Matched Pairs of Hermaphrodites: Behavioral Biology of Sexual Differentiation from Chromosomes to Gender Identity

by John Money

Gender-identity differentiation is programmed in humans to take place largely after birth, and also to be dependent to a large degree on stimulation from, and interaction with the social environment.

Gender identity in adulthood is the end product not of an either-or determinism of heredity versus environment, but of the genetic code in serial interaction with environment. From the time of conception, the genetic code unfolds itself in interaction, first with the intrauterine environment, then the perinatal environment, the family environment, and eventually the more extended social, biological, and inanimate ecological environment. Interactionism is a key principle, but an even more basic key is the principle of serial sequence of interaction.

Serial interactionism means that interaction between the genetic code and its environment, at a critical or sensitive developmental period in an individual's existence, from conception to death, may leave a permanent ineradicable residue upon which all else is subsequently built. This residue may be so indelible or insistent in its influence as to resemble the potency of the genetic code itself. Moreover, such indelibility or insistence may be residual to what has traditionally been referred to as learning—in which case learning should be referred to as imprinting, in recognition of the persistence and durability of its influence.

In a bygone era of medicine and behavioral biology, the differentiation of a person's sense of gender identity was confidently accepted as innately or instinctively determined. Among authorities of this bygone era, there was less confidence as to whether the innate determinism was genetic, gonadal (by reason of possessing ovaries, testes or, rarely, ovotestes), or hormonal. But there was an agreement of sorts, among these erstwhile experts. They wrongly agreed, in hermaphroditic cases of doubt owing to incompleted anatomical differentiation of the external sex organs at birth, that the sex of the gonads somehow had paramount importance in dictating what the sex of assignment and rearing should be. Therefore, they tried to palpate two testes—if not descended, then in the groin. These palpated lumps might be defective and infertile. No matter. The expert, in his ignorance, might omnisciently decree that an infant, despite a deformed hypospadiac penis resembling a mildly enlarged clitoris, be assigned and reared as a male—though Nature's effort to make a complete male had obviously been thwarted.

Today, one knows better than to use a single, dogmatic criterion, like gonadal sex, on which to base the decision of sex assignment and rearing in cases of congenital ambiguity of the reproductive anatomy. When all the variables, from chromosomal sex to fertility, have been properly evaluated and prognosticated, the one that

ultimately takes preeminence over all others is the criterion of erotic applicability in adulthood. It is useless to assign (or reassign) an hermaphrodite as a male, if all the medication, surgery, and psychotherapy in the world will fail to enable that individual to function in an adult erotic relationship as a male—and likewise in the case of female assignment.

Effect of Androgen Insensitivity on Differentiation

No matter what the genetically determined antecedents and components of gender-identity differentiation, the postconceptional and postnatal determinants can, in test cases, completely override them. The syndrome of androgen insensitivity (testicular feminization) in genetic males provides a graphic example of the extent to which the genetics of the sex chromosomes can be overridden in gender-identity formation. In this syndrome, suppression of the genetic program carried by the XY chromosome pair is itself a genetically transmitted trait. It has its effect at the cellular level by preventing cellular uptake of testosterone, the androgenic sex hormone of the male. The cells of the embryo and fetus are thus unable to utilize their quota of the testosterone released in normal amounts by the body's own testicles.

