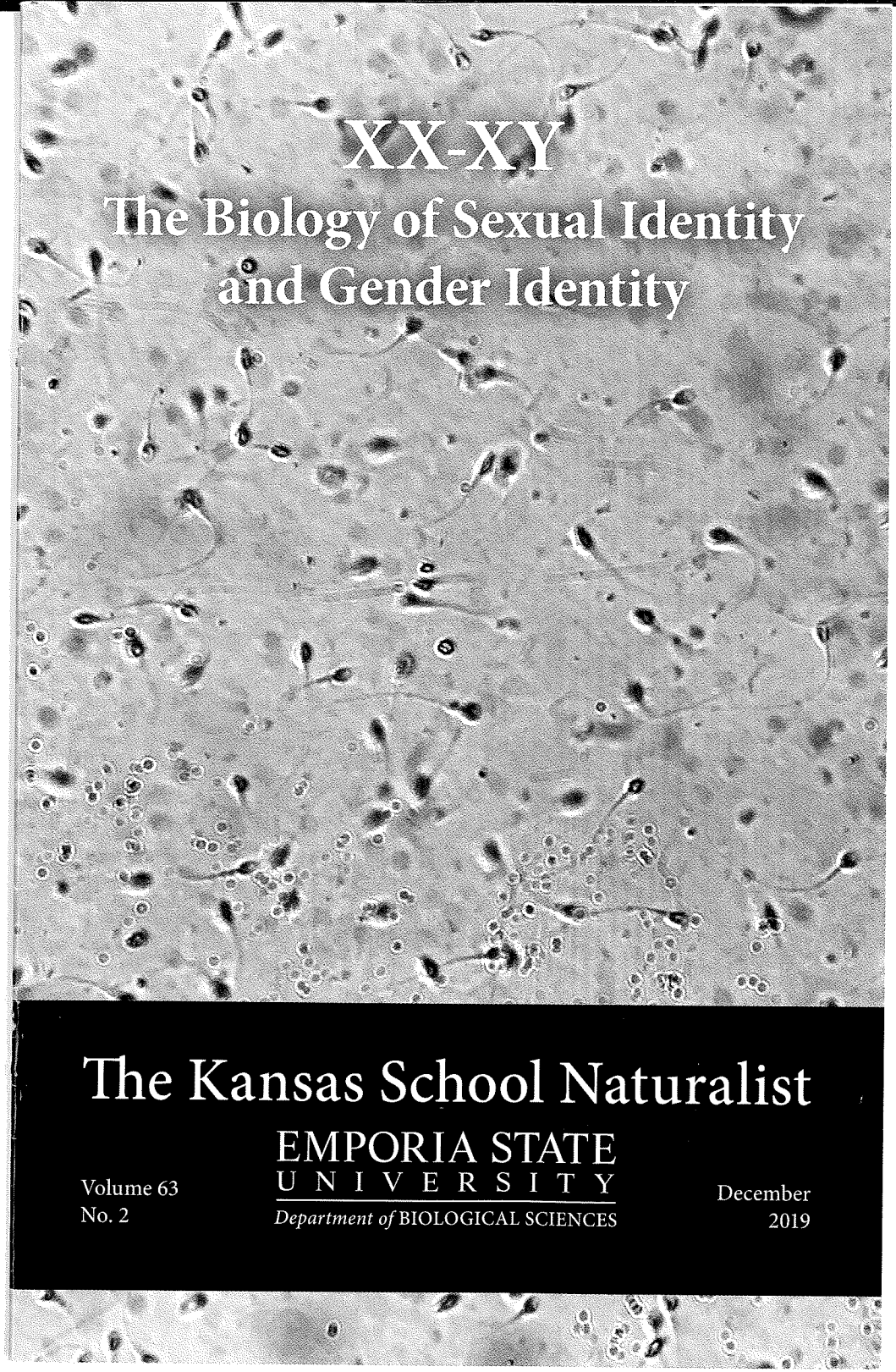

XX-XY

The Biology of Sexual Identity and Gender Identity

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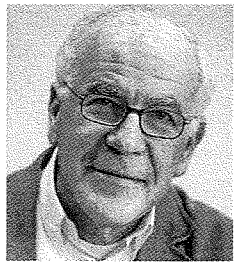
John Money (1921–2006) was Professor of Pediatrics and of Medical Psychology at Johns Hopkins School of Medicine in Baltimore, Maryland. John Money was also the founder and director of the Psychohormonal Research Unit at the Johns Hopkins Hospital. Money's extensive work concerning sexual ambiguity is well known in the research community.

KSN editor, **John Richard Schrock** met with John Money at the Psychohormonal Unit at Johns Hopkins University in 1995, and with Dick Swaab at Zhejiang University in Hangzhou, China in 2017 in consultation on this issue that compiles the research of many scientists.



Dick Frans Swaab is an internationally renowned researcher in neuroscience who founded the Netherlands Brain Bank that provides the international research community with clinical and neuropathological brain tissue. His work and that of his students has contributed to the expansion of brain banks worldwide. Swaab is a Distinguished Visiting Professor at Zhejiang University.

Liana Zhou is Librarian at the Kinsey Institute at Indiana University in Bloomington, Indiana. She worked closely with John Money in translating *Sex Errors of the Body and Related Syndromes*, a major reference for this issue.

We thank several anonymous reviewers for their helpful critique. Photo of John Money and Figures 1, 6, 7 and 8 reprinted with permission, "Copyright © 2017, The Trustees of Indiana University on behalf of the Kinsey Institute. All rights reserved." Figure 9 is used with permission from Oxford University Press.

This issue of *Kansas School Naturalist* summarizes current science that is applicable to the school teacher who is seeking to know "What can a science teacher say about the scientific differentiation of sex and of gender?"

XX–XY

The Biology of Sexual Identity and Gender Identity

When a mother is giving birth—and the couple have not seen sonograms beforehand—the first question is whether the baby is a boy or a girl. "I'll get back to you about that" is not the answer a couple expect to hear. Yet, ambiguity in sexual anatomy does occur (see Figure 8).

Over the last century, science has established that the development of our sexual identity is a complex process that involves much more than external anatomy. It begins with chromosomes but involves anatomical development, hormone levels, and differential brain development.

