GIRES / King's Fund / BCC Trans Group

In 2003, the Gender Identity Research and Education Society (GIRES) ran a small symposium in London, assisted by a BCC Trans Group (founded in 1993 to provide better care fro transsexual people). GIRES was awarded additional funding for this project from the King's Fund - an eminent charity providing funds for medical and scientific work.

The members of the symposium included physicians and specialists in the different areas pertinent to the understanding and the treatment of transsexualism, and also the Member of Parliament who chairs the Parliamentary Forum for Transsexualism. Transsexual people were represented within this group. Members came from the United Kingdom, The Netherlands, Belgium, Japan and the United States of America.

Professor Milton Diamond (USA) chaired the group who collaborated in producing the following paper. The team endeavoured to provide a balanced and comprehensive review of what is currently understood, in the scientific field, regarding atypical gender development and transsexualism.

ATYPICAL GENDER DEVELOPMENT – A Review

Besser, M., Carr, S., Cohen-Kettenis, P.T., Connolly, P., De Sutter, P., Diamond, M., Di Ceglie, D. (Ch & Adol.), Higashi, Y., Jones, L., Kruijver. F.P.M., Martin, J., Playdon, Z-J., Ralph, D., Reed, T., Reid, R., Reiner, W.G., Swaab, D., Terry, T., Wilson, P., Wylie. K.

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1. Atypical gender development is given the clinical label, Gender Identity Disorder (GID), in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV TR, American Psychiatric Association, 2000). This is a rare condition in which individuals experience their '*gender identity*'[1] (the psychological experience of oneself as male or female) as being incongruent with their *phenotype* (the external sex characteristics of the body). The personal experience of this discomfort is termed *gender dysphoria*. In its profound and persistent form, it is known as *transsexualism* (World Health Organisation, 1993, International Classification of Diseases 10, [F64.0]). Individuals experiencing gender dysphoria will have been raised, from birth, in the *gender role* (the social category 'boy' or 'girl') which is consistent with their phenotype. Both the phenotype and the gender role, therefore, cause them great discomfort. In contrast, the vast majority of people grow up with little or no inconsistency between their gender identity, their phenotype, their gender of rearing, and their social roles as men and women.

2. Where health, family and work circumstances permit, those experiencing transsexualism, the extreme form of the condition, adopt the gender role and the phenotype, consistent with the gender identity they are experiencing. The realignment of the phenotype is usually facilitated with the assistance of hormones, surgery and other interventions to make it as congruent as possible with their gender identity. Individuals' needs vary widely, and treatments, in terms of content and timing, should be undertaken in accordance with the specific requirements and circumstances of each person. This process of change to live according to the gender role opposite to that assigned at birth is referred to as 'transition'. Individuals who experience transsexualism may be referred to as trans people (or transsexual people) or, more

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[1] *The term 'gender identity' is used, in the UK, to indicate the self-identification as male or female. However, terminology varies around the world, and the term 'sexual identity' is preferred by many in the US. (pace Professor Milton Diamond). See "Sex and Gender are different: Sexual Identity & Gender Identity are Different", (2000) Clinical Psychology & Psychiatry 7 (3),320-334.*

specifically, as trans men (female phenotype in association with male gender identification = FtM) and trans women (male phenotype in association with female gender identification = MtF).[2] The issue of gender identity is independent of the issue of preference for a male or a female sexual partner.

3. Treatment practices and protocols may be subject to local variation, but will usually involve hormone support for the rest of the individual's life. In the case of trans women, treatment will, typically, include antiandrogen and oestrogen administration to induce feminisation, and some or all of the following: facial hair removal treatments, orchidectomy, penectomy, labiaplasty, clitoroplasty and possibly vaginoplasty, breast augmentation, facial feminisation and thyroid chondroplasty. For trans men, treatment will typically include testosterone treatment to induce masculinisation. Surgery will often involve mastectomy, salpingo-oophorectomy, hysterectomy and vaginectomy. Other surgical procedures, to create male genitalia for trans men, are a little less common but are becoming more popular now that surgical techniques have improved; they may involve a combination of one or more of the following: metoidioplasty, scrotoplasty, urethroplasty, testicular prostheses and phalloplasty. It is recommended that psychotherapeutic support be offered in conjunction with all the procedures outlined above, to facilitate adaptation to the appropriate gender role and address any associated emotional difficulties, especially in regard to family and social relationships.