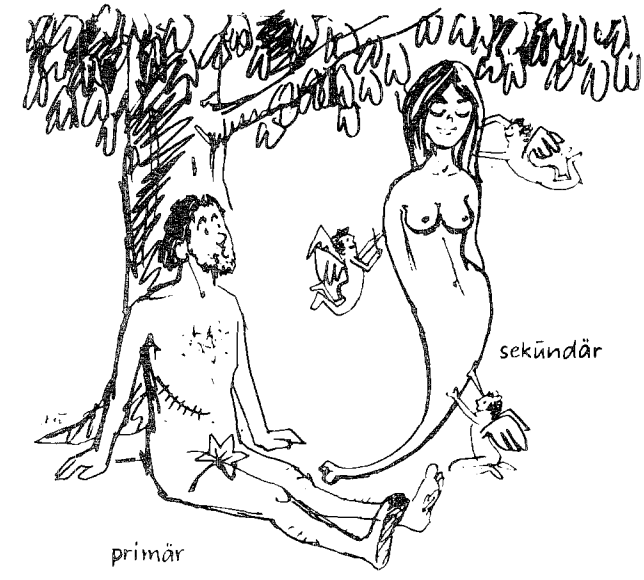
In consequence, the embryonic testes fail to inhibit, as they should, the primal tendency of the internal and external reproductive organs to differentiate as female. The failure is incomplete, so far as the internal organs are concerned, so that the uterus is poorly formed and incapable of menstruating at adolescence. By contrast, the failure of the testes to hormonally masculinize the external organs is total, with the result that the anlagen of these organs differentiate as 100 percent female. The baby is born with a female appearance so that, as for all babies with the same genital anatomy, she is announced and registered as a girl. It will not be until much later that a discrepancy will be recognized between the anatomical appearance, on the one hand, and the gonads and XY chromosome pattern, on the other.

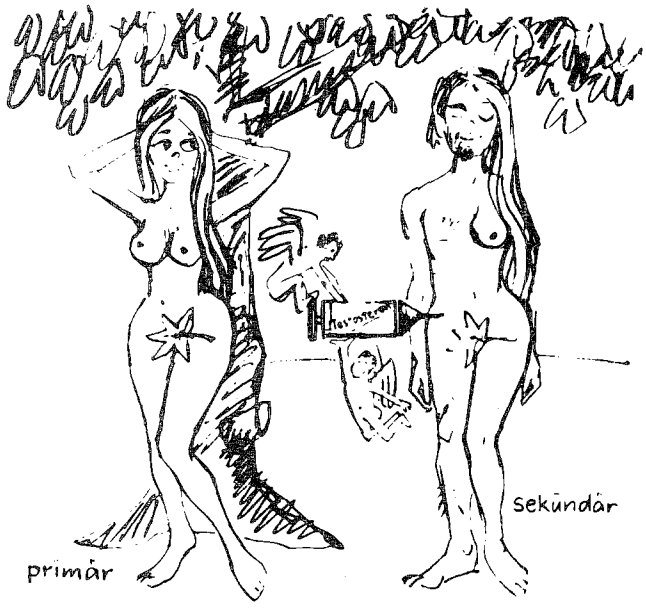
Very occasionally, the syndrome will be recognized in infancy, because of the appearance of the testicles as lumps in the groin, as they try in vain to descend. Occasionally also, an infant might be diagnosed in the course of a family checkup, when an adolescent sister has been diagnosed after a gynecologic examination for failure to menstruate. This latter age is, in fact, the most usual one when a diagnosis is made. By this time, the girl has developed her own breasts and a normal female body contour, for her body has continued to be cellularly unresponsive to male sex hormone, now being released in normal adult amounts by the Leydig cells of her own testes. Her body cells have responded only to the normal amounts of estrogen, the feminizing hormone, normally released by the testicles of normal males.

The girl with the androgen-insensitivity syndrome spends her infancy and childhood exposed to the same family and social influences as her normal sisters, cousins, and friends. She is reacted to as a girl, and she responds as one. Her gender identity differentiates as that of a girl. She shares the play interests of other girls her age, and in teenage she develops the same romantic and dating interests. Despite the bitterness and deprivation of infertility, and of knowing about it ahead of time, she typically gets married and achieves her motherhood by adoption. She is indistinguishable from other mothers on her street. No one, except her closest family and her medical advisers, knows, or even suspects, the uniqueness of her status as a genetic and gonadal male, though she is an hormonal, morphologic, and psychologic female. Her case is a prime example of how little the genetics program of the XY chromosome pair can achieve, of and by itself alone, when its proper developmental environment—cellular through social—is changed as a consequence of a quite limited biochemical impairment, itself genetically determined.