John Money introduced the terms "gender" and "gender role" to the science community in 1955 and later refined the definition (see block below). As is often the case in science, the details of complexity only become apparent when studies are made of cases where the biology of differentiation fails to work correctly. By 1968, Money had studied enough variations to state that there was a...

"...sequence of developmental steps, the orderly progression of which is prerequisite to normal sexual functioning. In normal development, each step follows the other in such logical progression that one does not think of them as possibly being independent of one another. It was only through the study of sexual anomalies, such as I have paid attention to since 1951, in which the sequence of development is not as expected, that it became possible to differentiate one step from another and to identify the developmental variables of sex, which may be independent of one another. One may list these variables as follows:

- Genetic or chromosomal sex
- Gonadal sex
- Fetal hormonal sex
- Internal morphologic sex
- External morphologic sex
- Hypothalamic sex
- Sex of assignment and rearing
- Pubertal hormonal sex
- Gender identity and role
- Procreative sex impairments

Each of these variables of development has its own probabilities of error or malfunction. Some of the errors overlap from one variable to another. One does not say that an anomaly is caused by a particular variable, because the cause is actually much more complicated than that and usually is a chain of events. Thus, a genetic error may lead to an error in the production of fetal hormones or an error in their use, which in turn leads to an error of sex-organ morphology, and so forth. For this reason, the principle of classification in what follows is a temporal and not a causal one."

The sequence of these factors has been diagramed in Figure 1 (Money & Ehrhardt, 1973). Money considered the "nature/nurture" debate to be outworn and found a "nature/critical period/nurture" formula more useful. "The critical period signifies that the interaction of nature and nurture together advances development, but only if that interaction takes place at the critical period, neither too soon nor too late, but precisely on time. Then, once the critical period passes, there is no backtracking...."

"**Gender-identity/role (G-I/R):** gender identity is the private experience of gender role, and gender role is public manifestation of gender identity. Gender identity is the sameness, unity, and persistence of one's individuality as male, female, or ambivalent, in greater or lesser degree, especially as it is experienced in self-awareness and behavior. Gender role is everything that a person says and does to indicate to others or to the self the degree that one is either male or female, or ambivalent; it includes but is not restricted to sexual arousal and response."

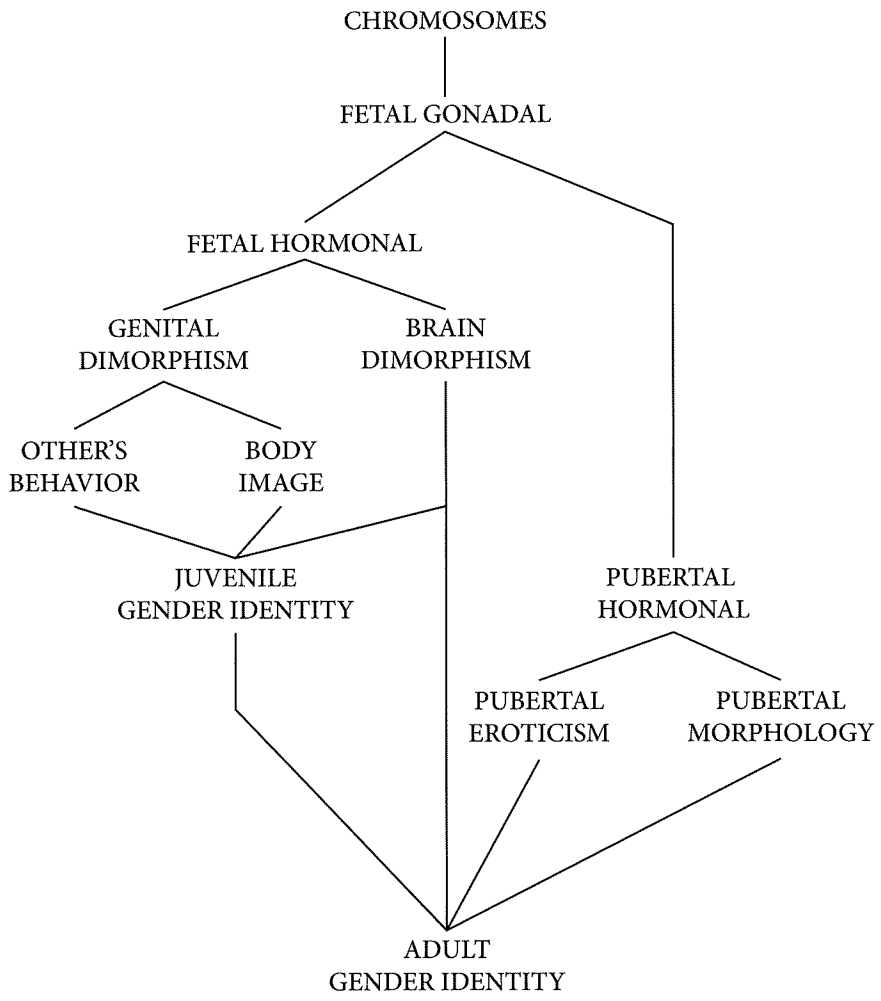


Figure 1. The sequential and interactional components leading from chromosomes to adult gender-identity. Reprinted with permission.

XX and XY CHROMOSOMES

When Tijo and Levan (1956) developed a method for preparing human cells so the chromosomes could be captured in early replication, photographed and aligned by size and shape (karyotype), it soon became obvious that women carried two XX chromosomes among the 23 pairs of chromosomes in adult cells, while men had one X and a much smaller Y chromosome.

Since a person receives one chromosome in each pair from each parent, and passes on one from each pair in their sperm or eggs, it was now obvious that the sperm determined the sex of offspring in humans. An egg can only supply an X-chromosome. But a sperm is either a Y-carrying or X-carrying sperm.

Since the Y chromosome is much smaller, containing only ~70 protein-coding genes compared to the ~800 protein-coding genes on the X chromosome, the Y-carrying sperm is slightly smaller.

