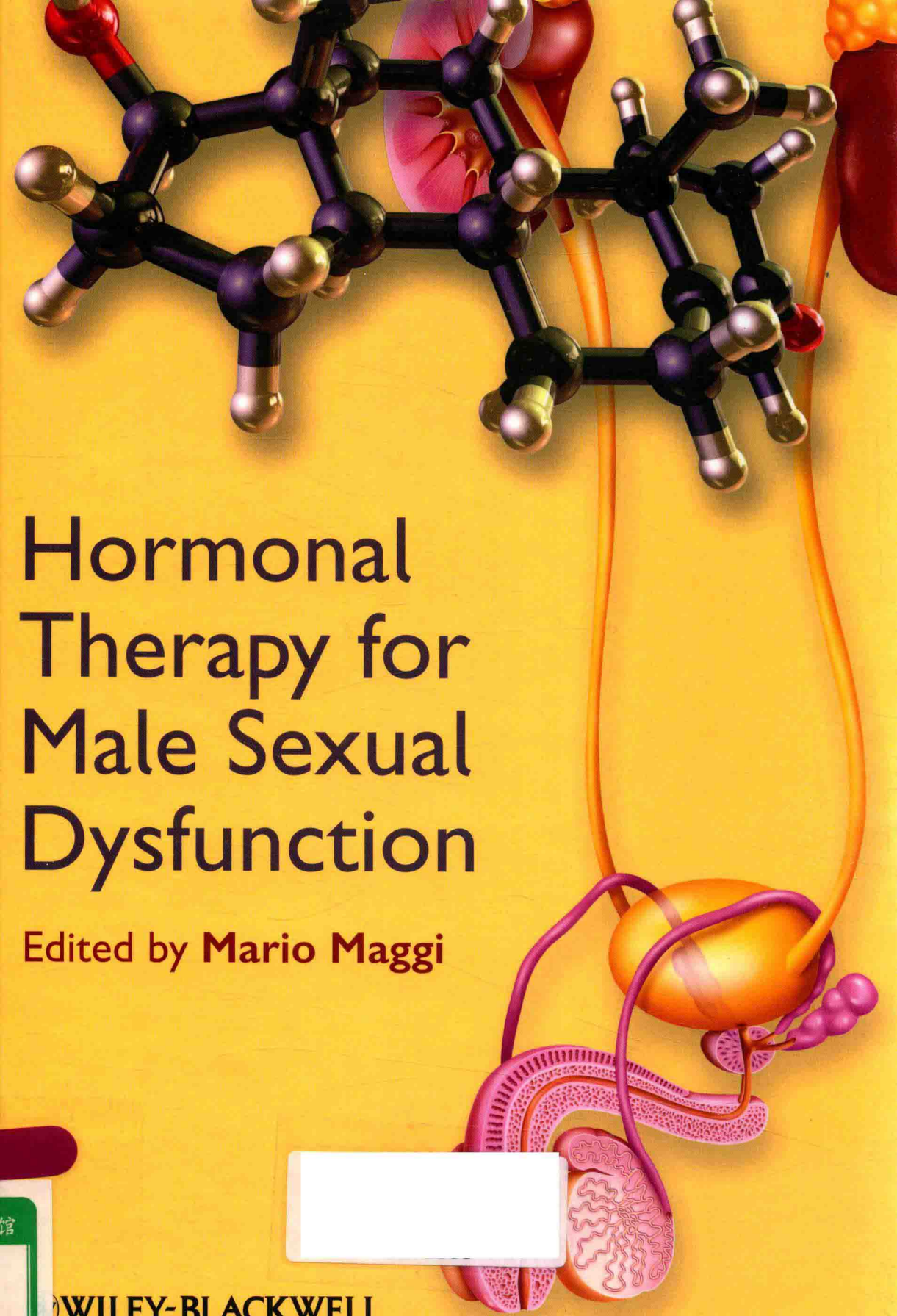

Hormonal Therapy for Male Sexual Dysfunction

Edited by **Mario Maggi**

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Preface

The sexual lexicon is based on messages continuously exchanged among individuals, which can be rephrased and read under various perspectives. The capacity of exchange in sexual messages within the body is made possible largely by two different mechanisms: the nervous system, which transmits electrochemical signals as two-way traffic between brain and peripheral tissues or between tissues in reflex circuits; and the endocrine system, which releases chemical mediators termed hormones into the circulation for action away from their original sites. Hence, the endocrine system is an integral part of the sexual lexicon. However, only receptive individuals know the language and can read the message. Hormones are messages written in a biological language that can be easily read by receptive cells (those expressing the cognate receptor). Sexual hormones allow communication among lover's cells, because, even though hormones and receptors are physically distinct structures, they ultimately perform the same function.

