



Commentary

Clinical implications of the organizational and activational effects of hormones

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ABSTRACT

Debate on the relative contributions of nature and nurture to an individual's gender patterns, sexual orientation and gender identity are reviewed as they appeared to this observer starting from the middle of the last century. Particular attention is given to the *organization-activation* theory in comparison to what might be called a theory of psychosexual neutrality at birth or rearing consistency theory. The organization-activation theory posits that the nervous system of a developing fetus responds to prenatal androgens so that, at a postnatal time, it will determine how sexual behavior is manifest. How organization-activation was or was not considered among different groups and under which circumstances it is considered is basically understood from the research and comments of different investigators and clinicians. The preponderance of evidence seems to indicate that the theory of organization-activation for the development of sexual behavior is certain for non-human mammals and almost certain for humans. This article also follows up on previous clinical critiques and recommendations and makes some new suggestions.

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Is it nature or nurture? Where did that come from? Did she learn that from her mother? Did he inherit that from his dad? Those trying to comprehend the myriad behaviors displayed by others, repeat such common questions and statements, or versions of them. All too often the responses are as simplistic as the questions are direct. Most of the time the implications for the answers given have minor importance. Occasionally however, the significance of the interpretation can be of major concern.

Consider the following. A mother reports that starting from about the age of two her son has always wanted to play with his older sister's dolls and dress as a girl. He has never shown any interest in playing with his brother's soldiers or sports equipment. He wears his hair long, plays with girls during lunch time at school, associates with the female characters when watching movies or T.V. and would like to be a beautician when he grows up. "At first I thought this was just a passing phase—but he is still acting that way at the age of 10 1/2. Things have come to a head lately because he wants to wear girl's clothes at school and the principle won't allow it. He refuses to go to school if he can't go as the girl he believes himself to be. His father and I are at our wit's end. What should we do?" Similar cases to this childhood display of gender dysphoria can be regularly found on the internet (e.g., <http://abcnews.com/2020/story?id=3088298>).

Or consider this scenario. A 28 year-old divorced female screen-writer who had been married for three years is now contemplating switching to live as a man. She says she has felt she should be a man since she started junior high school. At that time she also learned of some surgery she had as an infant. Currently she thinks the time is right since she believes the people she works with will accept the change and she can keep her job. She is convinced she wants to do so even if they won't. She asks your opinion.

Obviously whatever it was that prompted the boy's feeling that he is a girl and his display of stereotyped female preferences challenges everyday ideas of psychosexual development. So too does the woman's urge to transition to living as a man force our questioning of the origins of such behaviors. And currently there is disagreement as to a proper answer. My attempt at answering these questions and showing how the clinical appreciation of the *organization-activation* theory developed will essentially follow a chronological course.

In the late 1950s and 1960s questions similar to the above seemed to be getting increased attention. While the developmental theories of Freud contained within psychoanalysis with its id-ego-superego conflicts still held some clinical sway as did belief in his stages of development (Freud, 1953) they increasingly competed with the developmental theories of scholars such as B. F. Skinner and his theory of operationalism and conditioning (Skinner, 1953), George Herbert Mead and his sociological theory (Mead, 1934), William Sheldon and his constitutional theory ideas of body shape (Sheldon et al., 1970a; Sheldon et al., 1970b) and the work of others. The diverse theories of these scholars were hotly debated in the universities and elsewhere.

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Psychiatrists and other clinicians were mixing and matching theory and practice as they saw fit.

Meanwhile a psychologist, John Money, at the prestigious Johns Hopkins University, who had done research on individuals at that time known as hermaphrodites (Money, 1951) began to propose a theory of his own. Each of those persons he studied had been found to have been born with biological characteristics of both males and females. Some had been born with genitals ambiguously male-like and female-like. Others were born with one ovary and one testis or with gonads combined into ova-testes or they might have had sex chromosomes, not of the typical male XY or typical female XX composition but with some other combination such as XXY, XXXY and so on. The persons he studied are now identified as intersexed. From his studies Money concluded that regardless of the gender to which these intersexed persons were assigned, even if males were assigned as girls or females were assigned as boys, they generally maintained that gender of assignment and identified accordingly as boys or girls, men or women (Money and Ehrhardt, 1972a). Typical statements were “Now it becomes necessary to allow that erotic outlook and orientation is an autonomous psychologic phenomenon independent of genes and hormones, and moreover, a permanent and ineradicable one as well (Money, 1961)” and “it is more reasonable to suppose simply that like hermaphrodites, all the human race follow the same pattern, namely of psychosexual undifferentiation at birth (Money, 1963).” In essence it was proposed that regardless of one's actual sex a person's identification, attitudes and corresponding gender display were relatively independent of organizational prenatal biological forces and set by the boy or girl assignment at birth which are then reinforced by the experiences of life. This was dubbed the “psychosexual neutrality at birth” theory (Diamond, 1965).

At that time, in the 1950s, it was not obvious that three different and separate dimensions of psychosexuality would be considered since the statements were given as generalities. The first dimension of concern that became obvious was that of *identity*; how one sees self as a male or female, boy or girl, man or woman. A second dimension was in regard to *gender patterns* or gender roles; how one acts in regard to socially stereotyped sex-linked or associated masculine or feminine ways. And a third dimension was in regard to *sexual orientation*; the type of partner one prefers in erotic or love encounters.

Significantly at around the same time that these publications appeared the laboratory of William C. Young at the University of Kansas was heavily engaged in investigating just how the reproductive behaviors of animals were structured.¹ Several approaches were being taken in this laboratory's investigations. Different strains of guinea pigs were studied to see how their reproductive behaviors might be modified by genetics and research was ongoing in regard to the influences of different social conditions of rearing and housing.² The role of sex hormones applied in different ways was of particular

interest. How might hormones be able to influence reproductive behavior? The seminal results of these latter mentioned studies was the publication in 1959 by Phoenix, Goy, Gerall and Young of their paper in *Endocrinology* “Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig (Phoenix et al., 1959).” The central finding of that paper was, as is now well known, that the adult sexual behavior of animals could be significantly established (*organized*) by prenatal androgenic events and these behaviors in the adult could be later elicited (*activated*) by these same hormones. To put it simply: the research demonstrated that the neural tissues—somewhere in the brain—mediating adult sexual behavior could be modified during critical stages of prenatal development.

It wasn't long after that the general public's interest focused on the sexual implications of such pronouncements for humans. Young, however, was conservative about extending the findings. He was influenced by the writings and beliefs of prominent colleagues like, Alfred Kinsey, William Masters, Virginia Johnson, and Margaret Mead. These luminaries in the area of sex research basically accepted the reports of Money and, all accepted that human sexual behavior, unlike that of other mammals, was basically the product of rearing, life experiences and acculturation. Indeed Money and Mead, both contributed to Young's edition of *Sex and Internal Secretions* (Mead, 1961; Money, 1961) considered one of the endocrine bibles of its time. In that opus Money's collaborators John and Joan Hampson wrote a chapter reinforcing the uniqueness of human sexual behavior and its reliance on social forces as determining organizational factors (Hampson and Hampson, 1961). At about that same time, believing the forces of organization and activation uncovered by Phoenix and colleagues for the guinea pig held as well for all other mammals including humans and would follow evolutionary forces predisposing them in their functioning sexually as males or females, I submitted a critique to the *Quarterly Review of Biology* that challenged Money's hypothesis and conclusions (Diamond, 1965). I thought this journal an appropriate venue since I saw this argument as a major theoretical discourse worthy of wide debate. There was reason enough to challenge a “psychosexual neutrality at birth” theory of development.³

The evidence presented by Money and the Hampsons in support of a theory of psychosexual undifferentiation-at-birth primarily involved intersexed individuals who had successfully adapted themselves to an assigned gender role inconsistent with one or more morphological criteria of sex. The theory was not supported by any normative data. The *Quarterly Review of Biology* critique, on the other hand, argued that a theory of psychosexual organization prior to birth can use the same data and consider that humans, those intersexed in particular, are flexible enough to maintain a gender role either by choice or accident even when contradictory to their normal external genitalia. It was indicated that no non-intersexed persons had ever been shown to accept sex reassignment or any other measure of psychosexual neutrality.