Experimental Antiandrogenism

Though a genetic factor is responsible for initiating the train of events that produces human beings with the androgen-insensitivity syndrome, an analogous condition can be initiated in animals with no abnormal genetic trait. In this case, the hormonal environment of the fetus is changed at a sensitive period, critical for the differentiation of the external genitalia, by injecting the pregnant mother with the synthetic hormone that has an androgen-antagonistic effect. The sons are then born with the external genitalia anatomy of the normal female. Their testes remain undescended in the abdominal cavity where, if subject to no further antiandrogenic treatment, they will secrete masculinizing hormone at puberty. However, masculinzation can be prevented by removal of the testes, and feminization can be induced by cyclic injections of estrogen and progesterone. Then the animals will go periodically into heat, as regular females do, and will respond sexually as females to the males that try to mount them. The males respond to them in the same way as they do to normal females.





Nature's first intention in sexual differentiation is to make a female. So perhaps the story of Adam and Eve might be retold, with Eve no longer being created from Adam's rib, but with Adam being made out of Eve by an injection of testosterone.

The feminizing effect of antiandrogen on the sexual differentiation of the male was discovered by Neumann and his colleagues in West Berlin. Their experiment illustrates the principle, first demonstrated by Jost in Paris some 20-odd years ago, that Nature's first intention in sexual differentiation is to make a female. Jost had castrated fetal rabbits in utero and found that all, regardless of genetic sex, were born with the morphology of females. With no gonads and no gonadal hormones at the critical period of fetal life, differentiation of the external genitals is always female. Something must be added, namely male sex hormone, usually supplied by the fetal testicles, to initiate masculine differentiation of the primitive anlagen of the external sexual organs.

Neumann illustrates this principle humorously when he says that the story of Adam and Eve really should be retold. Eve would be created first, instead of from Adam's rib. Then an archangel would appear with a big injection needle and, by injecting woman with testosterone, create man.

Male Hermaphroditism: Matched Pair

With this principle of masculine differentiation in mind, let me describe another kind of hermaphroditism in man—that of a genetic (XY) male who is defective in developing the clitoris small enough to qualify as feminine, or since it's a genetic male, one should say a penis large enough to qualify as masculine. Such an example was a baby assigned as a female and raised that way. The father considered it malpractice when his local gynecologist told him nearly 11 years later that he had a son instead of a daughter. Fortunately for the girl, she ended up at Johns Hopkins, where she was given surgical feminization in two stages—the first for external appearance at the age of 11, and the second at the age of 19 when her insufficient vagina was lengthened.

Hormone treatments can do a great deal when they are started early enough. In this case the girl was beginning pubertal masculinization when we first saw her. But by surgical removal of the gonads and, therefore, of the male hormones, and with female-hormone replacement treatment, by age 19 she was a good-looking, feminine-acting girl. She was in love with a boyfriend who was number two in her experience. When she came to the hospital, number one was so anxious to be reinstated after being jilted that he took his vacation and visited her every day while she was recovering from her vaginoplasty. She still turned him down! Her psychosexual identity, as this anecdote indicates, had differentiated effectively as female.

This girl's example shows how complete can be a transformation, under an experiment of Nature of this type. It demonstrates that there is no preordained, mechanistic relationship between the genetic and genital structure, on the one hand, and the masculinity or femininity of behavior on the other. This lack of a direct determinism between genetics, anatomy, and sexual behavior is even