Male sexual disorders often derive from a local or generalized misunderstanding of sexual messages. A better understanding of how hormones work and communicate will lead to the discovery of effective therapies to improve sexual communication. This book will provide the rationale for hormonal therapy in male sexual disorders, explaining the language of sexual endocrinology and helping to rephrase it when necessary.

Endocrinology has traditionally been defined as a branch of biological science that concerns itself with the actions of hormones and the organs in which the hormones are produced. Sexual hormones not only regulate gametogenesis, but also control the dimorphic anatomical, functional, and behavioral development of males and females that is essential for sexual functioning. It is of particular interest in this regard that no exclusive male or female sexual hormones have been identified. All hormones characterized to date are present in both sexes, and both sexes have receptor mechanisms that allow responses to all hormones. Sexual dimorphism is the result of differences in the amounts of individual hormones and differences in their patterns of secretion, rather than their presence or absence. It follows that sexual endocrinology requires a precise genetic programming that allows for the synthesis of an appropriate enzyme complement in the ovary or testis, which in turn catalyzes the formation of the appropriate amounts of hormones during the critical stages of life. The endocrinological control of sexual activity encompasses every phase of the process, including many behavioral aspects.

Sexual hormones might have multiple effects. An example of such a hormone is testosterone. Some of its diverse actions include fusion of the labioscrotal fold in the male embryo during embryogenesis, induction of male differentiation of the Wolffian ducts, regression of the embryonic breast (in some species), growth of the male urogenital tract, induction of spermatogenesis, growth of beard and body hair, promotion of muscle growth, retention of nitrogen, increased synthesis of erythropoietin, temporal regression of scalp hair, hyperplasia of the sebaceous gland with increased sebum production, development of prostatic

hyperplasia in aging males of several species, secretion of the ejaculate, and virilization of the male external genitalia (including penis), along with discrete hypothalamic nuclei. It was originally believed that androgens exerted these diverse effects by distinct mechanisms. However, one of the most important findings from genetic studies and from modern molecular biology is that diverge effects can be modulated by a single mechanism: the androgen receptor.

So, at the end of the day, sexual endocrinology is an important part of sexual medicine: read this book faithfully!

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University of Florence
November 2011

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Male Gender Identity and Masculine Behavior: the Role of Sex Hormones in Brain Development

Baudewijntje PC Kreukels and Peggy T Cohen-Kettenis

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Typical male gender development

Prenatal sexual differentiation

Sexual differentiation is a stepwise process starting with a difference of the sex chromosomes (XX for females, XY for males). The embryo starts off with two basic pairs of reproductive structures, the Müllerian ducts and the Wolffian ducts. A gene located on the Y chromosome (SRY) induces the development of the testis. A few weeks after conception, the testes will start to produce testosterone and Müller Inhibiting Substance (MIS). These hormones of the testes direct male development. The Wolffian ducts develop into male internal reproductive organs, and the MIS, produced by the Sertoli cells of the developing testes, causes the Müllerian ducts to regress. In the absence of a Y chromosome (and therefore testes and androgens), ovaries will develop. The Wolffian ducts will regress and the internal sex organs will develop along the female line, the default route. The external genitals also develop from identical structures. In males, testosterone and its derivative dihydrotestosterone (DHT) direct the genital tubercle to become the penis and the genital swellings fuse to form the scrotum, whereas in females, in the absence of testosterone, these structures become a clitoris and a labia.