4. The hormonal, surgical and psychological procedures of transition reduce the dissonance between the psychological identification as male or female, on the one hand, and the phenotype and associated gender role on the other. Such treatments are regarded as highly successful; one study indicates a degree of satisfaction of 87% in trans women and 97% in trans men (Green and Fleming, 1990). Outcomes depend, however, on the individual's personal strengths as well as the level of social and professional support available during and after the process of transition. It is also significant that, whilst psychotherapeutic treatment remains, for many, a helpful ingredient in dealing with the inevitable distress caused by this condition, "severe gender dysphoria cannot be alleviated by any conventional psychiatric treatment. This is true whether treatment be psycho-analytic, eclectic, aversion treatment, or by any standard psychiatric drugs" (Green, 1999). The aim of psychiatric treatments is, therefore, not to remove the condition, but to mitigate its most stressful aspects.

5. An extremely low number of children experience their gender identity as being incongruent with their phenotype and, as a consequence, are uncomfortable with the gender role expectations imposed upon them. Adult outcomes in such cases are varied and cannot be predicted with certainty. Only in a minority of these children, some 23% according to one study (Cohen-Kettenis, 2001), will this incongruence persist into adulthood and manifest as transsexualism, regardless of phenotypical socialisation and nurture (Zucker 1985; Green, 1987; Zucker 1995; Ekins, 1997; Prosser, 1998; Di Ceglie, 2000; Ekins and King, 2001; Bates, 2002). Although few gender dysphoric prepubertal children become gender dysphoric adults, those

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[2] *The transsexual condition is also referred to in various ways (Diamond M, 2003) "What's In a Name? Some terms used in the discussion of Sex and Gender". Transgender Tapestry.*

experiencing the condition as adolescents, almost invariably do require access to adult services (Wren, 2000). Where an extreme form of gender dysphoria persists in a young person, there may be great distress with the onset of pubertal development. Under these circumstances, hormone blockers may be used to modify some of its manifestations (Gooren and Delemarre-van de Waal, 1996). This allows additional time for the youngster to explore his or her gender identity. This treatment is regarded as largely reversible, and will always precede partially reversible treatments, such as cross-gender hormone administration. Irreversible treatments, such as surgery, are very unlikely to be undertaken before the age of eighteen but each case must be considered on its merits. This model of management is known as a 'staged approach' (Di Ceglie 2000).

6. Autobiographical accounts of adult trans individuals indicate an early awareness of discomfort that is often not articulated during childhood. Rather than seeking access to the treatments outlined above, severely gender dysphoric young people frequently succumb to the considerable pressure to comply with the gender role expectations of family, friends and society generally. In cultures where greater allowance is made for gender expression which is less distinctly bipolar, the dissonance experienced by those with a form of transsexualism, seems considerably lessened. It is suggested that the likelihood of co-morbidity is thereby reduced (Connolly, 2003). However, in western societies most trans people give accounts of their strenuous efforts to fit their respective stereotypes. This may result in an appearance of conformity, whilst simply making the individuals more acutely aware of the dissonance. Despite these stereotypical behavioural expectations and even punishment of cross-sex behaviours, many of these individuals eventually undergo transition (Prosser, 1983; Carter, 1987; Ekins, 1997; Bates, 2002).