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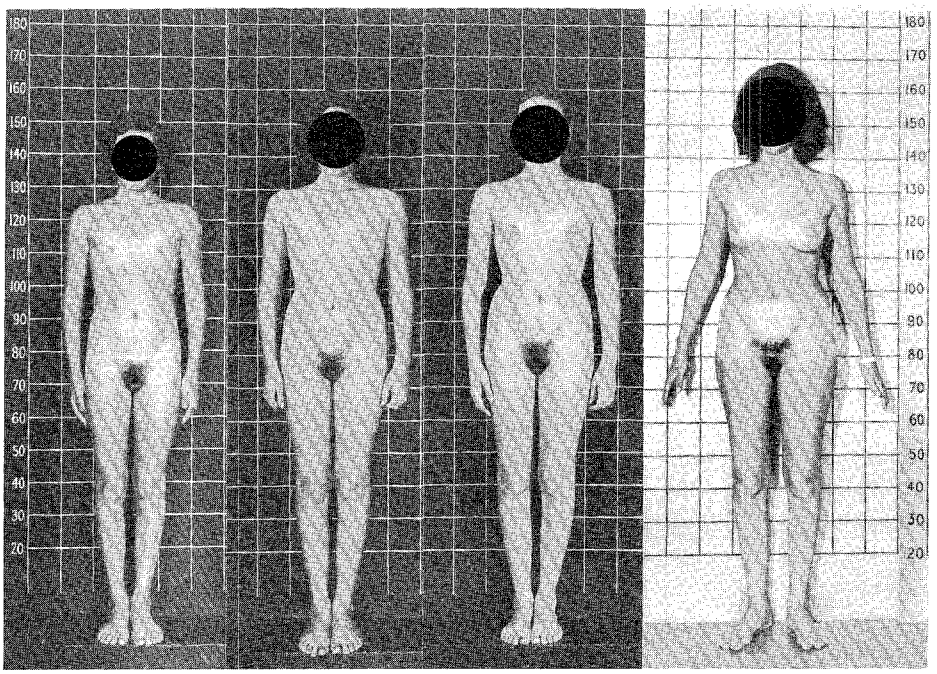
more vividly demonstrated when the case of the girl is matched against one of the same genetic and somatic diagnosis, in which the assignment and rearing has been not as a girl, but as a boy. This boy was recognized as genitally ambiguous at birth and, after some uncertainty, assigned as a male. Masculine repair of the genitalia required multiple admissions throughout childhood, and was finally successful, though the corpus of the penis is rather small. The testes at puberty secreted androgen in sufficient amount to induce spontaneous adolescent virilization. Fortunately the body was not androgen-insensitive, nor even partially so, with resultant breast growth and impotence, as is sometimes the case. The prognosis regarding fertility is unsure, as is the possibility of transmission of the genital defect to male offspring, should there be any. From infancy onward, the boy's psychosexual differentiation as manifested in his behavior, and in what he says, has been masculine. In adolescence, his romantic interests and imagery emerged as masculine. There was nothing that marked him as particularly different from his high school age mates.

The boy and the girl of the preceding case are theoretically important because of the sameness on which their differences are built. Both are genetically male with the XY sex-chromosome pair, and both were exposed before birth to the same fetal-hormonal environment. In infancy and childhood they were somatically similar, but they were exposed to quite different behavioral experiences. They developed correspondingly different behavior in relation to gender role and the differentiation of a gender identity. This remarkable antithesis in psychosexual (and sexo-behavorial) differentiation is indicative of a general principle: namely, that gender-identity differentiation is phyletically programmed in the human species to take place largely after birth, and also to be dependent to a large degree on stimulation from, and interaction with, the social environment.

Adrenogenital Female Hermaphroditism: Four Matched Pairs

The foregoing principle can be found illustrated also in matched pairs of individuals who are genetic females with the XX sex-chromosome pair. Let me now present four matched pairs of cases of female hermaphroditism of the type known as the adrenogenital syndrome. In this syndrome, masculinizing of the genetic female fetus is



This genetic (XY) male—shown at ages 11, 12, 13, and 19—was always raised as a female. At age 11 the mixup was discovered, and she got the first part of her surgical feminization; at 19 she received further feminization surgery. Her complete differentiation as a female shows how complete such a gender transformation can be.

"Dear Doctor,
I do not want to be a boy. I
want to be a girl, just like my sisters.
From Stanley"

initiated by a genetic anomaly that blocks the production of the hormone cortisone, in the adrenal cortex, and releases a masculinizing hormone instead. In a few rare instances masculinizing is so complete that the genital tubercle of the fetus develops not into a clitoris but a penis. The result is a genetic female born with a normal-appearing penis and empty scrotum. The tabs of skin that should form the labia minora of the female behave in the normal masculine developmental manner and wrap themselves around the protruding phallus to make a urinary tube in it. This genetic female will actually urinate through the penis. The outer swellings that should form the labia majora do the masculine maneuver of fusing in the midline to create an empty scrotum. Inside the body there are two ovaries and a uterus.