This challenge was soon answered. In 1972 and again in 1975 Money published about an individual, one of a set of male identical twins, that at the age of 8 months had his penis burned to ablation during phimosis repair using a cautery (Money, 1975; Money and Ehrhardt, 1972b; Money and Tucker, 1975). According to these reports the child at the age of 17 months was reassigned as a girl with orchidectomy and preliminary feminizing surgery. Monitored by yearly visits to the Johns Hopkins Hospital as well as at regular intervals with a psychiatrist in the twin's hometown the sexual reassignment was reported as successful. It was said that the boy accepted the switch to life as a girl. Money wrote in 1975, “No one ... would ... ever conjecture [that the girl was born a boy]. Her behavior is so normally that of an active little girl and so clearly different by contrast from the boyish ways of her twin brother, that it offers

¹ I entered into this environment as a graduate student in 1958. In addition to Dr. William C. Young as my major professor my mentors at the lab turned out to be Robert W. Goy, Charles H. Phoenix and Arnold A. Gerall. A better set of mentors could not have been wished for.

² In the 1950s it was rare for any university department to study aspects of sexuality per se. When and if it were done, research on *reproductive behavior* was most often the euphemistic approach for such investigations and was done principally in medical schools and on animals. Aside from the research of Kinsey et al. human studies were unknown at any major institution. It wasn't until the 1960s that psychology, sociology and other departments began to more actively engage in studies of human sexuality. It might be borne in mind that the work of Kinsey and colleagues was heavily criticized when it first appeared (Kinsey et al., 1948. *Sexual Behavior in the Human Male*. W. B. Saunders Company, Philadelphia and London, Kinsey et al., 1953. *Sexual Behavior in the Human Female*. W. B. Saunders Company, Philadelphia and London.). That research was initiated at the University of Indiana for its relevance to teaching courses on marriage and the family. And the works of Masters and Johnson were even more adversely castigated when they appeared in 1967 and 1970 (Masters and Johnson, 1966. *Human Sexual Response*. Little, Brown Inc., Boston, Masters and Johnson, 1970. *Human sexual inadequacy*. Little, Brown, Boston.). Their work was done under the auspices of the Reproductive Biology Research Institute.

³ In Money's papers he referred to psychosexual *undifferentiation* at birth. In my writings I simplified the concept to psychosexual *neutrality* at birth.

nothing to stimulate one's conjectures (Money, 1975).⁴ Reported in professional publications and the national media these writings dramatically confirmed the plasticity of gender. According to the reports an infant born unambiguously male had been surgically reassigned as female and successfully reared as a normal girl. This case has come to be known by the pseudonyms, John/Joan, Sigmundson and I used in our follow-up report (Diamond and Sigmundson, 1997). The child's actual name was David Reimer.

The effects of such reports were widespread. *Time* magazine (January 8, 1973) reported "This dramatic case ... provides strong support for a major contention of women's liberationists: that conventional patterns of masculine and feminine behavior can be altered. It also casts doubt on the theory that major sex differences, psychological as well as anatomical, are immutably set by the genes at conception (Time, 1973)." Numerous psychology and sociology texts (Robertson, 1977; Vander Zanden, 1977) and women's studies publications (Sargent, 1977; Tavris and Offir, 1977; Unger, 1979; Weitz, 1977) used reports of this twin case to support the contention that sex roles and identity and sexual behaviors are essentially learned. Masters and Johnson referred to this case as the "dramatic documentation of the importance of learning in the process of gender formation (Kolodny et al., 1979)." This case was certainly seen as a challenge to a theory of significant prenatal behavioral organization.⁴

Of particular crucial importance, drawing on this research and theory of psychosexual development, pediatricians and other clinicians caring for infants with ambiguous or traumatized genitalia inferred that genetic makeup and prenatal endocrinology could be ignored in the clinical assignment of sex if done early enough. For physicians, the evidence presented from this case affirmed that a theory of organization-activation did not hold for humans.

In a practical sense, for physicians, the reported success of the twin case substantiated earlier suggestions that if a male child's genitals were plainly absent or damaged, if given suitable attention, these children could be raised as girls from infancy on with no hint of abnormality. Accordingly pediatric surgeons would strive to benefit these patients by "normalizing" ambiguous genitalia; an occurrence of about 1 in 2–3000 births (ISNA, 2008). They would reduce enlarged clitorides eliminating visible penis-like structures in infants assigned as girls and, because of the technical difficulty of creating functional and cosmetically believable male genitals, refashion anomalous male genitalia as female and rear these males as girls. This practice became standard to the extent that in 1996 the American Academy of Pediatrics reported, "Research on children with ambiguous genitalia has shown that sexual identity is a function of social learning through differential responses of multiple individuals in the environment (Azziz et al., 1986; Catlin and Crawford, 1994; Donahoe et al., 1991). For example, children whose genetic sexes are not clearly reflected in external genitalia (i.e., hermaphroditism) can be raised successfully as members of either sex if the process begins before the age of 2 1/2 years. Therefore, a person's sexual body image is largely a function of socialization (Pediatrics, 1996)."

So while scholars in zoology, psychology, developmental biology, and other academic disciplines argued the relative influences of nature and nurture on psychosexual development it was not so among physicians. These clinicians, confronted with the real-world births of children with ambiguous or traumatized genitalia basically thought Money's writings gave them a practical and simple solution to their management of troublesome cases. They concluded that since

individuals are psychosexually undifferentiated at birth and since the appearance of the genitalia is considered crucial, surgery should be done to decrease gender ambiguity. In females any large clitoris should be reduced or removed. In males with less than an adequate penis, the preferred surgical approach would be castration, penectomy and sex reassignment to female since it is easier to make a vulva and vagina than a functional penis. And strangely, against all principals of individualizing treatment, all cases of ambiguous genitalia, regardless of etiology, would be managed by being painted with the same brush—dependent upon the size of the phallus (Diamond, 1999). Further supporting this method of medically managing cases of ambiguous or traumatized genitalia was a report that cases of genital surgery and sex reassignment were received well by parents of such children if they were counseled appropriately (Money et al., 1981).

Suffice it to say, a theory that supported prenatal organization of adult behavior had little sway among pediatricians, pediatric urologists and others. The American physician's derived management philosophy and belief in psychosexual neutrality at birth, spread throughout the medical world and essentially held from the 1970s. As far as the general public was concerned it also might be said that nurture was usually given prominence over nature in popular discourse of human sexual and gendered behavior. And this belief, in the public world and in the scientific world as well, held through the 1980s and into the late 1990s despite evidence mounting to the contrary.

