Etiopathogenetic Hypotheses of Transsexualism

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6.1 Introduction

Ever since the beginning of time, man has tried to understand the physical world and its human occupants. Traditional, archaic societies spun stories of creation in an attempt to explain the origins of the world and its mysteries. In these myths, supernatural beings possess human motives and animation.

Cosmogonic myths, those that explain the origins of natural phenomena, also identified the origin of sickness and cure. Indeed, many religious rituals involved recitation of the creation myth to summon a sacred power. This recapitulation was necessary to make a sterile womb fertile or to cure a body or mind [1].

Both Jung and Freud provided psychological explanations for the power of myth. For Jung, the repetition of strikingly similar figures in mythology was evidence of the collective unconscious, lending support to his theory of personality development. Freud, on the other hand, focused on primordial acts, such as patricide, as symbols of repressed personal libido. This provided confirmation of *his* theory of personality development [2, 3].

The medical profession has since made great contributions toward understanding the material or "real" world, particularly in regard to the pathophysiology of disease. But human behavior does not easily capitulate to taxonomy. Not surprisingly, in the absence of observable disease, diagnostic test, or organ deficiency, one reverts to theory—the modern equivalent of myth—to explain inscrutable phenomena. Such is the case with transsexualism, surely the most misunderstood area of human behavior.

6.2 Early Theories

Recorded accounts of men and women displaying cross-gender behavior date back to biblical times. Indeed, the Old Testament expostulated against such displays [Deuteronomy 22:5], and Ovid, a first-century BC poet, referred in verse to the extract of "stuff from a mare in heat," a reference to conjugated estrogen [4]. Nevertheless, the phenomenon was unknown in the Western world prior to the middle of the twentieth century.

Although accounts of sex-reassignment surgeries were published in Germany as early as 1930, it was not until 1952 when the Danish surgeon Paul Fogh-Andersen employed an innovative surgical technique on Christine Jorgensen, a US citizen, that media reports of "sex-change surgery" captured the public's attention [5]. Harry Benjamin, an endocrinologist, is credited with identifying the condition and in 1966 published the book *The Transsexual Phenomenon*, prompting some surgeons to perform the procedure. Thus, a taboo area of human behavior became a medical specialty [6].

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Opposition to surgery arose rapidly, in tandem with Ms. Jorgensen's fame. While some surgeons in Europe, Mexico, South America, and the USA were willing to perform reassignment surgery, most hospitals prohibited the procedure. The "Christine operation" generated legal controversies, religious opposition, and moral outrage. But it was the psychiatric community that was the most vociferous in challenging the legitimacy of transsexualism [6].

The debate centered on the etiology of gender dysphoria. The psychoanalytic model, which prevailed in Europe and the USA, regarded transsexualism as a psychiatric—not a biologic—disorder. The psychiatric community claimed the desire for reassignment surgery was a delusion, an obsession, or a symptom of severe psychopathology. The symptomatology arose from serious object relation disturbances: an inability to separate on the part of both mother and child giving rise to dysregulation of intrapsychic distance for the patient and an attempt to incorporate an alternate persona [7–11]. Some conceptualized this as a psychotic disorder [12]; others viewed it as a form of borderline psychopathology [13]. Lothstein opined that the transsexual was unconsciously motivated to "discard bad and aggressive features" and create in the fabric of the body "a new idealized perfection" [13].

The tenacity of the psychodynamic model, the inflammatory rhetoric of the debate, and the conflation of transsexualism, homosexuality, and transvestism left science and research trailing behind negative public perception. Many transsexual people requesting medical and surgical treatments were committed to mental institutions. The abject failure of the "talking cure" was attributed to resistance on the part of the patient, not to the failure of psychoanalysis [14]. Tragically, electroshock and aversion therapies were too often the default treatments.

Some researchers rejected the psychoanalytic explanation and continued to pursue a biological basis for the condition to "help to replace emotional controversy by rational assessment of facts" [15]. Early attempts to find an organic etiology included roentgenological examination of the skulls of transsexual patients [16], testing for anomalous hormonal milieus [17, 18], cytotoxicity assay inspection of h-y antigen status [19–22], and quantitative frequency EEG analysis. Despite the failure of these attempts to identify an organic marker of transsexualism, some investigators remained convinced that hormonal-dependent structural brain changes, although not documented, were a likely explanation [23].

Interestingly, support for a biological basis came from an unlikely source, namely, clinical psychologists [6]. By utilizing reliable and objective psychological tests, they could substantiate, or fail to substantiate, the claim that gender-dysphoric patients had rampant psychopathology. Several such studies indicated that applicants for sex reassignment showed "a notable absence of psychopathology" [24–27].

By the 1990s, significant numbers of people had sought medical interventions, and thus a "database" of historical and psychological information could be assessed. While all such persons suffered similar distress due to gender incongruity, they had no commonality in regard to biographical indices, childhood abuse, or trauma. There was no evidence to conclude that environment or parenting practices accounted for the development of the condition [28].