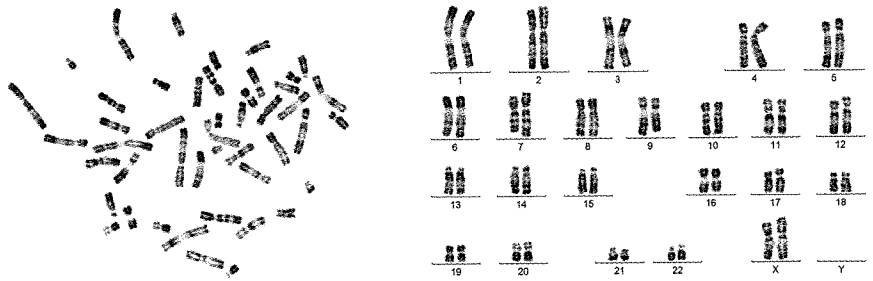


Figure 2. A spread of human chromosomes from the nucleus of a single cell (left) and their arrangement or karyotype (right). The presence of two X chromosomes and no Y chromosome indicates the female genotype. (EyeEm/Alamy Stock Photo)

Y-CHROMOSOME ACTION

In 1990, a region of the Y-chromosome was discovered to be necessary for male sex development and was named SRY (sex-determining region of the Y chromosome). This provided the testis-determining factor (TDF) necessary for testes to develop.

In very rare instances, the SRY region of the Y chromosome breaks off and recombines with an X-chromosome. This allows a child to inherit XX and yet be male. However, the other genes of the X chromosomes provide some feminization.

SEX CHROMOSOME ANOMALIES

During meiotic division (spermatogenesis and oogenesis), **nondisjunction** may occur, the failure of chromosome pairs to separate equally. Since meiosis is duplication-division-division, it is possible for a sperm or egg cell to be formed with extra chromosomes, or to be missing chromosomes. In addition, in the very earliest stages of cell replication of a new embryo, the sex chromosomes may be unequally divided, with the resulting person having a mosaic of different types of cells.

In addition, two fertilized eggs may fuse together (Mayr et al., 1979) to become one individual with mixed tissues; this is a chimera or mosaic. And a fertilized egg may split and move apart to become two individuals (Race & Sanger, 1962) which would normally produce identical twins but fail to include the Y-chromosome, thus producing one XO twin that is a female and resulting in identical twins of different sexes (Crew, 1965)!

Table 1. Sex chromosome combinations.

		frequency
46,XY	normal male	~1/2
46,XX	normal female	~1/2
45,XO	Turner syndrome female	1/5,000
47,XXX	triple X female	unknown
47,XYY	supernumerary Y male	1/1000
47,XXY	Klinefelter syndrome male	1/500
45,X/46,XY	mosaic syndrome male	unknown

FEMALE BODY PLAN IS "DEFAULT"

A person with XXY is male, not female, so the XX does not dictate female development. Generally in every case with a Y chromosome in Table 1, the person is male. In cases lacking a Y, the person develops as female.

Simply, an embryo will develop into a female unless there is a Y chromosome SRY gene to redirect it to become male. "Female differentiation and development is Nature's priority. For male differentiation and development to take place, something extra has to be added." (Money, 1994)

To use a computer-age metaphor, the female is the "default" setting. From the view of evolutionary biology, where males of some species do not exist and females reproduce by parthenogenesis, the female is the indispensable basic plan, the male a dispensable sperm delivery system for generating diversity.

Gonads that become testes under the direction of the SRY gene produce testosterone and affected body tissues respond and differentiate as male. In the absence of the SRY, the gonads develop as ovaries and affected body tissues respond to the resulting production of estrogens.

Androgens are sex hormones mostly derived from male sources but also the adrenal glands. **Testosterone** is derived specifically from the testes; variants include dihydrotestosterone.

Estrogens are female sex hormones produced by the Graafian follicles of the ovaries. Estrogens are also produced by the placenta and fat tissue and also the testes. **Estrone** and **estradiol** are major natural estrogens, but many chemicals released into the environment also act as estrogens.

HORMONES

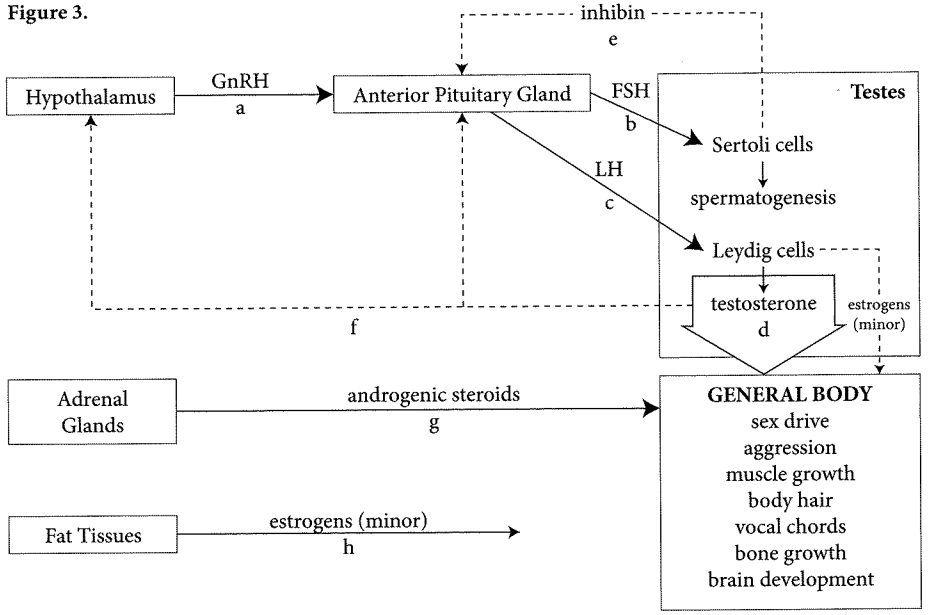
"One might easily assume that male sex hormones are found exclusively in males, and female sex hormones are found exclusively in females. However, this is not the case. The human sex hormones are shared by males and females. We all have some of each. The difference between sex hormones in men and women is quantitative. Men have a higher level of androgens than women do, and women have a higher level of female hormones than men do. If women had a zero level of male hormones, they would have no axillary or pubic hair. It is likely, but not absolutely proven, that without some androgen (from the ovaries and adrenocortical glands) women would experience a lack of the feeling of sexual drive or libido. A minute dose of androgen may be prescribed to enliven libido in women.... If men had no androgen, then the level of estrogen secreted normally by the testicles would be high enough to induce breast enlargement. A total lack of androgen would also prevent baldness in those who are genetically susceptible." (Money, 1994)

