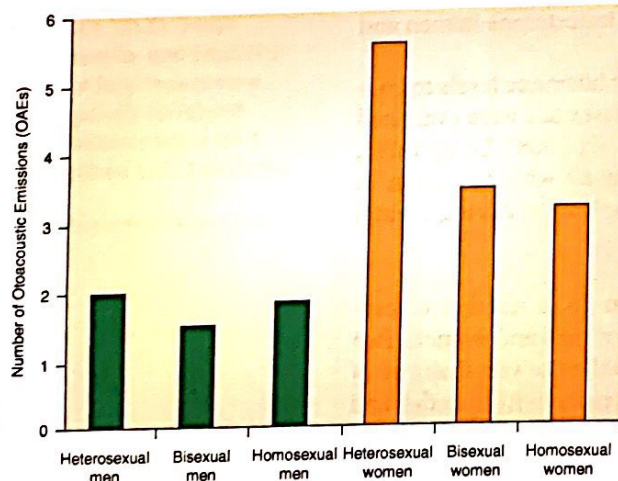
Early hormone exposure influences adult sexual behavior in animals and humans. As noted previously, male rats have a larger SDN-POA than female rats. Exposure to testosterone during a critical period accounts for this sexual dimorphism. If male rats do not receive exposure to testosterone during this critical period, their SDN-POA remains small, and their adult sexual behavior differs from rats receiving typical exposure to testosterone. Rats exposed to low testosterone are less likely to engage in sexual behavior with females and more likely to engage in sexual behavior with males than are rats exposed to normal testosterone levels (Matuszewich et al., 1999). In addition, exposure to testosterone during the critical period increases the size of SDN-POA in female rats and increases the likelihood that they will engage in sexual activity with females as adults. We have already seen that atypical conditions such as CAH, which involves prenatal exposure to androgens, can increase the likelihood that women will engage in bisexual or lesbian behavior as adults. However, the majority of CAH women are heterosexual. Also, the majority of lesbian and bisexual women do not have a history of CAH or similar conditions.

Earlier, we described the differences between otoacoustic emissions in men and women and explored the likelihood that these differences served as a biomarker of

prenatal androgen exposure. McFadden and Pasanen (1999) measured the otoacoustic emissions of lesbian, bisexual, and heterosexual women. As shown in ● Figure 10.21, the rate of the emissions in lesbian and bisexual women fell between the typical levels for heterosexual women and for men. McFadden and Pasanen suggested that exposure to prenatal androgens may have influenced both the ear structure and sexual orientation of the lesbian and bisexual women.

We also discussed another possible indicator of prenatal exposure to androgens, the 2D:4D ratio. Lesbians tended to show the more masculine pattern of finger length, suggesting that they might have experienced prenatal exposure to androgens (Kraemer et al., 2006). As shown in ● Figure 10.22, researchers do not find a systematic pattern of finger length among homosexual men as opposed to heterosexual men, however.

What could initiate the differences in prenatal hormonal environments associated with homosexuality? One interesting clue comes from the observation that birth order matters for homosexual men, although this finding continues to be debated (Kishida & Rahman, 2015; Blanchard & VanderLaan, 2015). Men who have older brothers are slightly more likely to be homosexual than men who have no siblings, younger siblings only, or older sisters, although the effect size of this difference is small (Blanchard,



● **Figure 10.21 Sexual Orientation and Otoacoustic Emissions** Men typically emit lower numbers of otoacoustic emissions (OAEs) than women, which is believed to be the result of different exposure to prenatal testosterone. Bisexual and homosexual males do not show different rates of OAEs than heterosexual males, but bisexual and homosexual women show rates that are midway between those found in heterosexual females and men.