6.3 Later Theories

Dramatic advances in brain-imaging capacity led to more sophisticated theories of the etiology of atypical gender identity. By the late 1990s, some researchers proffered a model known as "gender transposition" as the underlying principle. Based largely on evidence from animal studies demonstrating a link between steroid hormones, brain structure, and sexual behavior [29], this theory proposed that transsexualism occurred as a result of a switch of hormone-induced cephalic differentiation at a critical gestational point [30–32]. The theory, though appealing, proved too reductionistic. It suffered from the conflation of behavior and identity, its weighty reliance on animal study extrapolation, and the erroneous assertion of a fixed critical period anchoring sexual differentiation in the fetus [33, 34].

In 1995, one study broke new ground. Zhou et al. reported differences in autopsied brains of male-to-female transsexual persons in the bed nucleus of the stria terminalis (BSTc), an area of the hypothalamus central to sexual behavior. The examined male-to-female transsexual brains had a volume of the central sulci of the stria terminalis that was comparable to those of genetic females and unlike both heterosexual and homosexual male brains, which had greater volume [35]. The study generated a great deal of publicity, as it lent support to the conviction held by many: that a structure deep within the brain might hold the answer to complex areas of identity. It also resonated with the layperson's characterization of the transsexual person as someone who insists they have a female brain in a male body [36].

But the study raised additional questions. What if the volume differences found in the BSTc were artifacts resulting from contrary hormone use? A subsequent study was designed to address this issue. Krujiver et al. quantified the number of somatostatin (SOM) neurons in the BSTc, rather than volume. Neuron numbers of heterosexual males, homosexual males, heterosexual females, male-to-female transsexuals, male and females with sex hormone disorders, a female-to-male transsexual, and an untreated individual with gender dysphoria were compared. The findings were consistent with earlier results. Regardless of sexual orientation or adult hormone usage, there was a difference in the SOM neuron number in the human BSTc. Not only did the male-to-female postmortem brain tissue have levels corresponding to that of genetic females, but the opposite pattern was displayed in the female-to-male transsexual brain tissue [37].

6.4 Current Theories

A proliferation of studies arose in the past decade, due in no small part to technological advances and the expansion of databases. Now, meta-analyses could take place, combining data from several countries. Building on the previous brain structure studies, an assemblage of studies evinced evidence in support of biological theories, none of which were necessarily mutually exclusive, each seemingly contributing a piece of a yet unsolved puzzle.

6.5 Brain Structure

The previous significant finding of a sexually dimorphic subdivision of the BSTc bolstered support for the hypothesis that gender identity develops as a result of the interaction of a developing brain and sex hormones. However, in 2002, Chung et al. made the surprising discovery that the BSTc volume did not become apparent until adulthood. The late occurrence of sexual dimorphism in the BSTc had yet to be explained. The authors suggested that perhaps long before the difference in BSTc volume became manifest, changes in fetal hormone levels, neuronal activity, or differentiation were paving the way for structural change, which would appear at a later stage of life [38].

Pol et al. used magnetic resonance brain imaging to compare total brain volume before and after hormone treatment. They found that estrogen usage decreased brain volumes in male-to-female transsexual subjects causing them to fall in the range of female proportions. Androgen treatment in female-to-male transsexual subjects increased volume, causing the brain morphology to replicate male proportions. The authors concluded that sex steroid hormones are vital in the maintenance of sexual dimorphic brain organization throughout life [39].

In 2008, a region of the brain was identified that also appeared to be related to transsexualism, namely, the interstitial nucleus of the anterior hypothalamus (INAH3) [40]. In 2012, a study of postmortem human brain tissue determined that the gene-encoding neurokinin B (NKB) in the infundibular nucleus (INF) is sexually dimorphic. In children, both sexes had equivalent levels of NKB immunoreactivity, but adulthood brought dimorphism. As with the BSTc, there was a reversal in transsexual brain tissue, indicating that gonadotropin-releasing harmone (GnRH) secretion is regulated via estrogen feedback and that a mutation in the NKB produces gonadotropin

deficiencies. Clearly, the stage was set to implicate hormones, genes, and cephalic structure in the formation of gender identity [41].

6.6 Prenatal Hormonal Influences

The theory that early influences, possibly prenatal, were the precursors for later structural brain change was gaining traction. Dessens et al. reported an elevated incidence of transsexual offspring in women exposed to phenobarbital and diphenylhydantoin [42]. As phenobarbital enhances liver function, it was widely used in many countries as a prophylactic treatment of neonatal hyperbilirubinemia, prior to the use of phototherapy, and it caused a rise in postnatal testosterone. This demonstrated that certain substances could alter steroid hormone levels [43].