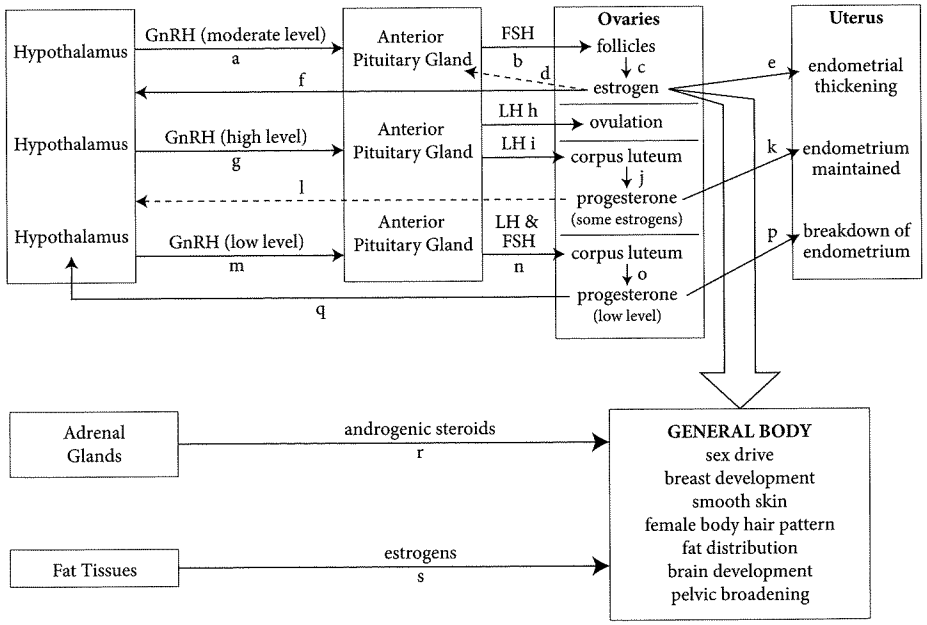
Hormones act in conjunction with behavior, as is the case where testosterone results in muscle growth only if there is substantial exercise.

Figures 3 and 4 detail the complex hormone interactions necessary in normal sexual development and functioning. The interactions in Figure 4 will begin with menarche and end with menopause. While many textbooks simplify the process and speak of general blood levels, for some tissues it is the timing or pulses of hormones that trigger target cell response.

Figure 3. Male endocrine glands and hormone actions. The hypothalamus (a) secretes gonadotropin releasing hormone (GnRH) which triggers the anterior pituitary to (b) secrete follicle stimulating hormone (FSH) and (c) luteinizing hormone (LH). FSH levels trigger the Sertoli cells to undergo spermatogenesis. LH (previously called interstitial cell stimulating hormone or ICSH) triggers the Leydig cells in the interstitial region between the seminiferous tubules to secrete testosterone (d). The stimulated Sertoli cells also secrete inhibin (e), a hormone that inhibits the anterior pituitary gland from secreting too much FSH and LH. Testosterone likewise inhibits both the hypothalamus and anterior pituitary gland (f). These two negative feedback loops help keep sperm and testosterone production level. Higher testosterone levels at puberty have a wide range of effects on body tissues. The low levels of androgens produced in the adrenal glands (g) are probably trivial in the presence of gonadal testosterone. Fat tissues also produce estrogens (h) in both males and females. Target cells may respond not only to the levels of hormone present but also to the timing of hormones released. Solid lines (—) indicate stimulation; dashed lines (- - - -) indicate inhibition. Effects of testosterone also depend on behavior; testosterone does not increase muscle mass without muscle exercise. Taking artificial testosterone convinces this system there is too much production; this feedback results in testicular atrophy.

Figure 4. Female endocrine glands and hormone actions controlling the menstrual cycle. The hypothalamus (a) secretes gonadotropin releasing hormone (GnRH) which triggers the anterior pituitary to (b) secrete follicle stimulating hormone (FSH). FSH levels trigger some follicles in the ovaries to mature and also secrete estrogen (c). Estrogens inhibit (d) the anterior pituitary gland, stimulate the thickening of the endometrial lining (e), and stimulate (f) the hypothalamus to increase levels of gonadotropin releasing hormone (GnRH)(g). Higher level of GnRH triggers the anterior pituitary gland to secrete luteinizing hormone (LH). The LH both encourages ovulation (h) and development of the corpus luteum (i). The corpus luteum secretes progesterone (j) and some estrogen. The progesterone maintains the endometrial lining (k) and inhibits the hypothalamus production of GnRH (l). Low levels of GnRH (m) drop the anterior pituitary gland's production of LH and FSH (n). The corpus luteum is no longer stimulated to secrete progesterone (o) and low levels of progesterone allow the breakdown of the endometrium (p) and stimulate the hypothalamus to increase GnRH production (q), thus beginning the cycle over again. The time it takes for feedback to occur results in a menstrual cycle of about 28 days. Fat tissue also produces a base level of estrogens (s) in females that underpins the ovarian estrogen reaching a level to trigger endometrial thickening and ovulation. Adrenal glands produce a low level of androgenic steroids (r) that appear to have a role in ovulation and may contribute to female sex drive. Solid lines (—) indicate stimulation; dashed lines (- - - -) indicate inhibition. (Modified from J. Marquardt after Schrock, 1988)





UNDIFFERENTIATED ANATOMY

Up to the sixth week of fetal development, there is no difference in the morphology (form) of the tissues that will become the sex organs (Figure 5). The **gonad** tissue is "bipotential" or able to develop into either male or female tissues.

Under the influence of the SRY gene, the inner portion of the gonad, the medulla, begins to develop as testes and the outer cortex regresses.

The developing testes begin secreting testosterone and remain in the abdominal cavity until the seventh month of pregnancy; then the testes migrate down through the inguinal canal into the scrotum.

In the absence of the SRY gene, the outer portion of the gonad, the cortex, starts toward development as an ovary about the 12th week. By the sixth month of development, between 300,000 and 400,000 immature eggs (ova) are already present (of which 300–400 will eventually develop further and the rest will degenerate). For full normal development of ovaries, the programming of two X chromosomes is usually needed.

At the sixth week, alongside the gonads lie two sets of ducts, the Mullerian ducts and the Wolffian ducts named after their discoverers.

The **Wolffian ducts** (also called mesonephric ducts) are closer and have tubules extended toward the gonad (Figure 5). Testosterone secreted by the developing testes causes growth and development of the Wolffian ducts into tissues that become the vas deferens, seminal vesicles, and ejaculatory duct.