Apart from the sexual differentiation of the genitalia, sex hormones in the prenatal environment influence the differentiation of the brain into male or female. Pre- and early neonatal exposure of the brain to sex hormones leads to permanent changes in the nervous system. These effects are referred to as organizational effects. From vertebrate models we learn that the steroid hormone testosterone accounts for the majority of the known sex differences in neural structure and behavior. In lower animals, the presence or absence of testosterone at the time of a critical period of brain sexual differentiation influences the morphology of certain brain nuclei. Like its influence on the development of the genitalia, the presence of testosterone leads to male sexual differentiation of the brain and results in male-typical behavior, while a

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female brain and female-typical behavior are found to be the outcome of the absence of testosterone. When the testes are formed, they begin to produce testosterone and from this moment on there is a sex difference in testosterone concentrations between male and female fetuses. Through its effects on neurogenesis, cell migration, cell death, and the differentiation of neural circuits, testosterone has its effects on neuronal organization.

Influence of prenatal hormones on male gender development in humans: evidence from non-clinical samples

Gonadal hormones are also thought to influence the sexual differentiation of brain and behavior in humans, but the exact mechanisms and timing remain unclear. Early in life, sex differences are observed in play behavior and preferences. An approach to study the effects of prenatal testosterone on gender development is to relate hormonal levels in maternal serum or amniotic fluid to variations in subsequent gender-related (play) behavior in non-clinical samples. Maternal testosterone predicted the amount of male-typical behavior in daughters, as measured by parent questionnaires. Amniotic testosterone was found to be related to male-typical play behavior, as assessed by maternal reports of childhood sex-typed activities in male as well as female offspring. However, other studies did not find support for the hypothesized relationship between prenatal testosterone exposure and postnatal gender-related play behavior.

A frequently studied indirect measure of prenatal exposure to sex hormones is the ratio of the length of the second digit (2D, index finger) to the length of the fourth digit (4D, ring finger). The ratio is lower in men than in women and is assumed to be affected by exposure to prenatal androgens. Normal polymorphisms in the androgen receptor (AR) gene are reported to correlate with digit ratios in men. Using 2D:4D as a marker, prenatal androgen exposure has been found to be associated with behavior more commonly displayed by men than women and to be related to aggression, risk-taking, and disorders more common in men such as ADHD and autism.

Another research paradigm to study the influence of prenatal brain exposure to sex hormones comes from the study of opposite- vs, same-sex twin pairs. It is assumed that fetal androgens may be transferred from the male to the female fetus and that the female twin might thus be androgenized by her male co-twin. However, results of such studies have been found to be inconsistent.

Early cognitive gender development

From cognitive developmental studies we know that learning about being a boy or a girl starts in infancy. Babies as young as 9 months are already able to visually discriminate between the sexes. The ability to verbally label the sexes comes later, at around 28 months. As toddlers are often hardly aware of genital differences, they use hairstyle and clothing as a criterion for classification.

With regard to the concept of gender, children first learn to identify their own and others' sex (*gender labeling*). Next, they learn that gender is stable over time (*gender stability*). Finally, they learn that superficial changes in appearance or activities (a boy does not become a girl overnight if he puts on a wig or plays with Barbie dolls) does not change one's gender. This is the last stage of gender constancy (*gender consistency*). This last phase is reached between 5–7 years, but long before that age, children appear to have knowledge about gender stereotypes (for an overview see Ruble *et al.* 2006). For instance, 3-year-old children, who saw videotaped infants labeled male, rated these infants as "big," "mad," "fast," "strong," "loud," "smart," and "hard." When labeled female, they were rated as "small," "scared," "slow," "weak," "quiet," "dumb," and "soft". Three-year-olds also believe that "boys hit people." Gender stereotype knowledge increases rapidly after 3 years of age and appears to develop throughout childhood. Once established,

gender stereotypes influence the way new information is processed. Children remember stereotype consistent information better than inconsistent information, and even distort inconsistent information. For instance, when a picture is shown to them of a woman flying an airplane, they may either report having seen a man flying the airplane or a woman doing something else, such as cooking.

According to some cognitively oriented theorists, children need only basic information rather than extensive knowledge about gender to further develop gender role behavior. For instance, children prefer same-sex toys, imitate same-sex models, and reward peers for gender-appropriate behavior before they reach complete gender constancy. Therefore, a complete understanding of gender is perhaps not important in the very early stages of gender development.

Gender development is a process that not only involves cognitive aspects but also involves affective meanings. As soon as a child identifies with one of the sexes, these values will affect their self-perception and self-concept. For instance, boys are usually proud of being a boy and look somewhat down on girls.

Gender segregation

At very early ages children become interested in same-sex playmates. Boys like other boys better than girls and spend a fair amount of time in the company of other boys. Changing this peer preference appears to be difficult.