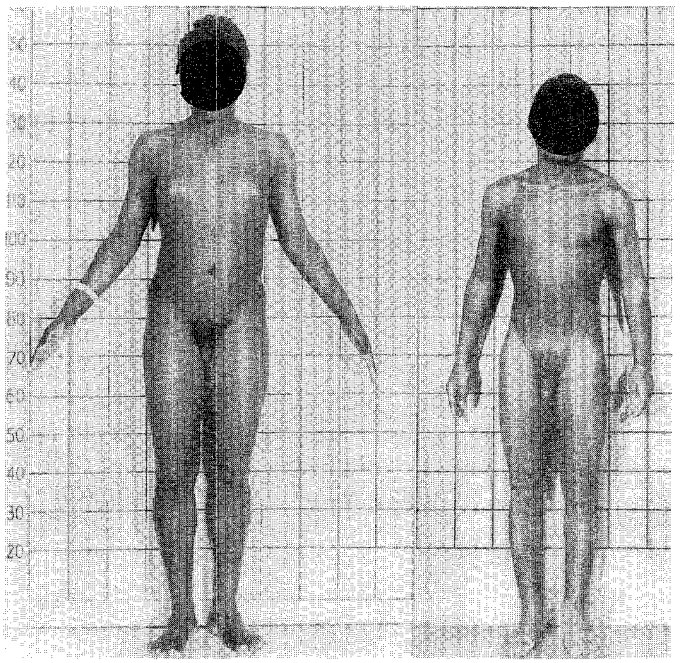
In the first matched pair, one baby was considered as a boy at birth. Coincidentally, symptoms of salt loss finally pointed the way to an accurate diagnosis, but too late to make a sex reassignment. The boy was allowed to stay living as a boy. Surgery was done in the masculinizing direction. The other baby, also because of acute salt loss, nearly died in the first few days after birth, and then was recognized diagnostically. After consultation with the parents (a very important thing, I might add, to get them to understand that doctors are not out of their heads when they tell them that their child with a penis is a girl), feminizing surgery was undertaken, and the baby was assigned and raised as a girl. Here again when two children have the same genetic sex, the same fetal hormonal history, and the same sexual anatomy at birth, it is possible to deflect one child to be raised and to develop a gender identity as a boy, and the other one as a girl.

In the second example, one child was again assigned as a boy and one as a girl. Each had masculinized external genitals, but not to the extent of a complete penis. We did not see them for treatment until they got to be around ten years old, by which time somebody had realized that something must be wrong. These were cases of imperfect, improper workup and diagnosis at the time of birth. When no treatment is given to genetic females with the adrenogenital syndrome, adrenal cortical androgen continues to be produced in excess and has its masculinizing effect—particularly noticeable by age ten as early virilizing sexual maturity. In the case of the child growing up as a boy, early virilizing was not too bad, but for the child growing up as a girl, it was a terrible mortification. The boy didn't like being sexually mature at so young an age, because no children like to be freaky and abnormal-looking, but at least he had the confirmation of being a boy. Nor did he like the final stigma of short stature, around five feet, as a consequence of early maturation.

Following diagnosis, both children had their careers continue unchanged, as boy and girl, respectively. The boy was able to maintain his body's masculinization, even without special treatment. Having had his penis repaired in childhood, he eventually got married. He did not keep his first marriage for too many years, but did not return to bachelorhood because of this, or feel that he was unmasculine. He tried again in a second marriage. Here is further evidence of the extraordinary importance and power of postnatal events and conditions in directing the differentiation of psychosexual identity.

The girl's story is opposite, involving hormone treatment with cortisone in order to permit the ovaries to produce feminizing puberty. Despite the years of hormonal masculinization, behavior outlook and ambitions were female in orientation. However, the girl's confidence as an erotic person, capable of an erotic life, and worthy of a boyfriend and a marriage was much delayed in maturing. (I've had to pilot quite a few of these girls through their anguish at feeling that they have a history of having been a freak, and that somehow this will be intuited by the boy who first has a sexual relation with them—that maybe he will find something wrong.) I have counseled this girl and her boyfriend, as they plan to get married, and she's finally triumphed. She's actually a very attractive young woman. The only telltale sign of her earlier medical history is a narrow configuration of the hips, because their fate was already settled by the time cortisone therapy was begun, owing to the years of the male-hormone influence on the fusion of the bones.