The developing testes also secrete Mullerian inhibiting substance (MIS) that causes the atrophy (wasting away) of the Mullerian ducts and other tissues that would develop into female structures.

In the absence of testosterone, the **Mullerian ducts** develop and the Wolffian ducts degenerate. The ovaries develop but do not migrate out of the abdominal cavity. Increasing estrogens and the lack of testosterone causes the female organs to develop.

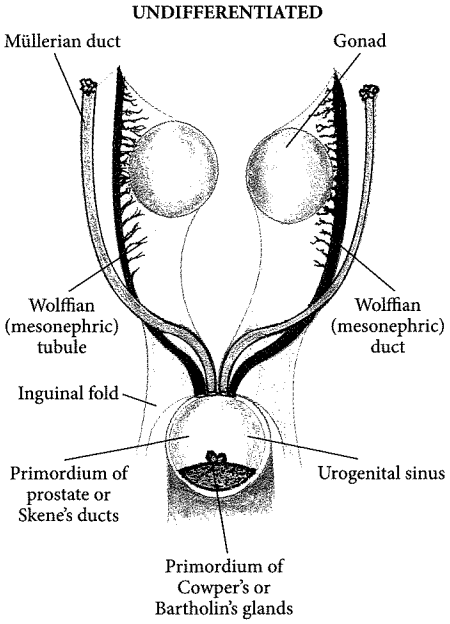


Figure 5. Initial undifferentiated human sexual tissues (top) where all humans have these same tissues in our early fetal stage.

HOMOLOGOUS TISSUES

Male | Female

testes = ovary

penis = clitoris

foreskin = clitoral hood

skin of penis = labia minora

fused scrotum = unfused labia majora

prostate = Skene's duct

Cowper's glands = Bartholin's glands

Some animals, such as earthworms, are **hermaphrodites** where the gonads partition into both male testes and female ovaries and both sets of ancillary structures develop. This is also an advantage in some marine fish. It doubles the chance they can cross-mate with another member of their species in the isolating soil or ocean.

A truly hermaphroditic human, who possesses both sets of reproductive organs, is extremely rare. This may be due to a fusion of two fertilized eggs, one male and one female, producing one mosaic individual.

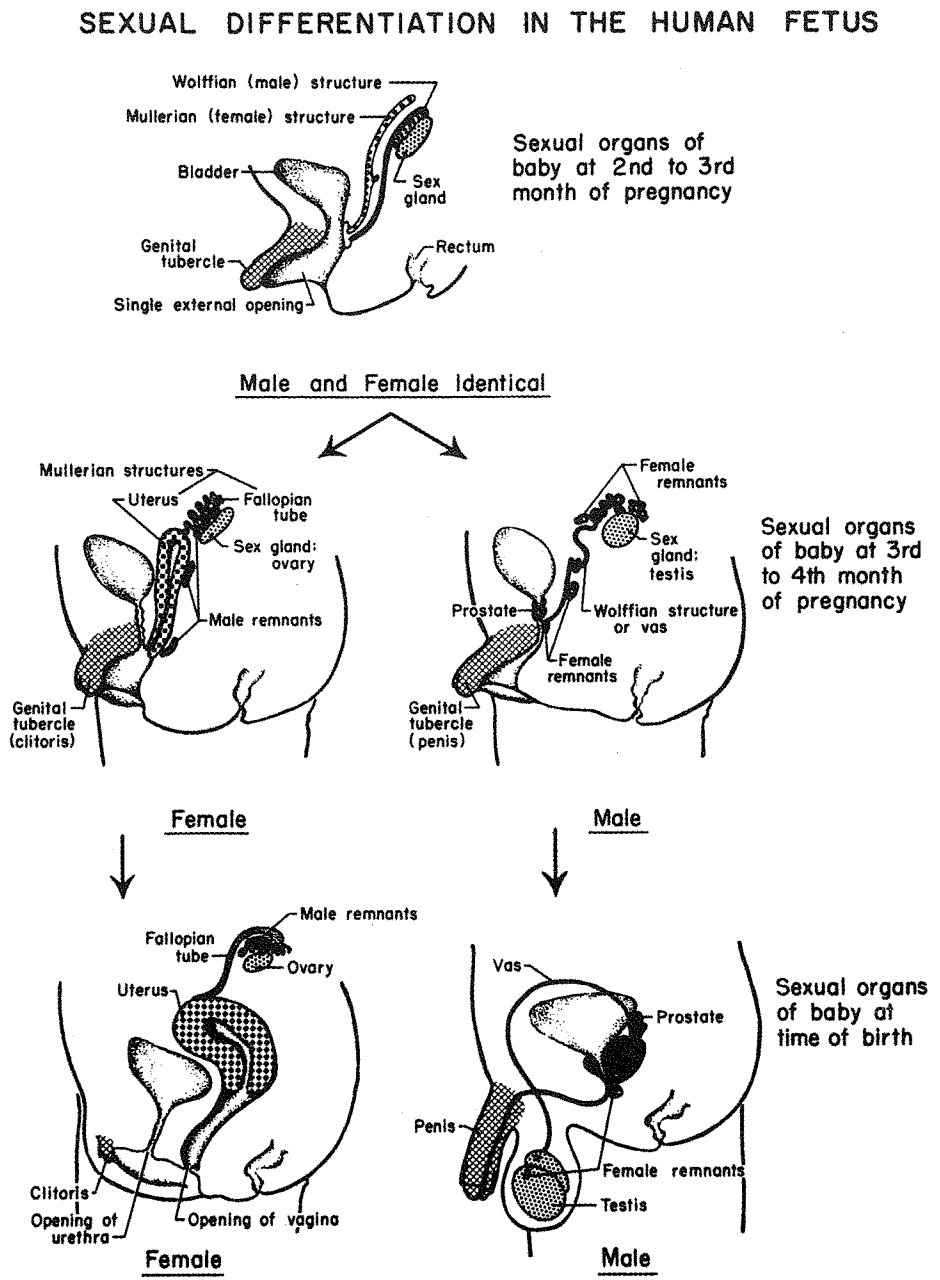


Figure 6. Three stages in the differentiation of the sexual anatomy, internal and external. The Mullerian ducts develop in the female and the Wolffian ducts become vestigial, while the opposite occurs in the male. Reprinted with permission.