Dramatically emerging to public attention in 1952 was the flamboyant Christine Jorgensen; the first publicly recognized transsexual (Docter, 2008). She and others like her began to appear and be noticed. Here were males and females openly and visibly challenging both their gender of rearing and denying that their genitals or gonads were determining their identity as men or women. And they said they felt of the opposite sex from as early an age as they could remember. Numerous TV and entertainment appearances of transsexuals, from the 1960s through the 1990s to the present, have made this phenomenon commonly known. These male and female persons, typical in appearance without any noticeable genital or other ambiguity, and with commonplace rearing, were denouncing both saying the sex/gender to which they were assigned was not in keeping with their sense of self. Their pronouncements were bolstered in the scientific and medical world by the clinical work of Harry Benjamin (Benjamin, 1956; Benjamin, 1966). Since no environmental influences could be linked to this transsexual phenomenon one might have thought it would be taken as particularly strong evidence for a theory of sexual development incorporating some prenatal organization. This did not occur. Instead transsexualism was seen as a mental problem (Gender Identity Disorder or Gender Identity Dysphoria) and so recorded in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR, 2000). Transsexuals were to be treated, not believed.

But medical research also began to significantly challenge a theory of sexual neutrality (or undifferentiation) at birth and bolster scientific and medical evidence for an organization-activation process. In the 1970s and 1980s the work of Imperato-McGinley and coworkers reported on males who were raised as females due to 5-alpha-reductase or 17-beta-reductase deficiencies precluding typical male genital development at birth (Imperato-McGinley et al., 1974; Imperato-McGinley et al., 1979a; Imperato-McGinley et al., 1981; Imperato-McGinley et al., 1979b). Subsequent to puberty, however, the great majority of such persons, on their own, reverted to living as men. These findings were particularly significant in adding support for a theory of prenatal organization of identity—and the power of testosterone—and lessening support for a theory of environmental forces being salient over them. Others too reported on comparable cases (Kohn et al., 1985; Rösler and Kohn, 1983; Savage et al., 1980).

Along a different level of inquiry, in those early years Hines (Hines and Shipley, 1984) and Berenbaum (Berenbaum, 1990; Berenbaum and Hines, 1992) and others showed that gender patterns such as

⁴ Interestingly by 1972 Money acknowledged the influence of prenatal endocrine effects and wrote "experimental findings on animals, which suggest that the prenatal hormonal environment does exercise, during a few critical days of brain development, a determining influence on neural pathways that will subsequently mediate sexually dimorphic behavior ... [never-the-less] ... the higher primates, and man especially, are more subject to the influence of postnatal biographical history (Money and Ehrhardt, 1972a. *Man & Woman, Boy & Girl*. John Hopkins University Press, Baltimore.)." While acknowledging an influence of endocrines Money basically believed any such influence would be trumped by environmental forces.

childhood play and other stereotyped behaviors were masculinized (organized) by congenital adrenal hyperplasia (CAH) and its prenatal androgen production. An extensive review of data from either normal or abnormal hormonal and other models of human development by Collaer and Hines concluded, “the evidence is insufficient to determine which model best explains the data. Sexual differentiation may involve several dimensions, and different models may apply to different behaviors. Gonadal hormones appear to influence development of some human behaviors that show sex differences. The evidence is strongest for childhood play behavior and is relatively strong for sexual orientation and tendencies toward aggression. (Collaer and Hines, 1995).”

Other types of evidence were also gathering regarding the effects of prenatal involvement on neural tissues mediating human sexual and gender behaviors. Regarding sexual orientation LeVay showed there was a difference between androphilic and gynecophilic males in their hypothalamus INH₃ (LeVay, 1991; LeVay, 1993) and Swaab and colleagues also demonstrated neural differences related to sex, gender and sexual orientation in the hypothalamus and at a region known as the bed nucleus of the stria terminalis (Swaab et al., 1985; Swaab et al., 1992; Swaab and Hofman, 1995).

And crucially by 1980 it was known that things were not going as had been reported for David, the “model” child for the determining influence of rearing. He was not responding well to his upbringing as a female and the absence of a penis didn't seem to dampen either his identifying himself as a male or decreasing his stereotypic male behaviors. Psychiatrists familiar with the case doubted the eventual outcome for him. Despite his being raised as a girl without knowledge of his history, and despite being administered estrogens to facilitate a female puberty and development, they reported they didn't believe he would ever make the adjustment as a woman (Diamond, 1982; Williams and Smith, 1980).

These negative findings, however, received little clinical notice. Meanwhile, research demonstrating the testosterone-generated organization of sexual behavior for animals continued to accrue (Beach, 1976; Gorski, 1991; Whalen, 1976). Belief generally continued that an organization-activation theory of behavioral programming probably held for animals but was less probable or at least questionable for humans (Goy and McEwen, 1980). In the minds of clinicians the “psychosexual neutrality from birth” theory for human sexual behaviors essentially continued to hold sway for another decade and a half.

In 1997 the neutrality belief was directly challenged. The year brought with it a report that the John/Joan case was not as originally described. Instead of satisfactorily accepting assignment as a girl it turns out that David had continually fought against his imposed displeasing life and had asserted and demonstrated from early on, behaviors more typically seen in boys. The earlier 1979 alert of the psychiatrists and Williams and Smith documentary was reinforced by a host of newly reported findings. Some major indications of David's male gender manifestations were his compulsion, despite the absence of a penis, to stand while urinating, his preference to play “soldier,” refusal to wear a dress, and saving his money to buy a truck or toy machine gun (Diamond and Sigmundson, 1997). At the age of 14 David—unknowing of his history—brought things to a head when he threatened suicide unless he could live as a boy and develop as a man. Only then was he finally told of how he came to be raised as a girl (Diamond and Sigmundson, 1997).

That publication in the *Archives of Pediatric and Adolescent Medicine* was directed at a clinical audience and strengthened by an accompanying editorial (Reiner, 1997) that also introduced the reader to one of the editorial writer's own similar cases. Reiner had reported on a male teenager, raised unequivocally from birth on as a girl, who announced herself to be a boy at the age of 14 (Reiner, 1996). The impact was immediate. Physicians began, for the first time, to seriously question their clinical practice of the previous several decades. And so too was the general public alerted to these findings by a front page report in the *New York Times* which began “A classic case

of a gruesome surgical accident and its consequences that was long used as evidence of the pliability of sexual identity turns out, in follow-up, to suggest the opposite: that a sense of being male or female is innate, immune to the interventions of doctors, therapists and parents (Angier, 1997).” The theory of psychosexual neutrality at birth was dealt a serious blow and that of prenatal organization and subsequent activation given support. An invitation to present a plenary address at the 1998 annual conference of the American Academy of Pediatrics (AAP) soon followed.

The unique opportunity to speak to the assembled members of the American Academy of Pediatrics allowed a chance to refute the idea of psychosexual neutrality and to strengthen a theory of prenatal organization and subsequent activation. Essentially evidence was presented from individuals with different transsexual and intersex experiences who had themselves switched from their sex of rearing to the gender they thought more appropriate regardless of their genital anatomy. This talk also used findings from the David Reimer story to support a concept of prenatal organization of gendered behavior rather than refute it (Colapinto, 2000; Diamond, 1999).

The experiences of transsexuals with their expressions of desperation in following their inner feelings despite the physical reality of their genitals and experiences of typical rearing were easily documented as were their demonstrated willingness to shift their gender despite overwhelming social prejudice, familial and religious rejection and economic loss (Diamond, 1996b; Kotula, 2002). No post-birth environmental or experiential occurrences could be found to foster their identity; organization-activation processes were believed to be involved. A second line of evidence presented against genitals and social rearing being the determining factors in one's appreciation of identity came from different categories of intersexed individuals. A steady appearance of articles from the 1960s and following had been published in medical and nonmedical publications documenting how, although reared as members of one sex, these persons not only claimed to be better suited to the other but insisting on making the transition to the gender in which they felt most comfortable e.g., (Diamond, 1996a; Diamond, 1999).