7. Prior to transition some trans men and trans women can feel especially pressured to pursue gender stereotyped pastimes and careers. They may embark on long term relationships, marriage and parenthood (Diamond 1996). Whilst this path to family life is followed for all the usual reasons: falling in love, the wish to have a long term partner, the desire to have children, some trans people will also admit that they hoped that engaging in family life would remove their gender discomfort. Anecdotally, aside from the inevitable stress occasioned by their efforts to suppress cross-gender behaviours, trans people do not describe any particular trauma to which their condition might be attributed (Kotula, 2002a).

8. Trans men and trans women are acutely aware that transitioning to live in the opposite gender role will put at risk their family relationships, their friendships and their employment. But the impetus to transition is overwhelming and may become, quite literally, a matter of life or death (Kotula, 2002b; 2002c).

9. In the general population, gender identity usually continues along lines that are congruent with the individual's phenotype; a baby assigned as a boy will identify as male, and grow up comfortably regarding himself as a man, and a girl will grow up identifying as a woman. Typically, therefore, when a child is born, gender is predicted in accordance with the appearance of external genitalia of the infant. 'Boy' or 'girl'

(male or female) is entered on the birth certificate and inferences are drawn about the infant's internal sex characteristics and future gender identity. It is assumed that these will be congruent (see Cohen-Kettenis and Pfäfflin, 2003).

10. In order to appreciate how this congruence occurs and to provide a context in which gender dysphoria may be understood, it is first necessary to understand typical sex differentiation. Individuals in the general population undergo sex differentiation in terms of external and internal genitalia and gonads (ovaries or testes) and nervous system structure and function. In females, the uterus, Fallopian tubes, and vagina develop and the central nervous system (CNS) is programmed for post-pubertal ovulatory and menstrual cyclicity. By contrast the CNS in the male does not cycle but is rather tonic in its relation with the male reproductive system. Also in males, the prostate, seminal vesicles, bulbo-urethral glands and penis, as well as associated ducts develop (Wilson et. al., 1993).

11. Dating back to the first half of the twentieth century, research on laboratory animals has shown that the formation of external genitalia is not the end point of the sex differentiation process; virilisation of the male brain ensures that male and female brains develop along sex differentiated pathways, largely predicting/correlating with future sexual and non-sexual behaviours, although it has been shown, in androgen treated female rhesus macaque monkeys, that sexual behaviours can be masculinised without much evidence of genital masculinisation (Goy, *et al.,* 1988; Phoenix *et al.*, 1959; Gooren, 1999; Gooren and Kruijver, 2002). Usually, however, these aspects of differentiation are consistent with each other and are also regarded as depending upon the karyotype. Typically, in humans there are 46 chromosomes arranged in pairs. In females, one pair is composed of two X chromosomes. In males, one pair is composed of an X and a Y chromosome. The chromosome derived from the mother is invariably an X, and that derived from the father may be either X or Y.

12. The genetic material on the X chromosome is known to be associated with the development of secondary sex characteristics in females, but has many other functions as well. In comparison, the genetic material on the Y chromosome is relatively limited. However, it does have an important function with regard to the endocrine system of the fetus and, therefore, its sex dimorphic development in utero. Certain genes on the Y chromosome, such as the SRY and the ZFY, direct the production of proteins that trigger a cascade of events leading to hormones that masculinise the fetus. Without the effect of these factors, especially testosterone, the fetus will proceed along a female path of development. SRY and ZFY remain expressed in the brain in adulthood and may also be responsible for direct genetic sex dimorphic effects bypassing hormones such as testosterone both during early development and in adulthood (Kawata, 1995; Mayer *et al.,* 1998).