Children thus spend an important part of their time in all-male or all-female groups. Boys tend to play in larger groups, play in more public places and with less proximity to adults, and play rougher and with more body contact. Boys fight more and their social interaction is oriented more toward issues of dominance. Girls' groups are less hierarchically organized and their friendships are more intense. Girls appear to use language to create and maintain relationships, to criticize others in acceptable ways, and to interpret accurately the speech of other girls. In boys, speech is used to attract and maintain an audience, to assert one's position of dominance, and to assert oneself when others have the floor. So gender segregation has far-reaching consequences for children's social development and friendships.

The influence of the environment on gender development

Children also learn about gender by observation of role models and by differential treatment. This differential treatment may be more or less direct (e.g. playing different games with boys than with girls) or be more subtle or indirect (e.g. blue and pink clothing). An immense body of literature supports the notion that parents, other adults, teachers, peers, and the media are gender-socializing agents. For instance, mothers talk more to daughters than to sons, teachers praise and criticize boys more than girls, and peers reinforce same-sex and punish cross-sex behavior. In experiments in which the actual sex of an infant is unknown, adults even interact differently with children labeled as boys than with children labeled as girls.

Adults and children are not just influencing gender development by their reinforcement of behaviors. As role models, parents and peers also shape children's gender attitudes and behaviors. Furthermore, gender development seems to be strongly influenced by the media. This was nicely illustrated by an older study among children living in a Canadian town unable to receive television. Before television was introduced, they were less traditional than a control group. Two years later their attitudes had changed dramatically in the more traditional direction.

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Besides biological factors, such as prenatal exposure to testosterone, environmental and psychological factors also play a role in male gender development.

Gender development: sex hormones and the brain after puberty

Later in life, neural circuits and behavioral patterns are activated by changing levels of sex hormones. An example of these so-called activating effects is the stimulation of the already sexually differentiated nervous system by gonadal hormones during puberty. Because steroid-dependent organization of brain and behavior also takes place during adolescence, it has been suggested that these activating effects should also be characterized as organizational effects. The timeframe for organizational effects may not be limited to prenatal and early neonatal periods, but may also include puberty and adolescence. Steroid dependent organization during puberty implies that certain adult sex-typical behaviors are expressed because pubertal hormones first have organized neural circuits in the developing adolescent brain and that these circuits are subsequently activated by gonadal hormones. One example of structural changes that may be the result of pubertal hormone changes is the white matter volume. This increases faster and reaches a bigger overall volume in boys than in girls during puberty and it is thought that white matter volume might be related to the activity of the AR. With regard to brain tissue in adulthood, sexual dimorphism is found for gray and white matter, but the white matter difference is more pronounced, with men having larger white matter volumes than women. Regionally, larger volumes of gray matter are detected in women than in men.

Other sex differences in brain and behavior in adulthood may also be related to the effects of sex hormones. Subcortically, in the hypothalamus, sex differences are observed in the interstitial nuclei of the anterior hypothalamus (INAH-1, INAH-2, INAH-3) and the central portion of the bed nucleus of the stria terminalis, with larger volumes in men than in women. These sex differences in the hypothalamus are thought to underlie sex differences in gender identity, reproduction, and sexual orientation.

Gender-related cognitive functioning has been related to size and shape of the corpus callosum. Sex differences have been reported for the corpus callosum, but there is disagreement about the direction of the sex effect and some studies failed to detect such an effect. Men do show more morphological asymmetry than women and appear to have a somewhat more lateralized brain with left hemisphere dominance for language processing and right hemisphere dominance for spatial processing.

Regions with developmentally high densities of estrogen and ARs show greater sexual dimorphism. For example, the amygdala has a larger volume in males. Sex differences in the amygdala's response have been mentioned as factors to explain sex differences in the prevalence of psychiatric disorders. For instance, depression is less common in men than in women and is associated with sex differences in the role of the amygdala in emotional memory.

Men and women also differ in the occurrence of other psychiatric disorders. Schizophrenia, attention deficit hyperactivity disorder, and autism primarily hamper men (for an overview see Bao & Swaab 2010), whereas eating- and anxiety disorders are more prevalent in women. Sex ratios for neurological disorders differ as well, with Rett syndrome (non-existent in men) and Kleine-Levin syndrome (non-existent in women) as extremes. Finally, personality characteristics also show sex differences. In general, physical aggression appears to be higher in men, whereas empathy has been found to be higher in women.