Information about intersex support groups was also presented. Such groups represented persons with different and specific conditions ranging from congenital adrenal hyperplasia (CAH), to androgen insensitivity syndrome (AIS), and Klinefelter's syndrome (KS). An umbrella organization, the Intersex Society of North America (ISNA), was formed in 1993. Many of these intersexed persons had in common their feeling of having been sexually mutilated and abused by having surgical modification (“genital normalization”) without their consent and being kept in the dark about their medical situations. Many were particularly incensed if they had been sex reassigned without their consent e.g., (Alexander, 1997; Holmes, 1997/1998). A significant number of persons reassigned themselves asserting they were reverting to the gender they felt most appropriate. Knowledge of these groups and findings were also presented.

These lines of evidence presented at the AAP Conference reinforced the idea that indeed human sexual behavior could be somehow organized prenatally and activated with puberty or later despite rearing, familial, religious, social and cultural opposition. The emergence of David's maleness, the manifestations of transsexuality and the self sex reassignment of intersexed individuals all seemed to indicate that people were psychosexually biased and predisposed from prebirth factors. The belief that one's sexual identity could be modified simply by rearing and that individuals were psychosexually neutral at birth lost footing (Diamond, 1999). It could also be said that organization-activation theory gained status.

To replace the previous postulates for the management of intersexuality four new ones were offered: 1) Individuals are psychosexually biased at birth. 2) Healthy psychological development is related to the appearance of the genitals but not crucially so. 3) Treatment must be individualized. Discuss openly, honestly and fully

any doubt as to identity and orientation, and provide options. 4) Allow mature individuals a change of gender whenever by informed choice. Associated with these postulates three recommendations for the medical management of Differences in Sex Development (DSD) were offered.⁵

Recommendation 1

"There should be a general moratorium on sex assignment cosmetic surgery when it is done without the consent of the patient."

At the time there was no evidence that the surgeries were harmful or helpful for the infant. And there still isn't. That prompted the second recommendation.

Recommendation 2

"This moratorium should not be lifted unless and until complete and comprehensive retrospective studies are done and it is found that the outcomes of past interventions have been positive."

These too have still not been done (see below).

Recommendation 3

"Efforts should be made to undo the effects of past physician deception and secrecy."

This recommendation related to the secrecy and obfuscation often used by clinicians in dealing with their intersexed patients. It was not unusual that even the parents would not be told full details surrounding their child's management (Karkazis, 2008; Kessler, 1998).

The talk concluded by basically saying that intersexed infants should be assigned a gender, not based on genitalia, but based on a specific diagnosis of their exact condition—with consideration of prenatal genetic and endocrine forces—and the best prediction for the child's future choice of identity (Diamond, 1999).

Relative to organization-activation theory the year 1998 saw two significant publications. One was a review paper by Cooke et al. (Cooke et al., 1998) which summarized much of the accruing evidence on the influence of pre and postnatal androgens in masculinizing the male nervous system and behavior in animals and humans. Their conclusion confirmed the androgen effects in animals but for the human cautiously stated "there is ample evidence of sexual dimorphism in the human brain, as sex differences in behavior would require, but there has not yet been any definitive proof that steroids acting early in development directly masculinize the human brain."

The second paper was significant for a publication that conflicted with the John/Joan case. Bradley et al. (1998) reported on an individual in which, like David, a circumcision-by-cautery accident resulted in a normal boy having his penis burned off. And like David, this male was castrated, had surgery and was raised as a girl. This person admitted that she was a tomboy as a child and adolescent but unlike David as an adult claimed to see herself as a woman. This individual, again like David, was reported to hold a male-typical blue-collar job and is predominantly gynophilic but considers herself ambisexual (Zucker, 1999). Obviously this case was said to bolster the force of rearing in structuring one's sexual identity. It was seized upon

as such by many but it might be argued that for someone who is gynophilic or ambisexual, being raised as a female and having a vagina might be thought an advantage and easy to internalize.

One immediate result following the presentation to the American Academy of Pediatrics was a call for a national conference to consider the implications of the findings and three recommendations presented. The conference was held in Dallas, Texas in the spring of 1999.

At the Texas conference the clinicians reacted to a host of different factors. Basically, without directly stating as much, there seemed to be general agreement on the ability of prenatal androgen to shape animal sexual and reproductive behaviors but its ability to overcome human rearing and organize human psychosexual behavior remained in question for some (Gorski, 2002; Meyer-Bahlburg, 2002). For others, however, there was little doubt. The presentations of Imperato-McGinley (Imperato-McGinley, 2002) and Reiner (Reiner, 2002) were strongly supportive of an organization-activation theory. Imperato-McGinley updated her reports of individuals with 5-alpha reductase that had, due to female looking genitalia at birth, been raised as girls in many different cultures but nevertheless switched to live as males:

"It appears from the observed natural history in subjects with this inherited condition, that if puberty is permitted to occur spontaneously without surgical or societal reinforcement of the female sex of rearing, then a male gender identity, although discordant with the sex of rearing, will prevail. Under these circumstances it appears that the extent of androgen (i.e., testosterone) exposure of the brain in utero, during the early postnatal period, and at puberty, has more of an effect determining male gender identity than does sex of rearing and socio-cultural influences... In subjects with inadequate testosterone production or action, if adequate androgen imprinting has not occurred, the sex of rearing becomes the predominant factor (Imperato-McGinley, 2002)."

Reiner, in discussing the etiology of gender identity stated:

"The etiology of gender identity may be neither obvious nor easily conceptualized. Yet what is obvious is that the presence of androgen is critical. It is the determining factor in the development of ... behavioral dimorphism in humans—genital structure, ... male-typical behaviors, masculinization of the brain ... The trendy notion that *Homo sapiens* must develop gender identity or any attribute in a divergent mechanism from other primates or even other mammals is species-narcissistic. That humans must develop gender identity at all—that is, under environmental influences—is an unproved assumption validated by little data (Reiner, 2002)."

Reiner supported his presentation which reinforced the power of prenatal organization by offering evidence from a group of individuals with cloacal exstrophy he had been following; 8 of 16 males assigned to female sex-of-rearing at birth due to the absence of a penis, had spontaneously declared themselves male and seven live as males.

Aside from such direct address of organization-activation theory or a competing "rearing induction theory" most attention at the meeting was toward management of specific DSD conditions. The general responses seemed to reveal few modifications over past practices. A good bit of attention did, however, revolve over consideration of the presence or absence of prenatal and postnatal androgens associated with any particular condition and how that might effect future behaviors and shed light on sex assignment. In the absence of long-term data, however, in most cases the discussions ended with anecdotal comments and an awareness that more long-term case studies were needed (Karkazis, 2008).

As an associated issue of clinical relevance the Texas conference also turned to practical questions of ethics that needed attention

⁵ It has been recommended that intersex conditions be referred to as Disorders of Sex Development (DSD) (Hughes et al., 2006. Consensus statement on management of intersex disorders. Archives of Disease in Childhood. 91, 554–563.). This I refuse to do. I consider using the adjective *disorder* to be demeaning and pejorative to the individuals so identified. And so too does it seem insulting to members of the Organisation Intersex International, the largest intersex organization in the world (<http://oii-usa.blogspot.com/2006/08/three-intersex-activists-defend.html>). I use the abbreviation but with the meaning of *Differences of Sex Development* Diamond and Beh, 2008. Changes In Management Of Children With Differences Of Sex Development (Nature Clinical Practice: Endocrinology & Metabolism. 4, 4–5).

