Sexual Differentiation

Reproductive behavior constitute the most important category of social behavior, because without them, most species would not survive. These behaviors—which include courting, mating, parental behavior, and most forms of aggressive behaviors—are the most striking categories of sexually dimorphic behaviors, that is, behaviors that differ in males and females (di + morphous, “two forms”). As you will see, hormones present both before and after birth play a very special role in the development and control of sexually dimorphic behaviors.

Sexual Differentiation (continued)

Genetic Differentiation

A person’s chromosomal sex is determined at the time of fertilization. However, this event is merely the first in a series of steps that culminates in the development of a male or female. All cells of the human body (other than sperms or ova) contain twenty-three pairs of chromosomes, including a pair of sex chromosomes. The genetic information that programs the development of a human is contained in the DNA that constitutes these chromosomes. The production of gametes (ova and sperms; gamein means “to marry”) entails a special form of cell division.

Sexual Differentiation (continued)

Genetic Differentiation

There are two types of sex chromosomes:
- X chromosomes
  - All the ova that a woman produces will contain an X chromosome (XX).
  - Males have an X and a Y chromosome (XY).
- Y chromosomes
  - When a man’s sex chromosomes divide, half the sperms contain an X chromosome and the other half a Y chromosome.
  - A Y-bearing sperm produces an XY-fertilized ovum and, therefore, a genotypic male.
  - An X-bearing sperm produces an XX-fertilized ovum and, therefore, a genotypic female.
Sexual Differentiation (continued)

Genetic Differentiation

- There are also genetic mosaics:
  - 47,XXY Klinefelter's syndrome a phenotypic male
  - 47,XYY a phenotypic male
  - 45,XO Turner's syndrome a phenotypic female
- It appears that the only function of the Y chromosome is to masculinize the organism.

Sexual Differentiation (continued)

- Men and women differ in many ways:
  - Their bodies are different,
  - parts of their brain are different,
  - and their reproductive behaviors are different.
- Are all these differences encoded on the tiny Y chromosome, the sole piece of genetic material that distinguishes males from females?
- The answer is no.

Sexual Differentiation of the Gonads

- The gonads — testes or ovaries — are the first to develop.
  - Gonads (from the Greek *gènos*, “procreation”) have a dual function:
    - They produce ova or sperms
    - and they secrete hormones.
- Through the first four weeks of embryonic development, male and female embryos are identical.
- Both sexes have a pair of *bipotential gonads* (genital ridge), which can develop into either testes or ovaries.
- The factor that controls their development appears to be a single gene on the short arm of the Y chromosome called SRY.
In fact, if this gene is inserted into one of the X chromosomes of a female (XX) embryonic mouse, the animal will develop as a male.

There are several outcomes that can occur at this stage; testes, ovaries, testes on one side ovaries on the other side, and ovotestes.

Once the gonads have developed, a series of events is set into action that determines the individual’s gender. These events are directed by hormones, which affect sexual development in two ways. During prenatal development these hormones have organizational effects, which influence the development of a person’s sex organs and brain. These effects are permanent; once a particular path is followed in the course of development, there is no going back.

The second role of sex hormone is their activational effect. These effects occur later in life, after the sex organs have developed. For example, hormones activate the production of sperm, make erection and ejaculation possible, and induce ovulation. Because the bodies of adult males and females have been organized differently, sex hormones will have different activational effects in the two sexes.

The internal genitalia are bisexual; that is all embryos contain the precursors for both female and male sex organs. However, during the twelfth week of gestation only one of these precursors develops; the other withers away. The precursor of the internal female sex organs, which develops into the fimbriae and fallopian tubes, the uterus, and the inner two-thirds of the vagina, is called the Müllerian ducts (Müllerian system). The gender of the internal sex organs of a fetus is determined by the presence or absence of hormones secreted by the testes. That is, if these hormones are present, the Wolffian ducts develop.