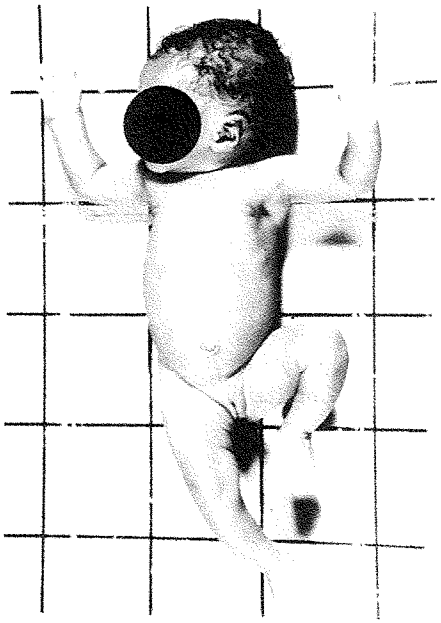


Figure 7. The body cells of this newborn baby are all XY, which should indicate a boy. But with androgen insensitivity testicular feminizing syndrome, she is indistinguishable in appearance from a normal female. Body cells are all 46,XY. Reprinted with permission.

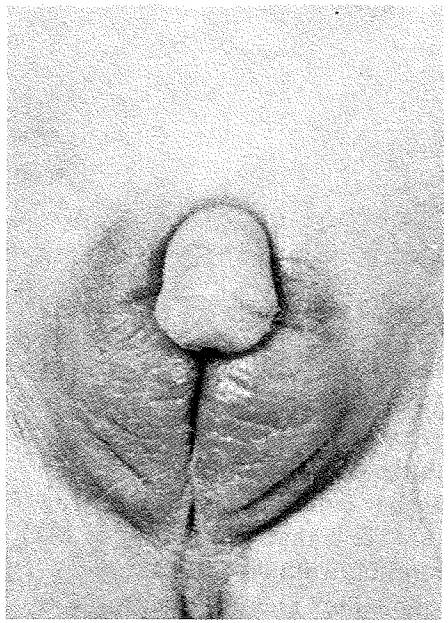


Figure 8. Incomplete masculinization of the external genitalia in a genetic female whose hermaphroditism was induced by synthetic progestinic hormone given to the pregnant mother to prevent miscarriage. Reprinted with permission.

VARIATIONS

When women athletes train in strenuous events to the point that they eliminate body fat, their menstrual cycles often shut down because the level of estrogens needed to complete the cycle in Figure 4 is too low. This actually served as a protective mechanism to prevent pregnancy in early human populations suffering from famine and where a pregnancy would result in the death of both mother and unborn child.

Variations in the amount of body fat will also vary the estrogen-androgen proportions and result in obvious natural variations in extent of hair, tone of voice, and other traits among the general population.

XXY males develop the normal male accessory structures but due to the presence of the extra X chromosome, the testes atrophy usually resulting in sterility.

The XO Turner syndrome female develops female anatomy and short stature, but the ovaries usually do not develop.

YO males do not survive but die during development.

If the embryonic testes do not produce testosterone, all female organs (except ovaries) and external genitalia develop.

Complete androgen insensitivity syndrome (AIS) exists in the 46, XY individual (Figure 7) who carries a defective gene that prevents cells in the body that require androgen from taking up and using the androgen they need. Since the cells do not recognize the testosterone in the bloodstream, they develop into females. The testicular structures secrete both testosterone and antimullerian hormone, and the later prevents the mullerian ducts from forming the uterus and Fallopian tubes. Cells of the body do absorb the lesser amount of estrogens present and develop external female anatomy.

If a pregnant mother has an androgen-producing tumor on her adrenal glands, the androgens will cross the placenta. In such a case, a female fetus will receive high doses of male hormones. Despite having ovaries that produce some estrogens, the tissues respond to the higher androgen level and will develop male accessory ducts, a penis, and an empty scrotum.

An infant girl with Swyer syndrome, also called 46,XY, has typical female external genitalia. Both the uterus and fallopian tubes are normal, but the gonads are undeveloped streaks of tissue and are not functional; affected individuals have undeveloped clumps of tissue called streak gonads. This tissue often becomes cancerous and must be surgically removed early in life. They are usually raised as girls and feel a female gender identity. Early hormone replacement therapy will trigger menstruation and female secondary sex traits including breast and uterine growth. They cannot produce eggs but may be able to carry a pregnancy from a donated embryo. Swyer syndrome was described by Gim Swyer in 1955 in England.

"Persistent mullerian duct syndrome is a 46,XY chromosomal syndrome in which the embryonic testes of a 46,XY male fail to secrete antimullerian hormone [MIS], although they do not fail to secrete androgen.... The outcome is that the mullerian ducts proliferate and form a uterus and two fallopian tubes. The baby is born with the testes, scrotum, and penis and with the internal structures of a male, and, in addition, with a female uterus and fallopian tubes. Because of the presence of androgen, which is secreted by the functioning testes, subsequent development in childhood and at puberty is as a male. However, in such individuals, one or both testicles may be confined in the abdominal cavity." (Money, 1994)

Disorders in sexual differentiation (DSD) can be assessed by the Prader scale for levels of female virilisation. Children who possess 46,XY but have ambiguous genitalia are assessed on the Quigley scale.

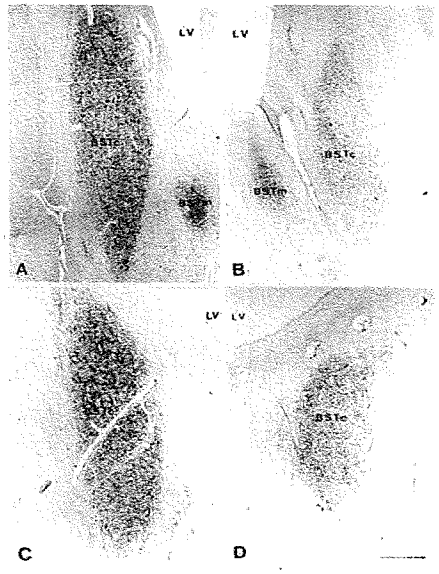


Figure 9. The volume of this brain area related to gender identity, the central subdivision of the bed nucleus of the stria terminalis (BSTc) is larger in men than in women: A)heterosexual man, B: heterosexual woman, C)homosexual man, D) male-to-female transsexual. After Zhou, Hofman, Gooren and Swaab, 1995. Published with permission.