(McCullough, 2002). How should the parents be involved? Can the parents accept a child with ambiguous genitalia and could the child cope without normalizing surgery? How is sex reassignment tolerated? Should/could the final choice of gender and surgery be postponed and any decision left to the maturing intersexed child, the attending physician, the parents, or some combination of “all the above?” And not least, what legal matters could be involved? No general summary statement about the determining factors of sexual identity evolved from the conference but several themes did emerge (Zderic et al., 2002). The first emergent theme specifically reinforced that more research with long-term studies pertinent to each type of intersex condition was needed. The second topic reinforced was that patients should be as informed as soon as possible as to their condition. Thus, it can be said that the second, and aspects of the third, recommendations from the 1998 AAP conference were essentially agreed to. A third concept strongly emerged: the human brain was recognized as a sexual organ and “since the human brain is essentially dimorphic, it is not always possible to predict whether the adult will be happy with their gender 20 or 30 years after such a critical decision has been made in the first days of life” (Zderic, 2002). It was not yet clear to the participants whether or not human psychosexual development, particularly regarding identity, was primarily dependent on rearing or prenatal forces. In any case a moratorium on infant surgery was considered unrealistic; mostly because it was hypothesized that it would not be accepted by parents (Glassberg, 1999).

Some definite clinical changes did follow the 1998 AAP and 1999 Texas conferences. The American Academy of Pediatrics reviewed their policy in regard to DSD management and issued new recommendations (Pediatrics, 2000). Similarly, the British Association of Paediatric Surgeons soon modified their standard of care for intersexed children (Rangecroft, 2003). The American group did attend to the question of rearing in regard to different conditions. For them, however, the first priority went to considerations of preserving fertility in females with the potential functionality of the male phallus their second priority. Their statement in regard to sex assignment was “Historically, it has been assumed that the psychosexual development of infants with an intersex disorder is largely the result of rearing rather than intrinsic. However, in the last decade it has become apparent that testosterone imprinting of the fetal brain may play a role in determining male sexual orientation.” They then proceeded to acknowledge the male-like behavior patterns of girls with CAH and potential for adjustment problems.

Neither group referred specifically to the possible prenatal influences on psychosexual identity nor sexual orientation. Neither the US or the British group accepted the idea of a surgical moratorium. Both groups, however, recognized the need for more caution in treatment and increased research on the topic, greater candor and honesty when dealing with families and patients and the advisability of counseling. In any case it might be said that the medical and scientific community had dramatically shifted their clinical thinking and management policies of psychosexual development in the half dozen years 1997 to 2003 (Diamond, 2004).

The last half dozen years, from 2003 to the present, has seen a great deal of activity, both lay and professional, in discussing the development of human sexual identity and the possible role of prenatal organization. Several important papers appeared as have a goodly number of reviews. One paper from 2003 is significant in countering the idea that parental influences are responsible for fostering the development of male-like behaviors and interests in girls with CAH. Servin et al. (2003) presented children from 2 to 10 years of age with different toys from which they could select freely. They also evaluated the girl's interests and other behaviors. They summarized “No parental influence could be demonstrated on play behavior, nor did the comparisons of parents' ratings of wished for behavior versus perceived behavior in their daughters indicate an effect of parental

expectations. The results are interpreted as supporting a biological contribution to [masculinized] differences in play behavior between girls with and without CAH.” In 1999 Servin and colleagues had reported that children as young as 12 months of age demonstrated sex differences in toy choice (Servin et al., 1999).

The year 2004 started off with a call for a much-expanded appreciation away from development of the individual as something totally self-contained but toward one of understanding the cultural and social forces that might influence a child's sexual development. In this vein Herdt called for notice of not only what societies and cultures fostered postnatally, regardless if they were intrinsic to the individual (prenatally organized) or not, but also what societies and cultures denied, sanctioned against or exhibited antagonism toward; how society could or might control any display of sexual behaviors (Herdt, 2004). This call was echoed by many feminists and deconstructionists but had little influence on clinicians dealing with matters of sexual development. The increasing number of studies that did assess biological versus environmental influences on development were generally unknown or ignored by the critics.

Melissa Hines and colleagues reported on a look-back study of adult men and women with CAH in 2004 (Hines et al., 2004). These investigators found that adult women with CAH reported significantly less satisfaction with the female sex of assignment and less heterosexual interest than did unaffected women. The amount of dissatisfaction seemed, according to these investigators, to be correlated with the relative amount of male-like play and activities they enjoyed as children. They further suggested that those girls with CAH who showed the greatest alterations in childhood play behavior may be the most likely to develop a bisexual or homosexual orientation as adults and to be dissatisfied with the female sex of assignment. The study also provided additional evidence that recalled male-play, core gender identity and sexual orientation seem unaffected in men with CAH (Hines et al., 2004).

A review by Swaab in 2004 discussed transsexuality and summarized the relevant evidence found applicable till that time. “Male sexual differentiation of the brain and behavior are thought, on the basis of experiments in rodents, to be caused by androgens ... observations in human subjects with genetic and other disorders show that direct effects of testosterone on the developing fetal brain are of major importance for the development of male gender identity and male heterosexual orientation. Solid evidence for the importance of postnatal social factors is lacking. In the human brain, structural differences have been described that seem to be related to gender identity and sexual orientation (Swaab, 2004).” Recently this paper by Swaab was followed with a report by Garcia-Falguera and Swaab that found “the sex reversal of the INAH₃ in transsexual people is at least partly a marker of an early atypical sexual differentiation of the brain and that the changes in INAH₃ and the BSTc may belong to a complex network that may structurally and functionally be related to gender identity (Garcia-Falguera and Swaab, 2008).” Adding to these findings regarding transsexuals, it was reported that genetic influences were definitely involved in the condition. Among male monozygotic twins if one transitioned to live as a woman his brother was twice as likely to transition as was found among male dizygotic twins (Diamond and Hawk, 2004).

Zucker in 2004, prepared a review of gender identity development and related issues regarding children with gender dysphoria (Zucker, 2004). In considering organization-activation he had this to say: “Although there is no known prenatal hormonal anomaly that is associated with GID, it is possible that less pronounced variations in the prenatal hormonal milieu that do not affect genital differentiation, but do account in part for intrasex differences in the expression of sex-dimorphic behavior, play a role. For example, an avoidance of rough-and-tumble play and a low activity level ... [in boys] ... probably are determined, in part, by biological factors.” Regardless of whether or

not this is so, Zucker concludes “Most clinicians, [to reduce suffering] take the position that therapeutics that are designed to reduce the gender dysphoria, lessen the degree of social ostracism, and reduce the degree of psychiatric comorbidity constitute legitimate goals of intervention.”

An important clinically related survey was conducted in 2004 by Sandberg and colleagues. These investigators questioned more than 300 members of the Lawson Wilkins Pediatric Endocrine Society and the Society for Pediatric Urology regarding their opinions and treatment policies for different intersex conditions. As applied to humans both groups reported strong belief in the power of androgen imprinting prior to birth. They reported a definite shift away from sex reassigning males with ambiguous genitalia; they viewed prenatal exposure to androgens as the major determinant of gender identity (Sandberg, 2004). Judging from anecdotal expressions these beliefs and this practice shift seemed based on the clinician's acceptance of the animal data and clinical findings from different experiences they've had or knew about (Karkazis, 2008). However, the survey also showed the physician's continuing belief in early surgery to “normalize” ambiguous genitalia. On the positive side, also expressed was an “overwhelming willingness to incorporate more details regarding medical and psychological risks within informed consent for genital surgery.” There was also a strong showing of support for psychological help and counseling in the management of intersex conditions.