13. Prior to sex differentiation, which commences at about week six of gestation, the rudimentary reproductive systems appear identical in male and female fetuses. Typical fetuses with karyotypes 46,XX and 46,XY have both (female) Müllerian ducts and (male) Wolffian ducts. At around 6-7 weeks, in a typical XY fetus, the gonads differentiate into testicles that elaborate testosterone and Müllerian Inhibiting

Hormone (MIH).   Testosterone prompts the development of internal male reproductive structures whilst MIH causes the Müllerian ducts to regress. In a typical XX fetus, the absence of testosterone and MIH allows the Müllerian ducts to develop into the uterus, Fallopian tubes and the upper part of the vagina, whilst the Wolffian ducts wither away (Cohen-Kettenis and Pfäfflin, 2003).

14. Between the sixth and twelfth week of pregnancy, in an XY fetus, testosterone and its derivative, dihydrotestosterone, promotes the masculinisation of the genital tubercle and genital swelling. The structures now develop into a penis and scrotum into which the testicles descend just prior to birth. In an XX fetus, without the influence of testosterone, the primitive genitalia develop into a clitoris and labia. The results of these two developmental pathways are babies whose appearance at birth is either that of a typical male, or of a typical female (Wilson *et al.,* 1993).

15. The assumption that genital appearance will inevitably be clearly either male or female at birth, and that all other sex/gender characteristics are congruent with that appearance is, usually, accurate. However, it is not always so. Estimates of the incidence of atypical sex differentiation range from 0.1% to 2% (Blackless *et al.*, 2000; Fausto-Sterling, 2000). Many of these occurrences are known as Intersex conditions, others may be regarded rather as developmental anomalies or potential anomalies. Sometimes their manifestations are slight and cause little difficulty. Some are evident at birth, but others will not be diagnosed until puberty, or adulthood, and some cases may remain undiagnosed. These factors make it likely that the higher estimates of incidence cited here, may not necessarily reflect the clinical experience of most physicians.[3]

16. The inconsistencies which arise in the factors by which people experience themselves as being, and are assessed by others as being male or female, are associated with a range of manifestations. There may be a failure to meet the typical criteria within a single characteristic, or there may be several elements that are incongruent with others. The variations from the typical route may occur in any phase of sex

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[3] *Although the term 'intersex' embraces many and varied conditions, some of which are touched upon in this paper, there is no universal agreement about which conditions should fall under the intersex umbrella. Some clinicians and researchers include virtually all examples of atypical sex/gender differentiation, whereas others include only a few. Figures drawn from clinical samples (especially if involving sibling groups) rather than epidemiological studies, may result in an overestimation of the population size in some of the conditions. On the other hand, the secrecy and stigma associated with intersex conditions, especially those that are obvious at birth makes any kind of accurate assessment of their incidence problematic. All these factors, inevitably, impact on incidence figures, hence the wide range in population estimates. Transsexualism is regarded, by many, as falling under the same umbrella of atypical differentiation as intersex conditions, although it has not been included in the estimates given above. In the population over 15 years old, the Scottish study (Wilson et al. 1999) yields 0.00818% (1:12,225) and the Netherlands study (Van Kesteren et al., 1996) 0.00472% (1:21,186), ratio of trans men to trans women, roughly 1:3 or 1:4. These estimates should not be regarded as an entirely reliable measure of prevalence.*

differentiation, may be complete or incomplete, and may have an impact on one or more physical sex characteristic (Cohen-Kettenis and Pfäfflin, 2003).

17. External morphological variations exist where the genitalia appear neither clearly male nor clearly female. These variations may elicit an arbitrary sex assignment based largely on genital appearance (a small penis or a large clitoris). Gonads may also contain a mixture of testicular and ovarian tissues and may be inconsistent with the chromosomes and/or the genitalia. Internal sex organs such as the uterus may be absent in an apparently female person or present in an apparently male person (Grumbach, 1998; Grumbach and Conte, 1998; Grumbach *et al.*, 2003). Similarly, gender identity may be inconsistent with chromosomes and/or gonads and/or genitalia, or indeed with all these three sex characteristics (Gooren and Kruijver, 2002).