Genetic studies

Independent of the role of hormones, other biological factors, such as genes, may also influence gender development. Even before the production of gonadal hormones, genes may directly affect brain sexual differentiation. Evidence for the role of genetic factors in sex differences in behavioral traits has been found for play behavior and

aggression. For a review of the evidence for direct genetic effects on sex differences in brain and behavior we refer to Ngun *et al.* 2011.

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Gender identity: a persons' sense of self as being male or female.
Gender role: behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as more typical of the male or female social role.
Disorders of Sex Development (*DSD*) (previously referred to as intersex conditions): congenital conditions in which the development of chromosomal, gonadal, and/or anatomical sex are not entirely male or female.
Gender dysphoria: is the distress resulting from conflicting gender identity and gender of assignment.
Transsexualism or gender identity disorder: extreme end of the spectrum of gender dysphoric conditions, usually characterized by a pursuit of sex reassignment.

A typical development of gender identity and gender role behavior

Research on factors that influence typical gender development generally focuses on gender role or gender related behavior. We have already seen that in non-clinical groups, prenatal exposure to higher levels of androgens may lead to more masculine behavior. Because gender identity usually develops in accordance with an uneventful sexual differentiation, it is difficult to study factors that may influence gender identity development in typically developing individuals. However, studies in individuals with atypical prenatal hormonal levels or individuals that have a gender identity that is not in accordance with their natal sex could help in elucidating the mechanisms underlying gender identity development. Three groups are of interest: children of mothers who took medication during their pregnancies that might have influenced their children's gender development, individuals with disorders of sex development, and transgender individuals.

Intoxications during pregnancy

Daughters of mothers who took diethylstilbestrol (DES), a synthetic estrogen that masculinizes and defeminizes brains and behavior in female rodents, have been found to show higher rates of homosexual imagery or homosexuality than controls, but no masculine gender identity. Effects of exogenous hormones on male behavior and interests are less clear and often conflicting.

In a study among, adults who had prenatally been exposed to phenobarbital- and phenytoin, known to influence sex steroid metabolism, it was found that the individuals as a group did not differ with respect to gender role behavior, but that higher numbers of prenatally exposed subjects reported current or past gender variant behavior and/or gender dysphoria. Gender dysphoria is the distress resulting from conflicting gender identity and gender of assignment. In a group of 147 subjects, there were also 3 transsexuals. This is a remarkably high rate given the rarity of transsexualism.

Disorders of Sex Development (DSD)

Gender development in individuals with CAH

Congenital adrenal hyperplasia (CAH) exposes female fetuses to elevated testosterone levels. This condition is extensively studied to infer the relationship between prenatal hormones and postnatal gender development. These women, who are born with more or less virilized external genitalia, are generally treated early in life to normalize hormone levels and often undergo surgery to feminize

their genitalia. Girls with CAH generally show increased male-typical play behavior. Masculine gender role behavior also appears to be common in women with CAH across the lifespan. In women with CAH, a dose-response correlation has been found; with the more seriously affected "salt-losing" women showing more masculine behavior than the less affected "simple-virilizing" women.

In contrast, women with CAH, who were raised as females, mostly have feminine gender identities. However, these women show a less strong female identification, elevated levels of gender discomfort, and even gender dysphoria (~5%) than non-DSD women.

Gender development and 5α-reductase-2 deficiency (5α-RD-2) and 17β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3)

Children with 5α-RD-2 have an enzyme defect that prenatally blocks the conversion of testosterone into dihydrotestosterone. Consequently they are born with external genitals that are female in appearance. They are usually raised as girls and seem to have a female gender identity, but, if the condition is not discovered in childhood, these children develop male sex characteristics in puberty: growth of their "clitoris" and scrotum, lowering of the voice, beard growth, masculine muscle development, and masculine body fat distribution. After puberty, many of these youngsters start living as males and develop a sexual attraction toward females. These transitions have been primarily documented in non-Western cultures. When raised as boys, these children have a male identity and behave like boys.