A noteworthy 2005 paper by Hines and colleagues followed up their gender role studies of the previous year. Boys and girls from 3 to 10 years of age with congenital adrenal hyperplasia were assessed regarding their choice of toys when presented with a host of male and female typical samples. Also assessed were their unaffected siblings. Girls with CAH displayed more male-typical toy choices than did their unaffected sisters, whereas boys with and without CAH did not differ. As in the paper by Servin and colleagues mentioned above (Servin et al., 2003), a part of this study also assessed the interactions of the parents. Fathers as well as mothers encouraged sex-typical toy play in children with and without CAH. Girls with CAH received *more* positive feedback for play with girl's toys than did unaffected girls. These investigators concluded: “Data show that increased male-typical toy play by girls with CAH cannot be explained by parental encouragement of male-typical toy play. Although parents encourage sex-appropriate behavior, their encouragement appears to be insufficient to override the interest of girls with CAH in cross-sexed toys (Pasterski et al., 2005).”

Data from three additional studies in 2005 seemed to view findings differently on the role of prenatal androgens in psychosexual development. A follow up study of intersex children and how they were managed in the Netherlands by Cohen-Kettenis concluded that “prenatal brain exposure to androgens plays some part in the development of gender role behaviour, [but] the current evidence is not in line with the idea of determination of gender identity through prenatal sex steroid exposure. Recent reviews on gender dysphoria and gender change in patients with intersex conditions show that initial gender assignment still seems to be the best predictor of adult gender identity (Cohen-Kettenis, 2005).” Meyer-Bahlburg reviewing similar data concluded “The findings clearly indicate [in 46XY persons] an increased risk of later patient-initiated gender reassignment to male after female assignment in infancy or early childhood, but are nevertheless incompatible with the notion of a full determination of core gender identity by prenatal androgens (Meyer-Bahlburg, 2005)”. In contrast were the conclusions from a study on both DSD individuals and others with the non-intersex condition of cloacal exstrophy. This updated study by Reiner found, as has had his previous work “active prenatal androgen effects appeared to dramatically increase the likelihood of recognition of male sexual identity independent of sex-of-rearing. Genetic males with male typical prenatal androgen effects should be reared male (Reiner, 2005).”

A 2005 review by Rahman accumulated the data for behaviors related to sexual attraction and sexual orientation. He writes:

the data “support(s) the proposal that sexual orientation in humans may be laid down in neural circuitry during early foetal development. Behaviour genetic investigations provide strong evidence for a heritable component to male and female sexual orientation ... Further evidence demonstrates a role for prenatal sex hormones, which may influence the development of a putative network of sexual-orientation-related neural substrates. However, hormonal effects are often inconsistent and investigations rely heavily on ‘proxy markers’ ... These current theories have left little room for learning models of sexual orientation. Future investigations, across the neurosciences, should focus to elucidate the fundamental neural architecture underlying the target-specific direction of human sexual orientation, and their antecedents in developmental neurobiology (Rahman, 2005).”

A most comprehensive review on the influences of prenatal hormones on child and adult gender patterns, and thus an evaluation of the organization-activation hypothesis, appeared in 2005. This study by Cohen-Bendahan, van de Beek and Berenbaum evaluated endocrine evidence from clinical populations, in which prenatal hormone exposure is atypical for a person's sex but there is increasing evidence from the normal population for the importance of these hormones. They discuss the premises and pitfall of various types of studies that had been used in the past, including those using clinical populations of individuals with different DSD and other conditions. They also reviewed studies that measured hormones in the general population (assayed through umbilical cord blood, amniotic fluid, and maternal serum during pregnancy) and included indirect measures of hormones in the general population (inferred from interuterine position and biomarkers such as otoacoustic emissions, finger length ratios, and dermatoglyphic asymmetries; Cohen-Bendahan et al., 2005). From their review they concluded prenatal androgens seemed definitely involved with many aspects of personality and behavior including sexual orientation, sex-typed interests, spatial ability, and aspects of personality. They strongly assert that androgens are responsible for the differences between the sexes in these traits.

Directly related to the clinical application of belief in the strength of organization-activation theory for humans was a survey of physicians conducted in 2005 by David Diamond and colleagues (Diamond et al., 2005). These investigators asked pediatric urologists specifically how they would clinically deal with infants with ambiguous genitalia. They overwhelmingly favored female gender assignment for females even if they were extensively masculinized (Prader V) considering that preservation of female fertility was of foremost importance. For a case involving a male with cloacal exstrophy 70% of respondents recommended male and 30% a female gender assignment. The factor they thought most important in choosing a male identity was the likelihood of brain imprinting by androgens. Those preferring a female gender assignment thought the most important factor to consider was the chance of surgical success. They were less concerned with male fertility. The likelihood of choosing a male or female gender assignment was strongly influenced by respondent characteristics; younger practitioners seemed more willing to attend to brain potential while those older seemed more concerned with surgical outcome. As these investigators summarized, the implications of the different attitudes and practices are great.

In 2006 transsexuality again drew attention to viewing the influences of rearing and possible prenatal organization of behavior. The Gender Identity Research and Education Society (GIRES) reviewed factors they felt of significant biological and social findings associated with the development of this condition. Data were presented that again pointed to behavioral organization prior to birth. First, in most cases no unusual rearing or environmental

influences could be found to account for the compulsion to leave the gender of rearing to the opposite. In the more than 50 years since the phenomenon became public no evidence could be found that environmental-rearing factors were responsible for the condition. Second, many individuals reported their awareness of “being in the wrong body” as early as they can remember and this again hinted at prenatal influences. The review contained previously presented evidence reporting neurological differences in persons with transsexuality (GIREs, 2006).

Byne in 2006 (Byne, 2006), from a definite clinical perspective, reviewed the relevant endocrine influences on the development of gender identity he felt significant considering intersex and nonintersex conditions. From his findings he wrote “The likelihood of rejecting female assignment appears to be increased in androgen-responsive individuals born with testicular tissue the longer the tissue is in place [however] the data do not justify the conclusion that prenatal androgen exposure produces a brain that is hardwired for male gender identity at birth. Instead, an effect of prenatal androgens may be reinforced by the elevated androgen secretion that occurs in the neonatal period and again at puberty.” Byne does, however, report that evidence from different clinical conditions suggests “very little testosterone is required to bias gender identity in the male direction.” He then goes on to say—based on the findings that androgenized females often develop a bisexual or gynecophilic orientation—that sexual orientation is even more sensitive than identity to the prenatal influences of androgens and cautions that psychological, social and cultural factors might act as co-mediators of gender development. And, as increasingly seen in many papers and reviews that followed the AAP and Texas conferences, Byne ends his review with a call to reconsider the management techniques and ethics involved in the clinical practices associated with DSD conditions.

Baum in 2006, reviewed mammalian animal models of psychosexual differentiation asking when they might be comparable or applicable to humans. Paying particular attention to brain studies with species ranging from rodents to pigs, ferrets and quail as well as humans he states “it is a stretch to liken the organizational actions of prenatal testosterone or estradiol on the differentiation in males of male-typical sexual behavior (often coupled with the defeminization of female-typical mating capacity) to the contribution of fetal testosterone exposure to male gender identity and role behaviors in humans.” He then concludes “No data exist that link fetal differences in testosterone exposure to the ... differences between men and women (Baum, 2006).”