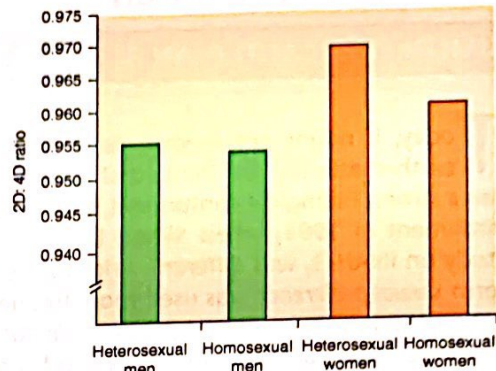
Source: Adapted from McFadden and Pasanen, 1999.

1997; Cantor, Blanchard, Paterson, & Bogaert, 2002). The protein products of genes located on the Y chromosome might provoke the mother's immune response, which should become greater with each successive pregnancy with a male fetus. A strong immune response from the mother could affect her fetus's brain while not affecting the gonads or genitals.

Brain Structure and Sexual Orientation

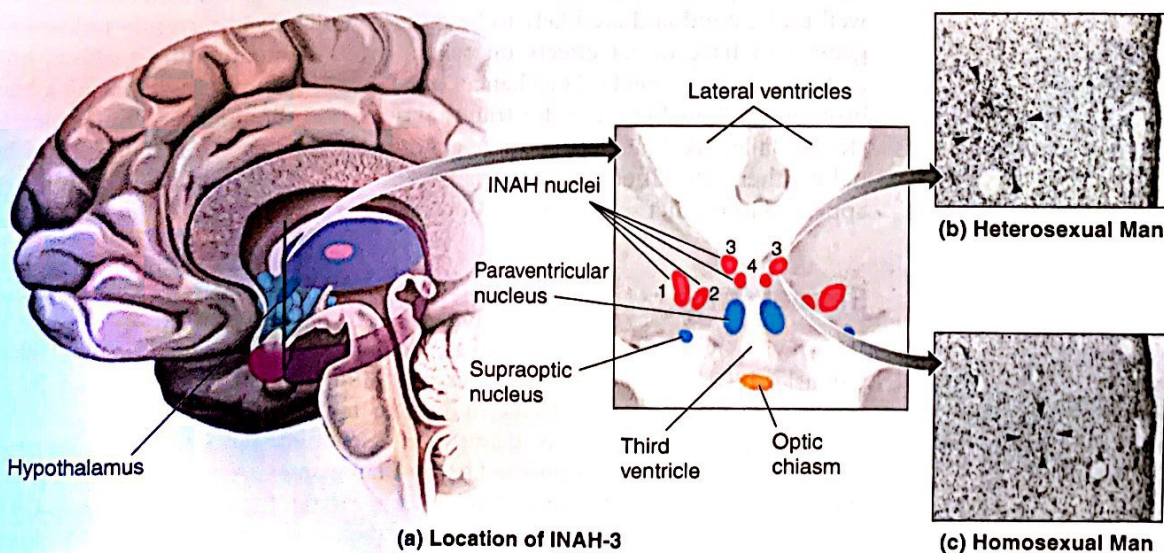
As we have seen previously, several brain structures are sexually dimorphic, especially INAH-3 in the hypothalamus. Building on these observations, Simon LeVay (1991) asked whether INAH-3 might be different in heterosexual and homosexual men. Lesions of INAH-3 in monkeys impairs heterosexual behavior but does not affect overall sex drive, as indicated by rates of masturbation. He found that INAH-3 was two to three times larger in heterosexual men than in homosexual men. The size of INAH-3 among LeVay's homosexual subjects was not significantly different from the size observed in female subjects. • Figure 10.23 shows the location of INAH-3, as well as heterosexual and homosexual examples from LeVay's research.

The anterior commissure, a small band of fibers connecting the two cerebral hemispheres, is also among the structures known to be sexually dimorphic in humans. Laura Allen and Roger Gorski (1992) reported that the size of the anterior commissure varies reliably between homosexual and heterosexual males. Unlike the hypothalamus, the anterior commissure has no direct role in sexual behavior. The observed differences in this structure might simply be an additional marker like otoacoustic emissions for the fetal hormone environment.