Simultaneously, there was rampant evidence that environmental assaults were causing endocrine disruption in wildlife. Disturbing evidence that synthetic chemicals can disrupt sex steroids and the complexity of feedback loops was mounting. Animal researchers exposed the extreme sensitivity of developing mammals to very slight shifts in hormone levels in the womb stating "hormones permanently organize or program cells, organs, the brain, and behavior before birth, in many ways setting the individual's course for an entire lifetime" [44]. Could this explain the escalating incidence of disorders of sexual development, infertility, hypospadias, cryptorchidism, double uteruses, blind vaginas, and other disorders in the human population [45]?

Diethylstilbestrol (DES), the most studied endocrine disruptor, has been implicated in numerous health problems in female offspring of exposed women [46]. Curiously, few studies have examined the impact on male offspring, the DES sons. An online forum, DES Sons International, conducted a survey of members. Of 500 respondents, 90 members indicated they were transsexual; 48 described themselves as transgender; 17 identified themselves as "gender dysphoric"; and 3 identified themselves as "intersex." By 2004, more than 130 individuals had joined a forum called "DES Trans" [44]. Clearly, the prevalence of gender dysphoria in persons exposed to DES warrants further study.

It has been well established that the ratio of the second to fourth finger (2D:4D) is smaller in human males than females. This sexually dimorphic trait was presumed to be established prenatally, due to hormones [47–49]. Galis et al. analyzed the digit ratio in deceased male and female fetuses. They determined that at 14 weeks of gestational age, there was a small but significant difference in the 2D:4D ratio among male and female fetuses and that the ratio increases during childhood. They concluded that early levels of sexual hormones have a lasting impact and that the ratio increases after birth in both males and females. Therefore, both prenatal and postnatal processes are involved in sexual dimorphism [50]. Schneider et al. compared the digit ratio between transsexual individuals and controls. They found that male-to-female transsexual subjects had a digit ratio observed in control females, a finding that clearly supports a biological etiology to the condition. No such difference was found in the female-to-male subjects or control females. The authors concluded that decreased prenatal androgen exposure is implicated in the development of male-to-female transsexualism [51].

6.7 Genetic Theories

In 2000, Green reported on familial concordance of gender dysphoria in ten sibling or parent-child dyads. He forecast that advances in technology would make the exploration of genetic variants a viable area of exploration in the quest to discover the origins of atypical gender identity [52].

Other researchers also found a co-occurrence of gender dysphoria in families. Gomez-Gil et al. looked at a sample of 995 transsexual people, both male to female and female to male, and found 12 pairs of transsexual non-twin siblings. They state, "According to our data, the probability that a sibling of a transsexual will also be a transsexual was 4.48 times higher for siblings of MF than for siblings of FM transsexual probands, and 3.88 times higher for the brothers than for the

sisters of transsexual probands. This study suggests that siblings of transsexuals may have a higher risk of being transsexual than the general population" [53].

In 2005, Swedish investigators hypothesized that the sexual differentiation of brain structures is mainly due to the influence of testosterone acting on androgen receptors (ARs) and estrogen receptors (ERs) as was the case with animals. They therefore sought to examine the potential role of three particular polymorphisms for implication in the development of male-to-female transsexualism. They found one of the three, ERbeta repeat polymorphism, to differ in mean length between 29 transsexual subjects and controls. However, the small number of individuals studied demanded caution in interpreting the results [54].

Diamond reported on an investigation of transsexualism among 112 sets of twins, illuminating the relative contribution of genetics and social factors in the phenomenon. He found a 33.3 % concordance for transsexual identity among monozygotic male twins and a 22.8 % concordance among monozygotic female twins. Interestingly, among the twin probands, there were three sets of twins who were reared apart but concordant for gender transition [55].

Two landmark studies undertook to directly assess the role of specific genes. Bentz et al. found female-to-male transsexuals to differ from female controls in a gender-specific allele distribution pattern and to have an allele distribution akin to male controls. The identified gene, CYP17, is associated with female-to-male transsexualism, as is the loss of the female-specific genotype distribution [56]. Hare et al. looked at polymorphisms in genes involved in steroidogenesis. Specifically, they examined repeat length variants in the androgen receptor (AR), the estrogen receptor beta (ERbeta), and aromatase (CYP19) genes. They found a significant association between male-to- female transsexualism and the androgen receptor (AR) gene. The transsexual subjects had longer AR repeat lengths than cisgender male control subjects. The investigators concluded that male gender identity is partially mediated through the androgen receptor, as reduced androgen and androgen signaling may contribute to the formation of a female gender identity. Theirs is the largest genetic study of transsexualism, to date [57].

Conclusion

The etiology of gender identity, typical and atypical, presently remains unknown. However, the mounting evidence for a biological basis is compelling. No doubt the next decade will bring new data that elucidates the complexities of identity formation and amplifies understanding of the transsexual phenomenon.

What is clear from the existing body of knowledge is that theories that rely on consensus, rather than science, have stigmatized people by "blaming the victim." The attribution of psychopathology, deficient parenting, or childhood trauma as the "cause" of gender dysphoria must be forever relegated to the status of myth.

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