An extensive accompanying review of psychosexual differentiation appeared in 2006 by Gooren (Gooren, 2006). This researcher examined the data from experimental studies, clinical reports and personal experiences. His analysis critically looked at different types of studies. On the one hand he sees transsexuality as going against the influence of androgens in gender development. He writes “Obviously, male-to-female transsexuals, with a normal androgen exposure prenatally (there is no serious evidence to the contrary) develop a female gender identity, through unknown biological mechanisms apparently overriding the effects of prenatal androgens.” Nevertheless, primarily drawing evidence from DSD and related cases his final analysis states “the conclusion is warranted that prenatal androgenization predisposes to a male gender identity development, but it is apparently not decisive ... evidence accumulated over the past 30 years, supports a role for testosterone in the development of gender identity and sexual orientation in the human species. A role for estradiol has not been convincingly demonstrated (Gooren, 2006).”

And a relatively current 2008 study by Brunetti and colleagues deserves mention. These researchers investigated the relationship among cerebral responses, sexual arousal and psychosexual identity of individuals exposed to erotic stimuli and measured by fMRI (Brunetti et al., 2008). Their results showed a significant positive correlation between cerebral activity in bilateral hypothalamus and male

psychological identity. These investigators conclude “the psychosexual identity of male subjects is strictly related to functional features of a bilateral hypothalamus, a dimorphic brain region implicated in instinctual drives including reproduction (Brunetti et al., 2008).” These investigations have obvious clinical implications as they link arousal mechanisms to intrinsic reactions.

A last comment of clinical relevance can be associated with the Freudian theories mentioned at the beginning of this paper. Psychoanalytical psychiatrists, Friedman and Downey have written, “The sexual differentiation of the brain and behavior occurs as the result of prenatal hormonal influences. Knowledge of this area is helpful for the construction of an appropriately modern psychoanalytically informed developmental paradigm of psychosexuality (Friedman and Downey, 2008).” Freud had written “some day all our provisional formulations in psychology will have to be based on an organic foundation. It will then be seen that it is special chemical substances and processes which achieve the effects of sexuality and the perpetuation of individual life in the life of the species (Freud, 1949).” It thus seems that organization-activation theory and the role of androgens is taken, albeit reluctantly by some, as influential in human psychosexual development.

Since the most controversial area of development seems to be in regard to gender identity I will direct the remainder of this contribution to it.

Before going further I think consideration of two particular animal experiments are of value in appreciating the workings of the organization-activation model. The first comes from the work of Roger Short (Short, 1979). Short castrated male Red Deer calves (*Cervus elaphus*) within a week of birth and followed their development in their natural habitat. Red Deer males, when castrated, do not develop any of the typical male secondary sex characteristics such as antlers or neck mane and develop looking like females. Other Red Deer, males or females, then subsequently interacted with these castrated males as if they were females. They were gathered as hinds when the stags accumulated a harem during the rutting season. Any intact male would have been driven out. Significantly these castrated males, seemingly accepted as females by all the other animals with which they were in contact, attempted to copulate as males and showed typical male flehmen displays and mounting. Thus, despite looking like females and being considered as females by all the other animals with which they were associated, they displayed male behaviors when the rutting season arrived. To quote Short “surely a most dramatic example of the long-lasting imprinting effect of male sex hormones on the brain during fetal life (Short, 1979).” This might be seen as an animal model of identity development. The second experiment is that of Goy and colleagues (Goy et al., 1988). These investigators using Rhesus macaques showed that dependent upon the amount, period and duration of testosterone administration during pregnancy, the effect on the female offspring could be significantly manipulated toward different male-like sexual/reproductive behaviors. But, regardless of how these behaviors were altered the genitals might or might not be masculinized. This too can be taken as an animal model of human occurrences. In other words, these two experiments demonstrate that central nervous system differences can be prenatally organized and these can be more sensitive than those manifest by somatic changes.

It seems clear from the volumes of animal research reported since the 1959 Phoenix, Goy, Gerall and Young publication (Phoenix et al., 1959) that the evidence in regard to non-human mammals clearly supports the organization-activation doctrine. Female animals experimentally exposed to testosterone during critical periods show reproductive behavior patterns that are masculinized and males deprived of androgens prenatally or by pre or post birth castration display female behavior patterns or the absence or decrease in male-typical ones. In regard to humans, it might be considered, as said in legal terms, while “the case is not proven beyond a shadow of doubt

the preponderance of evidence” points to organization and activation effects for the human. The evidence seems strongest for behaviors that are considered gender patterns or role stereotyped. The next strongest appears to be related to sexual orientation and partner selection. The evidence related to identity is perhaps the least convincing; nevertheless I believe organization-activation theory still holds. But another factor must be acknowledged. Biological features as seen everywhere in nature are not always set with “on-off” switches or “black or white” characteristics although that is what society often wishes for or generally thinks should be so. Aspects of sexuality can be seen as arranged with a wide range of variations. Features of gender patterns probably have the widest latitude, aspects of sexual orientation less range and gender identity probably the narrowest. But even with gender identity there exist more than boy-girl and man-woman dichotomies. Certainly many will see themselves as simply male or female. Others, however, clinically and in everyday life accept androgyny or other options and may or may not be treated accordingly.

The transsexual condition seems to defy explanation in keeping with organization-activation theory. I see it instead as an example of the findings analogous to those of Short (1979) and Goy et al. (1988). Transsexuals have modified behaviors that are not mirrored in anatomic changes in their genitals or other somatic tissues but are different in their brains (GRES, 2006; Kruijver et al., 2000; Swaab, 2004; Zhou et al., 1995). The noted changes are reflective of the “brain desired” sex rather than the assigned sex. And there is evidence of functional differences in the nervous system as reflected in at least two distinct sensory modalities, olfaction and hearing. Berglund et al. (2008) found that Male-to-Female (MtF) persons differed significantly from male controls in their ability to display cerebral activation when smelling the androgen 4, 16-androstadien-3-one. They conclude, “These data suggest a pattern of activation away from the biological sex, occupying an intermediate position with predominantly female-like features ... possibly as a consequence of a variant neuronal differentiation.” And Govier et al. (2009) report on hearing differences. Male-to-female (MtF) transpersons hear more like females than do male controls. These authors conclude “The marked difference in dichotic pattern between MtF trans people and typical males in the less lateralized direction is a strong indication that the brains of Male-to-Female transpersons are, in some respects, feminized.” And a most recent paper has demonstrated that androgen receptors in the brains of Male-to-Female transpersons have also been found different from those in control males (Hare et al., 2009). These investigators concluded, “This study provides evidence that male gender identity might be partly mediated through the androgen receptor.” And why should we not take the verbal declarations of transsexuals’ feelings in regard to their identity with any less credibility than that given to their statements about sexual orientation? I predict we will continue to find additional evidence that transsexuals are biologically intersexed in their brains and thus different from typical males and females.