The precursor of the internal male sex organs, which develop into the epididymis, vas deferens, seminal vesicles, and prostate, is called the Wolffian ducts (Wolffian system). The gender of the internal sex organs of a fetus is determined by the presence or absence of hormones secreted by the testes.
Sexual Differentiation (continued)

Sexual Differentiation of the Internal Genitalia

- If they are not, the Müllerian (female) ducts needs no hormonal stimulus from the gonads to develop; it just normally does so.
- In contrast, the cells of the Wolffian (male) ducts do not develop unless they are stimulated by a hormone.
- Thus, testes secrete two types of hormones.
  - The first, a peptide hormone called Müllerian inhibiting hormone, does exactly what its name says:
  - It prevents the Müllerian ducts from developing.
  - It therefore has a defeminizing effect.
- The second, a set of steroid hormones called androgens, stimulate the development of the Wolffian ducts.
  - Androgens have a masculinizing effect.
  - Two different androgens are responsible for masculinization.
    - The first, testosterone, is secreted by the testes – and gets its name from these glands.
    - An enzyme called 5-α reductase converts testosterone into another androgen, known as dihydrotestosterone.
  - The precursor of the male internal genitalia – Wolffian ducts – contains androgen receptors that are coupled to cellular mechanisms that promote growth and division.

Sexual Differentiation of the Internal Genitalia

- Ovarian hormones play a small role at this early stage of development.
  - The lack of both the estrogen receptors results in ovaries that resemble testes and produce Müllerian inhibiting hormone.
- The fact that the internal genitalia of the human embryo are bisexual and could potentially develop as either male or female is dramatically illustrated by a genetic disorder.
  - Persistent Müllerian duct syndrome, has two causes:
    - A failure to produce Müllerian inhibiting hormone or the absence of receptors for this hormone.
    - When this syndrome occurs in genetic males, androgens have their masculinizing effect but defeminization does not occur.
- Thus, the person is born with both sets of internal genitalia, male and female.
- The presence of the additional female sex organs usually interferes with normal functioning of the male sex organs.
At about 12 week of fetal life, the primordial structure of the external genitalia of both sexes are identical, and have the capacity to differentiate in either direction. In the absence of dihydrotestosterone the genital tubercle develops into a clitoris. The outer swelling on either side of the genital slit becomes the labia majora. If dihydrotestosterone is present the genital tubercle develops into a penis. The outer swelling, on either side of the genital slit, fuses in the midline to form the scrotum to receive the testes.

Sexual Differentiation of the External Genitalia

Sexual Differentiation of the Central Nervous System

There are greater number of synapses on spines in the preoptic region of the hypothalamus in normal female rats compared to the equivalent region in males. This difference was linked with ovulatory behavior and was found to be directly under the influence of hormones during development. A nucleus found in male rodent hypothalamus that is essentially missing in female is the sexual dimorphic nucleus (SDN) located in the medial preoptic area (MPA). This nucleus is responsible for the different sexual postures of rodents during coitus, and develops under the influence of hormones.

Sexual Differentiation of the Central Nervous System

Ventromedial nucleus of the hypothalamus (VMH) plays an essential role in female sexual behavior. There are four cell grouping within the anterior hypothalamus of humans, collectively called the interstitial nuclei of the anterior hypotalamus (INAH; the nuclei are numbered 1-4 from dorsolateral to ventromedial). INAH-3 is more than twice as large in males as they are in females. INAH-1 is the same size in females and males up until 2-4 years of age; it then becomes larger in males. INAH-2 is larger in females of childbearing age than in prepubescent and postmenopausal females.

Sexual Differentiation of the Central Nervous System

One aspect of human reproduction in which these nuclei have been implicated is the choice of a sexual partner. In addition to heterosexual behavior, some people express interest in both females and males (bisexuality), and some only in members of their own phenotypic sex (homosexuality). Still other people are interested in the opposite sex but have a gender identity that is at odds with their phenotypic sex (transgenderism). INAH-3 is twice as large in heterosexuals male as in homosexuals. It has been suggested that this difference is related to sexual orientation.