TRANSSEXUALISM

Individuals who have completely normal sexual anatomy and physiology, but who want to be reassigned as the opposite sex are classified as "transsexuals" by the American Psychiatric Association.

"Transsexual individuals have the body image of the other sex and are fixated...on changing their actual body to agree with their body image, and on living the role of the sex of the body image. In some individuals, the transsexual fixation has been present and unremitting since childhood, whereas in others it may be episodic until, later in life, it becomes permanent." (Money, 1994)

The case of Emma Martin provides an example: "When I was four years old...I was playing in the back garden in my pedal car and I suddenly realized there was a little girl in the next yard. And I just realized that they

had made a mistake. I couldn't understand why my parents were treating me as a boy." (WGBH, 2001) Emma Martin, born with normal male anatomy, spent her whole adult life as a woman.

Dick Swaab, researcher at the Netherlands Institute noted that: "Transsexuals don't describe themselves as having a female brain. They describe themselves as being female. But of course this strong feeling to be a female comes from somewhere and we are certain it is not coming from the heart; it is coming from the brain." (WGBH, 2001)

U.C.L.A. researcher Roger Gorski had conducted experiments injecting testosterone into a pregnant rat and found the resulting female babies grew up to act like males. He subsequently found that a nucleus in the pre-optic area (SDN-POA) differed in male and female rats, and the prenatal injections shifted that brain development in female embryos to provide them with a male-like brain nucleus.

Swaab and fellow researchers then found a difference in cell count or cell size in a region of the brain between men and women that aligns with transsexual gender orientation (Figure 8). However this section of the brain did not change with sexual orientation, providing biological evidence that sexual ideation is not the same as gender identity.

IS THERE A GENE FOR HOMOSEXUALITY?

Previous studies of the occurrence of nonheterosexuals in twins and along family lineages found a slight genetic influence. In 2019, Ganna et al. published a large-scale study in the journal *Science*.

"We performed a genome-wide association study (GWAS) on 477,522 individuals, revealing five loci significantly associated with same-sex sexual behavior. In aggregate, all tested genetic variants accounted for 8 to 25% of variation in same-sex sexual behavior, only partially overlapped between males and females, and do not allow meaningful prediction of an individual's sexual behavior. Comparing these GWAS results with those for the proportion of same-sex to total number of sexual partners among nonheterosexuals suggests that there is no single continuum from opposite-sex to same-sex sexual behavior. Overall, our findings provide insights into the genetics underlying same-sex sexual behavior and underscore the complexity of sexuality."

While there is no single gene, there is a slight influence from a combination of genes (polygenic) but this is not predictive.

Heterosexuality, Homosexuality and Bisexuality

by Dick Frans Swaab

Alfred Kinsey did not attract any notice when he published his doctoral thesis on gall wasps. But when, in 1948, he produced the report *Sexual Behaviour in the Human Male* and, five years later, *Sexual Behaviour in the Human Female*, he became a celebrity overnight. He developed the 'Kinsey scale', which went from 0 to 6, 0 signifying exclusively heterosexual and 6 exclusively homosexual. He himself would have been classified as a 'Kinsey 3', being bisexual. Your position on the scale is determined in the womb by your genetic background and the effects of hormones and other substances on your developing brain. Studies of twins and families show that sexual orientation is 50% genetically determined, though the genes in question have not yet been identified. It is in itself curious that a genetic predisposition for homosexuality should persist in populations over the course of evolution, given that this group reproduces less. An explanation is that these genes do not just increase the likelihood of homosexuality, but also promote fertility in the rest of the family. If they are passed onto brothers and sisters who are heterosexual, they produce a larger than average number of offspring, causing the genes to remain in circulation.

Hormones and other chemical substances importantly affect the development of our sexual orientation. Girls with the adrenal gland disorder CAH, who are exposed to high testosterone levels in the womb, are more likely to become bisexual or homosexual. Between

1939 and 1960, around two million expectant mothers in the United States and Europe were prescribed the synthetic oestrogen DES in the belief that it would prevent miscarriages. (It did not, in fact, but doctors like to prescribe things and patients are always keen to be treated.) DES turned out to increase the likelihood of bisexuality and homosexuality in the daughters of women given the drug. Pre-birth exposure to nicotine or amphetamines also increases the likelihood of lesbian daughters.

The more older brothers a boy has, the greater the chance that he will be homosexual. This is due to a mother's immune response to male substances produced by boy babies in the womb. It is a response that becomes stronger with each pregnancy. Pregnant women suffering from stress are also more likely to give birth to homosexual children, because their raised levels of the stress hormone cortisol affect the production of fetal sex hormones.

Although it is frequently assumed that development after birth also importantly affects our sexual orientation, there is no proof of this whatsoever. Children brought up by lesbians are not more likely to be homosexual. Equally, there is no evidence at all for the common opinion that homosexuality is a "lifestyle choice."

The above-mentioned factors alter the development of the child's brain, particularly the hypothalamus, which is important for sexual orientation.

In 1990 Hofman and I found the first brain difference in relation to sexual orientation: the brain's body clock turned out to be twice as large in homosexual men as in heterosexual men. We were actually looking for something else at the time. I had discovered earlier that Alzheimer's damages the body clock, which explains why people suffering from this disorder wander around at night and doze during the day. I did some more studies to see if the same applied to other forms of dementia. In the case of AIDS dementia I found that the body clock was twice as large as normal. Follow-up studies showed that this was not caused by AIDS, but was related to homosexuality. In 1991, Simon LeVay reported a second difference in hypothalamic structure between homosexual and heterosexual men, and in 1992 Allen and Gorski found that the structure on top of the hypothalamus that connects the brain's left and right temporal lobe hemispheres is bigger in homosexual men.

Scans have also revealed functional differences in the hypothalamus with regard to sexual orientation. A study by Ivanka Savic of the Stockholm Brain Institute involved pheromones, scented sex hormones that are given off in sweat and urine. Pheromones influence sexual behaviour unconsciously. A male pheromone stimulates activity in the hypothalamus of heterosexual women and homosexual men, but does not provoke a response in heterosexual men. It seems that male scents don't turn them on.