Another condition affecting testosterone biosynthesis, which might lead to impaired virilization in male infants, but excessive virilization when these children become adolescents, is 17 β-HSD-3. Gender transitions in 46,XY children with 17β-HSD-3 raised as girls have also been reported. However, such changes did not happen in all affected individuals. De Vries and colleagues (2007) reviewed the literature on gender identity outcome and DSD and found that 59% of the female-raised 5α- RD-2 individuals (69 of 117), and 39% of the 17β-HSD-3 individuals (20 of 51), all above age 12, had gender dysphoria to the extent that they chose to live as males later in life.

Gender development and CAIS/PAIS

Individuals with complete androgen insensitivity syndrome (CAIS), who are raised as girls, are described as very feminine in their gender role behavior, although there may be more variability in their behavior than has long been assumed. They have a female gender identity and in the review by de Vries *et al.* (2007), none of the women with CAIS reported suffering from gender dysphoria or made a gender transition. But in the partial form of this condition, partial androgen insensitivity syndrome (PAIS), another picture emerges. In female-raised individuals, 11% were gender dysphoric or changed gender (5 of 46). In the male-raised group, this percentage was even higher, where 14% were gender dysphoric or changed gender (5 of 35).

Gender development and ablatio penis

A famous case of male identical twins is illustrative in this nature/nurture debate as well. One of the boys lost his penis due to a circumcision accident. The parents were advised to re-assign the child to the female gender and raise him as a girl. Early reports showed that, in contrast to the twin brother, the reassigned child seemed to develop as a "real girl," despite the fact that she had many tomboyish traits. Later, the boy became increasingly unhappy as a girl, and as an adolescent he reassumed the male role. He married and became the stepfather of children. The easily drawn conclusion from this case, that prenatal hormones determine gender identity, seems to be premature, however. In a review reporting on 6 more cases of ablatio penis, the majority lived as females without gender dysphoria.

CAUTION

Male gender role behavior in female-raised children should not be mistaken for a male gender identity.

Concluding remarks

Many parents of children with DSD are concerned about their gender. Some parents are ignorant about the sex of their child for some time. Children with DSD may be ill at birth and may need medical interventions. In addition, the conditions that have been studied vary widely. Levels of prenatal hormones, and timing and duration of the exposure differ between conditions or between individuals with similar conditions and are usually unknown. Therefore, extrapolating the above findings, on atypical gender role development to normal development, has obvious limitations. It is clear from the results of studies of DSD individuals, that a distinction between gender-*role behavior* and gender *identity* has to be made. These study results support the aforementioned findings in nonclinical samples, indicating a relationship between prenatal androgenization and masculine *behavior*. Whether and to what extent prenatal androgen brain exposure results in a male gender *identity* is less clear.

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Prenatal testosterone appears to influence the development of masculine gender role behavior more than the development of a male gender identity.

Transsexuals

Transsexuals have a gender identity that is inconsistent with their natal sex and strongly desire to live in accordance with their gender identity. A complete cross-gender identity may be present from very early ages on. Parents often report that their sons never showed male-typical behavior. Why such young boys identify with girls and want to behave like girls is still an enigma. A supposed discrepancy between genital differentiation on the one hand and hormone induced brain sexual differentiation on the other has been invoked as an explanation for the phenomenon. Because it is impossible to determine prenatal hormone levels in adulthood, postmortem brain studies, cognitive, handedness and imaging studies are employed to investigate whether the brains of transsexuals resemble those of their natal sex or of their gender identity.

Post-mortem studies

Postmortem studies into the brain material of transsexuals revealed a sex reversal in volume and neuron number in the central portion of the bed nucleus of the stria terminalis and the interstitial nucleus 3 of the anterior hypothalamus in male-to-female transsexuals (MtFs) and a female-to-male (FtM) transsexual. Because all subjects had received hormone therapy, it remains unclear if the differences should be ascribed to this treatment. However, nontranssexual males, who had taken estrogens for medical reasons, did not show a smaller central portion of the bed nucleus of the stria terminalis.

Luteinizing hormone (LH) regulation

Based on the assumption that neuroendocrine regulation of LH is a reliable indicator of the sexual differentiation of the brain, it was postulated that MtFs, like females, would show a rise in LH levels after estrogen stimulation (estrogen positive feedback effect) as a consequence of prenatal exposure to imbalanced sex steroid levels. The opposite was expected to occur in FtMs. However, studies with thorough methodology found no support for a sex reversal in the neuroendocrine regulation of LH in transsexuals.