• **Figure 10.22 Sexual Orientation and 2D:4D Ratio** Lower 2D:4D ratios are related to exposure to prenatal testosterone. Heterosexual and homosexual males do not show different 2D:4D ratios, but the 2D:4D ratio of homosexual women falls midway between the ratios of heterosexual women and men, possibly indicating greater exposure to prenatal testosterone.

Source: Data from Williams et al. (2000).



• **Figure 10.23 INAH-3 Size Correlates with Sexual Orientation** Simon LeVay reported that INAH-3 is smaller among women and homosexual men than among heterosexual men. (a) This image shows the location of INAH-3. The micrograph in (b) is taken from a heterosexual man, whereas the micrograph in (c) is taken from a homosexual man.

Connecting to Research

SIMON LEVAY AND INAH-3

Today, it might not seem exactly revolutionary or earth-shattering to think that sexual orientation has a strong biological component, but the cultural environment of 1991, when Simon LeVay published his study on INAH-3, was different. Prior to the 1990s, the term *sexual preference* was used more frequently by scientists than the current term, *sexual orientation*.

LeVay was cautious in interpreting his results. First of all, because INAH-3 is too small to observe in living participants with available imaging technologies, LeVay studied autopsied brains. This obviously prevented him from obtaining a detailed history of his subjects' sexual behavior. The homosexual men's medical records documented their sexual behavior, as this was relevant to their diagnosis of AIDS, but those of the presumed heterosexual men did not. The study could not be extended to the sexual orientation of women, because their medical records also lacked this information. In addition, LeVay raised the possibility that the AIDS condition, which affected his homosexual participants, could have caused shrinkage of INAH-3. However, he

didn't give this argument much credibility because INAH-3 in the heterosexual subjects with AIDS followed the heterosexual male pattern. Finally, critics have suggested that engaging in different types of sexual behavior might influence the size of INAH-3. LeVay again discounted this interpretation and suggested that the differences he observed were more logically the result of organizing prenatal factors.

Because this type of research is quite difficult to conduct with human participants, other researchers have investigated the correlation of brain structure and sexual behavior in animals. Among domestic sheep, 6 to 8 percent of rams (males) mate exclusively with other males. Kay Larkin and her colleagues (Larkin, Resko, Stormshak, Stellflug, & Roselli, 2002) studied SDN-POA (a non-primate equivalent of INAH) in rams who engaged in same-sex behavior, in rams that mated with ewes (females), and in ewes. SDN-POA in rams that engaged in same-sex behavior was about the same size as in ewes and differed from SDN-POA in rams that mated with ewes. These results provide a parallel to LeVay's findings in INAH-3.

Genes and Sexual Orientation

Genetics appear to influence sexual orientation, although the exact mechanisms are not well understood and are likely to be quite complex. It is currently unknown whether genes can have direct effects on sexual orientation or indirect effects on prenatal androgen environments. The chances of a homosexual male twin having a homosexual brother are 20 to 25 percent for fraternal twins and about 50 percent for identical twins (Kirk, Bailey, & Martin, 2000). A genome-wide analysis of 409 pairs of homosexual brothers identified two regions on Chromosome 8 and the X chromosome that appeared to predict sexual orientation (Sanders et al., 2015).

Sexual Orientation and Cognition

We previously observed that males and females differed on visuospatial tasks and verbal tasks. Like the biomarkers and sexually dimorphic structures, will we see variations in performance of these tasks based on sexual orientation?

In one large-scale study using mental rotation tasks for assessing visuospatial skills, men consistently performed better than women, regardless of sexual orientation (Peters, Manning, & Reimers, 2007) (see • Figure 10.24). Taking sexual orientation into account, heterosexual men outperformed homosexual men, with bisexual men scoring between these two groups. Homosexual and bisexual women scored at about equal levels, and both groups outperformed heterosexual women. Similar findings were reported for the results of three tests of verbal fluency. Homosexual men outperformed heterosexual women, but both of these groups outperformed heterosexual men and homosexual women, who performed at about the same level (Rahman, Abrahams, & Wilson, 2003).