Lesbian women were found to react differently to pheromones than heterosexual women. Savic also showed that the functional connections between the amygdala and other brain areas were more extensive in the case of heterosexual women and homosexual men than in that of heterosexual men and homosexual women, proving that brain circuits function differently according to our sexual orientation. Functional scanning also showed changes of activity in other brain areas. In the case of heterosexual men/homosexual women, the thalamus and prefrontal cortex responded more strongly to a photograph of a female face, while in the case of homosexual men/heterosexual women these structures responded more strongly to a male face. In other words, there are many structural and functional differences in our brains according to our sexual orientation, and these develop in the womb during the second half of pregnancy. They are not caused by the behaviour of dominant mothers, who are the traditional scapegoats in this context. Just for the record, I made a habit over the years of asking the medical students I taught (250 at a time) which of them did not have a dominant mother. No one ever put their finger up.

Transsexuality

Transsexuals feel that they have been born into a body of the wrong gender and are desperate for a sex change, or gender reassignment. This is a gradual process that starts with an individual adopting the social role of the opposite sex and taking hormones, then undergoing a series of extensive operations which only 0.4% later regret. The first person in the Netherlands to respond to the plight of transsexuals was Otto de Vaal, an endocrinologist and pharmacologist, who treated them for free in Amsterdam from 1965, because he felt that his university pay was sufficiently ample.

The gender team of the VU University Medical Centre in Amsterdam (VUmc) subsequently took on a pioneering role, headed first by Louis Gooren and now by Peggy Cohen-Kettenis.

Since 1975, 3,500 people have undergone gender reassignment at the VUmc.

The first time I learned about transsexuality was as a medical student in the 1960s. Coen van Emde Boas, a professor of sexology, entered the lecture room of the obstetrics and gynaecology department with a bearded man. It was not exactly the place you would expect a man to be demonstrating anything. But he turned out to be a genetic woman, a female to male transsexual. This made a deep impression on me, and set me thinking about the possible underlying mechanism.

Male to female transsexuality (MtF) occurs in 1 in 10,000 individuals, and female to male transsexuality (FtM) in 1 in 30,000. Gender problems tend to become apparent from an early age. Mothers typically relate how their little boys would dress up in their frocks and shoes, were only interested in girls' toys and mainly played with girls. But not all children with gender problems want to change sex later. If necessary, puberty can be delayed with the help of hormones to gain extra time in which to decide whether or not to undergo treatment.

All the data indicates that gender problems arise in the womb. Tiny variations in genes associated with the effect of hormones on brain development have been found to increase the likelihood of transsexuality.

It can also be increased by abnormal fetal hormone levels or by medication taken during pregnancy that inhibits the breakdown of sex hormones. The sexual differentiation of our sex organs takes place in the first months of pregnancy, while the sexual differentiation of the brain occurs in the second half of pregnancy. Since these two processes take place at different times, the theory is that in the case of transsexuality, they have been influenced independently of one another.

If this is the case, one would expect to find female structures in male brains in MtF transsexuals and vice versa in the case of FtM transsexuals. In 1995 we indeed found, in post-mortem studies of donor brains, a small structure in which the usual sex difference was reversed.

We published our findings in *Nature*. The brain structure in question is the Bed Nucleus of the Stria Terminalis (BST), an area that is involved in many aspects of sexual behaviour (F 9). The central part of this nucleus, the BSTc, is twice as large in men as in women and contains twice as many neurons. We found MtF transsexuals to have a female BSTc.

The only FtM transsexual we could study - the material in question being yet rarer than the brains of MtF transsexuals - indeed proved to have a male BSTc. We could rule out the reversal of the sex difference in transsexuals being caused by altered hormone levels in adulthood. So the reversal must have happened at the developmental stage.

If you publish something truly interesting, the nicest thing you'll probably hear your colleagues say is, 'It'll need to be confirmed by an independent research group.' And that can take a while, because it took me twenty years to collect the brain material for my study. So I was delighted when in 2008 the group headed by Ivanka Savic in Stockholm published a study involving functional brain scans of living MtF transsexuals. They had not yet been operated, nor given hormones. As a stimulus they were given male and female pheromones, scents that are not consciously perceived. In control groups, these were shown to produce different patterns of stimulation in the hypothalamus and other brain areas in men and women. The stimulation pattern for MtF transsexuals fell between that of men and women. In 2007 V.S. Ramachandran published an interesting hypothesis and provisional research findings on transsexuality. He believes that the body map in the brains of MtF transsexuals lacks a penis and that those of FtM transsexuals lack breasts, due to these not being programmed into the neural map during development. As a result, they do not recognize these organs as their 'own' and want to get rid of them. Everything therefore points to the fact that the early development of the sexual differentiation of the brain of transsexuals is atypical and that they are not, in fact, simply psychotic.... At the same time, it is of course essential, before initiating treatment, to make sure that the desire to change sex is not part of a psychosis, being an occasional symptom of schizophrenia, bipolar depressions and serious personality disorders." –D.F. Swaab

TEACHER NOTES:

-Most students who learn and understand the complexity of gender identity described here feel fortunate to have undergone "normal" gender development and sexual differentiation.

-Altogether, some form of sexual ambiguity is more common than all cases of Down syndrome and cystic fibrosis combined. Therefore most schools will have one or more students dealing with this issue. Broad knowledge among classmates of the factors in sexual differentiation can lessen the social trauma and pressures for those affected.

-Students should understand the many ways that: chromosomal sex does not always equal anatomy which does not always equal hormones which does not always equal gender or sexual identity/role and erotic ideation.

-Recent research shows that differences in brain morphology affect both gender and sexual identity/role.

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Cover: Human sperm each carry 23 single chromosomes, normally one-half of the 23 pair found in human body cells (except RBCs). One of these chromosomes is usually an X or Y chromosome. About half of these sperm carry an X-chromosome and, upon fusing with an egg, will normally produce an XX female. Half will carry the smaller Y-chromosome and usually produce an XY male. Because the Y-carrying sperm has fewer genes, it is slightly faster in the race to the egg and a factor that likely contributes to the slightly larger number of male infants born worldwide. Normal human sperm counts range from 15 million sperm to over 200 million sperm per milliliter (mL) of semen. Counts under 15 million sperm per milliliter or 39 million sperm per ejaculate are considered low. In addition to total count, the morphology (structure) and the motility (speed) of the sperm are also factors in male fertility. (Cover photo: DepositPhotos)