The next two people, who again have the same adrenogenital diagnosis as the previous four, were recognized at birth. They were given the modern cortisone treatment (discovered in 1950) to regulate the adrenal cortical glands and make them behave normally. Physically they both grew at a normal rate for childhood, without early virilizing, so ugly for a girl. At puberty, the girl got her breast development from her own ovaries, which were allowed to come into estrogenic hormonal action instead of being suppressed by malfunctional adrenocortical glands. The boy, also maintained on cortisone to regulate somatic growth, got his masculinization by being given injections of testosterone. He got his testicles implanted as artificial prostheses. His penis had been repaired earlier in life. The girl, at a time soon after birth, had had a



Both these people are genetic females with the adrenogenital syndrome. The one on the left was identified at birth as a boy, the one on the right as a girl. But in both cases the assignment was uncertain, and the uncertainty was conveyed to the growing children. Both, at age 11, changed their sex identity.

reconstruction of the vulva and vagina. Now both of these people have their romantic interests in teenage, appropriate respectively to their lives and roles as boy and girl.

There is a special, very fascinating point to mention here. This girl, like others of similar diagnostic and treatment history, has a certain special flavor to her behavior. Although completely acceptable as a female in our society today—not a lesbian, not falling in love with other girls—she is a tomboy and puts marriage second in her life. Also, she is very bright and has her sights set on a high-level academic career. (These people, by the way, tend to have high IQ's, which is probably related to the hormonal factor in prenatal life while the brain is being formed.) Maybe she will get married one day, and maybe she will have a child, but she's not strongly "turned on" by maternalism. Parenthood and a sex life are something that she can, without sacrifice, postpone.

The final example consists of two people whose position in life, by late childhood, was that somebody must have been a knave or a fool who put them in the wrong sex. As in the preceding six cases, each of them has the adrenogenital syndrome and is genetically a female. One, by age 11, thought he ought to change from being assigned as a boy to live as a girl; the exact opposite happened to the other one. In both cases, when the children were sent home from the hospital at birth, the parents were left with the uncertain possibility of a change of sex later, in view of the ambiguous appearance of the genitalia. Consequently, the parents did not know exactly what kind of child they were rearing—a boy or a girl. This type of uncertainty is as contagious as the measles, and the children contracted it.

Now, if you're a girl who is not sure that you're supposed to be a girl because of your funny-looking genitals, you have an alternative choice. It's a simple law of binary logic that, if you feel everything is wrong the way you are, maybe the correct way is the other way. I think therein lies the explanation of why both these children developed themselves in life as members of the sex other than that to which they were officially assigned. They finally reached the point where they felt that the only way they could belong to the human race was to be allowed to change. They both did, and now they both *do* belong to the human race.

In the course of their treatment I encountered two very telling documents. Both patients were electively mute on matters of sex; it was just too painful for them to talk about it. They were willing to be examined physically and to be cooperative in every way possible, but totally inhibited in the matter of talking. After about six sessions with the first of them, I found an illiterate note on my floor: "Dear Doctor, I do not wemt (want) to be a boy. I wemt to be a girl, just (like) my sisters. From Stanley."

I used this note as a parable, three or four years later, when talking with the other youngster who also suffered from elective mutism on matters pertaining to the dilemma of sex. From this second patient, among many other documents, I finally got one for the father and one for the mother. It was on a particular day when it was very important for the parents to get a message in person directly from the child, so they could be sure that their child was not being forced into a decision in the hospital. The situation was very tense and dramatic as this 11-year old, after a period of listening and doodling, finally wrote, with all the strength of his dyslexic and pre-primer level of achievement: "I gotta be a boy." Nobody had any doubts after that.

The lesson of my story of the four pairs of adrenogenital cases, each with the same genetics and each with the same prenatal history, is once again that—if we ever needed any convincing of it—one must always understand in matters of the biology of sexual behavior that a chain of interactive events leads from the genes to the final product. Only very rarely might one find a direct correlation on a cause-and-effect basis between genetics or any other single variable and behavior.