Sexual Differentiation of the Central Nervous System

The suprachiasmatic nucleus in male homosexuals has twice the volume as male heterosexuals. There was no difference between heterosexual males and females. It has been suggested that the difference in nuclear size between homosexual and heterosexual men might be related to sexual orientation. In comparing male-to-female transgendered individuals to heterosexual males, another hypothalamic structure, the bed nucleus of the stria terminalis, is smaller in transgendered males, being close in size to that of females.
Many studies have been done with rodents. There appears to be three critical factors that influence sexually dimorphic behaviors. Exposure to androgen perinatally, the presence or absence of gonads, and exposure to hormones in adulthood.

Male rats castrated at birth and put on hormone replacement therapy in adulthood (estrogen and progesterone) show all of the copulatory behaviors of a female rat. That is, they do not mount females and let males mount them. They show the stereotypic lordosis response. If ovaries are implanted in these males the ovaries function in a cyclic manner. That is, they show normal estrous cycles and ovulations.

A female rat exposed to testosterone with in the first five days of life show all of the copulatory behaviors of a male rat. That is, they mount other female rats and don’t allow males to mount them. They exhibit all of the behaviors, even ejaculatory spasms, even though they do not have a penis nor do they ejaculate. These female with ovaries intact are anovulatory. That is, they do not have an estrous cycle nor do they ovulate.

Castrated male rats show all of the maternal behaviors of female rats. They build nests when pups are present and retrieve the pups when they leave the nest. Female rats exposed to testosterone do not show maternal behaviors. When artificially impregnated they do not build nest and they do not retrieve the pups when they leave the nest.
Sexual Differentiation (continued)

Sex Difference in Animal Behavior

- Sexually dimorphic behaviors of Rhesus macaques:
  - Males perform more threat behaviors,
  - Initiate more social contact,
  - Participate in more rough-and-tumble play,
  - Participate in more chase play,
  - And withdraw less often from the initiations, threats, and approaches of other monkeys.

- Female rhesus exposed to androgens prenatally their nonsexual behaviors were shifted in the masculine direction.
  - These results generalized across group size and make-up of the group (same sex, mixed sex).

Sex Difference in Animal Behavior

- Their mating behavior was more male like than female.
  - That is, they did not let males mount them and they mounted other females.

- When impregnated they were not good mothers.
  - They did not care for their young.

- Male rhesus when castrated at birth acted like normal males.

Sexual Differentiation (continued)

Human Clinical Syndromes

- Congenital Adrenal Hyperplasia (CAH) a genotypic female.
  - A genetic recessive trait in which excessive production of adrenal androgens is caused by an enzymatic defect in the biosynthesis of cortisol.
  - Causes virilization of the female fetus and subsequent precocious virilization at puberty.

- Treatment: cortisol replacement therapy and surgical feminization of the external genitalia.
  - Higher than normal IQ.
    - < 60% had IQ at 110 while in a normal population one would expect only 25%.
    - < 30% had IQ above 130 while only 2% would be expected.

- These girls were often described as tomboys by themselves and their mothers.
  - Tomboyism – high energy level, strong interest and participation in outdoor physical activities.
  - Minimal interest in dollplay, dresses, and girls activities.
  - Less concerned about marriage and child care and more interested in careers.

- No differences between cortisone treated and noncortisone treated groups, eliminating postnatal androgen levels.

Progestin-induced hermaphroditism a genotypic female.