In 2006 I wrote how I saw the development of male and female psychosexuality and how individuals arrived at their identity (Diamond, 2006). Bolstered by clinical findings, and so-called experiments of nature over the years, the paper argued, as said in 1965, that human development is a complex association of prenatally derived genetic-endocrine influences interacting with environmental and rearing factors of all sorts (Diamond, 1965, 1976, 1979, 1993, 1995). The biological influences are the human’s evolutionary heritage, family genetics, uterine environment and overall health upon which are superimposed genetic and endocrinal organizing factors. The *organizing factors* are those genetic and hormonal (androgenic) influences laid down prenatally that influence adult behaviors set in motion by pubertal or post pubertal *activation processes* or events. While these organizing factors appear able to *force* behaviors in non-human mammals, in the human they can be seen to *bias* (influence in a particular direction) behaviors and attitudes. It is with these biases

that the individual responds to environmental influences of rearing or whatever (Diamond, 2006).

In addition to a developing individual’s biases a second factor is crucial in the development of gender identity. That is the child’s instinctive tendency to compare him or herself with others. All children have this in common (Goldman and Goldman, 1982). Consciously or not—according to *biased-interaction* theory—all children analyze their basic interests and preferences and compare them with those of their peers and adults. In doing so they analyze “Who am I like and who am I unlike?” Parents or others as role models can be of utmost importance but they may not be. There is no way to know if one will be chosen or not, or who will be chosen and why. The child is not responding to any inner model or brain template of male or female but to characteristics that are *same* or *different*. The child is establishing where to fit, boy or girl. He or she is comparing personal biases in behaviors and attitudes with those of others. The typical boy, even if effeminate, sees himself “same enough” to fit the category “boy” and “male” and accepts that identification and path. It is similarly so for the typical girl, even if quite masculine. She will see herself “same enough” to accept that identification and expect to grow as a woman. This flexibility in analyzing the “best fit” allows for a great deal of cultural variation. But what happens if there is no culturally or socially apparent “best fit?”

Let us use as an example the occasional boy who becomes confused with thoughts such as “Mommy and Daddy call me boy, and yet I am not at all like any of the others that I know that are called ‘boy’.” “I am very different and more the same as those called ‘girl’.” And after a period of introspection and struggle this male comes to think he might be or should be or is a girl because his interests and behaviors are significantly more like theirs. How should this person react and identify? What options exist? Certainly he can remain a boy and live as assigned. Or he can rebel and transition to live as a girl or express a desire to. Both choices, remaining as is and rebellion, come at a cost and the price may be high. It is thus that the crucial evaluation of whether to retain the identity assigned or adopt one associated with transition becomes of issue. Both those persons that remain in the assigned gender and follow rearing/social/cultural/environmental forces as well as those who are transitioning are responding to analogous forces. Rearing, upbringing, society and culture all have to be seen as having the capacity to be negative and inhibitory as well as a positive and motivating. And not all persons presented with any set of circumstances will respond similarly. That is where the biases and how they interact with experiences come to the fore. While most people are undoubtedly content with their assigned gender and think it appropriate, not all persons who stay in it do so securely and happily. For some it is an exchange to gain something of value elsewhere. Certainly it is also true that many individuals fabricate some intermediate choice.

About 1.5% of the Dutch population claimed in a recent large-scale representative study by the Rutgers-Nisso group that they identify more as the other sex than the gender assigned at birth. And almost 3% of the male population of the Netherlands identify as cross-dressers (Eakker and Vanwesenbeeck, 2006). But only a fraction of these persons have transitioned and these percentages of the population were most probably not raised ambiguously or as the opposite gender. And it is most likely that few have somatic manifestations of DSD. There are many factors that induce an individual to retain or deny a gender identity. And there is no sure way to measure the degree of frustration or satisfaction with the decision and no way to know if that decision would not be subsequently reversed. Many individuals transition gender in their 30s and 40s and even later. Thus a person remaining in an assigned gender can indeed be reacting to social forces but only temporarily or only to benefit from other social situations.

Lastly, it is worth commenting that more than a decade has passed since Kipnis and I spoke of the need for long term follow-up studies on

the management and outcome of different DSD conditions (Diamond, 1999; Kipnis and Diamond, 1998). And a decade has passed since the AAP and Texas conferences where such a need was repeated (Diamond, 1999; (Zderic et al., 2002). While a host of reviews have appeared e.g., (Brinkmann et al., 2007; Creighton et al., 2001; Diamond and Watson, 2004; Mazur, 2004; Meyer-Bahlburg et al., 2004; Warne et al., 2005; Wisniewski and Migeon, 2002) long-term comprehensive studies have yet to be done. To best answer the clinical questions associated with aspects of organization-activation theory and matters of particular value in the management of intersex conditions, particularly the wisdom of sex reassignment, it is recommended that a national registry be established where these cases are recorded with their associated treatment and results. A similar registry should be established for the treatment/management of cases of transsexuality/GID. And these should be maintained for as long as possible. Infants with intersex conditions that have been sex-reassigned or had genital surgery will typically not become erotically active until after puberty and maybe not until in their 20s or later. And children with manifestations of GID may remain as assigned for many years only to transition as adults. As the treatment of different cancers are registered and monitored to observe the success or failure of different management techniques, so too can we learn the best way to manage different DSD and GID situations and better learn the significance of prenatal and postnatal factors.

As mentioned above different physicians treat identical sexual conditions in very different ways. Regarding the surgical intervention for cloacal exstrophy, for instance, we saw above a dramatic difference of opinion allowing for a potential failure rate of 30%. It is wrong to allow such lack of knowledge to continue. There is a body of evidence for dissatisfaction with many clinical experiences with intersexuality and, as seen most recently in the treatment of children displeased enough with their gender to want to change, the treatment modalities can be 180° apart. One psychotherapist recommends treating a child who manifests gender dysphoria with methods of denial and restriction trying to make him comfortable in his sex of birth while another therapist treats a similar gender dysphoric child with permissiveness and license trying to help her adjust to her gender of choice (Spiegel, 2008). These two examples mentioned are symptomatic of general occurrences. Certainly it is of benefit to know, for these not-uncommon clinical conditions, which is the best treatment technique, which has the most likely chance of success and which leads to the most satisfying outcome for the patient or client (Zucker, 2008a, 2008b). Without these resources clinicians are relying, not on evidence based medicine or techniques of best practice, but to hunches, anecdotes and limited knowledge. Intersexed persons deserve better. Those with transsexual and related conditions deserve better. And certainly clinicians of all sorts, from pediatricians, urologists, surgeons, psychologists and psychiatrists, deserve better. It is suggested that the opportunities to analyze such cases be formalized. Surveillance is a key component of the core public health function of health assessment. Mandatory registration of intersex and transsexual cases and their management and outcomes should be required and maintained to better future clinical health care and increase professional knowledge and management of differences in sex development and gender identity.

Conclusions

The evidence for androgen-induced organization-activation in nonhuman mammals is clear. The preponderance of evidence does point in that direction for humans as well but the evidence is less clear. Due to pre birth conditions the human appears to be biased towards sex appropriate patterns of behavior, sexual orientation and gender orientation. The reason for the lack of surety is simple. With animals experimentation is possible so one can modify parameters of study to get a better understanding of cause and effect relationships.

This is not ethically proper for humans. For humans it takes so-called experiments of nature and different clinical situations to offer opportunities for analysis. And basically the human experiments of nature are in the areas of intersex and different trans conditions, principally transsexuality.

At these levels of clinical concern the information available is high on anecdote but low on long-term evidence. Nevertheless, direction toward treatment has to a large degree come from the theory of organization-activation. Its significance in this regard cannot be overstated. From its inception to current times organization-activation theory has stimulated all sorts of experimental animal studies resulting in important conclusions. The organization-activation theory has also provided great insight to clinical conditions and their management. It has served us well over these past 50 years.

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