- Pregnant women were given synthetic progestin in order to prevent threatened miscarriages.
- Progestin seems to act in some ways like testosterone, producing partially virilized female babies (maculinized external genitalia).
- Surgical corrected female and exhibited normal feminization at puberty, with menstruation and ovulation occurring.
Sexual Differentiation (continued)

Human Clinical Syndromes

 findViewById(response)

\text{Androgen-insensitivity-syndrome} (AIS) a genotypic male but a phenotypic female.
- Gonads testes;
- Internal genitalia female
- External genitalia female

Surgically feminization of external genitalia and put on hormone replacement therapy (estrogen and progesterone).
- Two test in which these girls did best were comprehension and similarities
- and their poorest scores were in the object assembly and block design subtest, two test of visual-perceptual organization.
- These results parallel the performance configuration of genetic females and are in contrast to the average male performance.

These girls were not described as tomboys and as children preferred to play with girls and dolls.
They had strong desire for marriage, and had minimum interest in outside jobs.

\text{Turner Syndrome} is an XO, genotype.
- Genetic abnormality 45,XO a missing sex chromosome.
- Lack gonads and no exposure to any gonadal hormones during the critical periods.
- Phenotypic female

Behavioral characteristics;
- more passive than their controls with respect to childhood fighting,
- more likely to withdraw from attack rather than defend themselves,
- less interested in outdoor play,
- showed strong interest in doll play

Absence of gonadal steroid hormones produces feminine patterns of behavior.

Taken together, this evidence suggests a plausible explanation of the continuum of human sexuality:
- Small differences in the relevant brain structures generate significant differences in sexual identity and behavior.
- These brain dimorphisms are probably established by the early influence of hormones acting on the brain nuclei that mediate various aspects of sexuality.
- For instance, low levels of circulating androgens in a male early in life could lead to a relatively “feminine” brain in genotypic males.
The primary sex characteristics include the gonads, internal genitalia, and external genitalia. These organs are present at birth. The secondary sex characteristics, such as enlarged breast and widened hips in women or beards and deep voice in men, do not appear until puberty. Without seeing genitals, we must guess the sex of a prepubescent child for his or her haircut and clothing; the bodies of young boys and girls are rather similar. However, at puberty the gonads are stimulated to produce their hormones, and these hormones cause the person to mature sexually.

The onset of puberty occurs when the cells in the hypothalamus secrete gonadotropin-releasing hormones (GnRH), which stimulates the production and release of two gonadotropic hormones by the anterior pituitary gland. The two gonadotropic hormones are:
- follicle stimulating hormone (FSH)
- luteinizing hormones (LH), named for the effects they produce in the female.
  - The production of a follicle and its subsequent luteinization.

However, the same hormones are produced in the male, where they stimulate the testes to produce sperm and secrete testosterone. In males FSH is called Interstitial Cell Stimulating hormone (ICSH). The pituitary gland is bipotential.
- If male and female pituitary glands are exchanged in rats, the ovaries and testes respond perfectly to the hormones secreted by the new glands.

In response to gonadotropic hormones, the gonads secrete sex steroid hormones.
- The ovaries produce estradiol, one of a class of hormones known as estrogens.
- The testes chiefly produce testosterone.
- Both gonads produce a small amount of the hormones of the other sex.
Both estradiol and testosterone initiate closure of the growing portion of the bones and thus halt skeletal growth. Estradiol also causes breast development, growth of the lining of the uterus, changes in the deposition of body fat, and maturation of the female genitalia. Testosterone stimulates growth of: facial, axillary (underarm), and pubic hair; lowers the voice; alters the hairline on the head (often causing baldness later in life); stimulates muscular development; and causes genital growth.

This description leaves out two of the female secondary characteristics: axillary and pubic hair. These characteristics are produced not by estrogen but rather by androgens secreted by the cortex of the adrenal gland. The bipotentiality of some of the secondary sex characteristics remains throughout life. If a man is treated with an estrogen, he will grow breasts and his facial hair will become finer and softer. However, his voice will remain low, because the enlargement of the larynx is permanent. Conversely, a woman who receives high levels of an androgen will grow a beard, and her voice will become lower.