18. Atypical chromosomal configurations may be associated with unusual sex differentiation. Several examples of this are, 47,XXX; 47,XXY; 47,XYY; 45,XO. There may even be mosaicism, that is, different tissues may have a variety of chromosomal configurations within the same individual (Grumbach 1998; Grumbach *et al.,* 2003). It is also possible, although rare, for individuals with apparently typical 46,XY chromosomes to have a female phenotype and, even more rare, is the association of 46,XX karyotype with the male phenotype. There is a raised incidence of gender discomfort associated with 47,XXY (Klinefelter's syndrome) (Money and Pollitt, 1964; Seifert and Windgassen, 1995; Diamond and Watson, 2004) and also, to a lesser extent, 47,XYY (Taneja *et al.*, 1974; Haberman *et al.*, 1975; Snaith *et al.*, 1991; Buhrich & McConaghy, 1978; Buhrich, *et al.*, 1978;). Gynæcomastia and cryptorchidism may also be associated with these conditions, suggesting an underlying atypical hormone milieu (Klinefelter *et al.*, 1942; Fryns *et al.*, 1995).

19. Studies of the treatment and experiences of individuals who have intersex conditions provide helpful insight into the development of gender identity in the general population and also in trans individuals. These studies offer opportunities for assessing the relative influences of phenotypical appearance, gender of rearing, and early brain differentiation, in shaping the adult gender identity. Conditions of 5α reductase deficiency (5α-RD) and 17β hydroxysteroid dehydrogenase deficiency (17β-HSD), for instance, give rise to ambiguous or female-like external genitalia in XY infants. In these conditions there is a lack of dihydrotestosterone, required for the gestational development of male external genitalia. Müllerian ducts, however, regress appropriately. It is usual for such individuals to become virilised at puberty. In a study of eighteen individuals with 5α-RD, raised unambiguously as girls, seventeen rejected the female role and adopted a male gender role during or following puberty (Imperato-McGinley *et al.*, 1974; Imperato-McGinley *et al.*, 1979a). Similar findings in 5α-RD cases are recorded by Hurtig (1992) and by Wilson *et al.,*1993). Comparable results were also found in individuals with 17β-HSD (Imperato-McGinley *et al.,* 1979b; Rösler & Kohn, 1983; Kohn *et al.,* 1985; Rösler, 1992). The altered gender expression may be, in part, a response to the virilisation of the phenotype during adolescence, it is, however, in clear contradiction to the gender of

rearing and, therefore, appears to have been resistant to it (Sobel and Imperato-McGinley, 2004)

20. Many intersex conditions, as with gender identity disorder, are not recognised at birth and remain undiagnosed for many years. One example of such a case is complete Androgen Insensitivity Syndrome (cAIS), where the cells of the fetus itself are insensitive to the virilising influence of androgens. Such individuals develop as phenotypical girls despite the presence of a 46,XY chromosome configuration (Grumbach and Conte, 1998; Grumbach *et al.*, 2003). Undescended testes will be present and, since MIH is produced normally, these individuals have no uterus or ovaries and have a short, or more-or-less non-existent vagina. In these cases the gender identity is usually consistent with the phenotype, but inconsistent with the karyotype and the gonads (Sobel and Imperato-McGinley, 2004).

21. An XY infant with partial AIS (pAIS) may have ambiguous genitalia at birth and be assigned as a girl. In the past, such assignments were usually accompanied by surgery to effect a female-looking vulva. Some of these individuals, having been raised as females, have later sought reassignment as males (Gooren and Cohen-Kettenis, 1991; Stein et al., 1994; Phornphutkul, *et al.,* 2000; Slijper *et al.,* 1998; Diamond and Watson, 2004). The same is true in some cases of penile agenesis, cloacal extrophy and mixed gonadal dysgenesis, where male infants were raised as girls (Feitz, *et al.*, 1994; Dittman *et al.*, 1998; Birnbacher *et al.* 1999; Reiner and Kropp, 2003; Reiner, 2004; Reiner and Gearhart, 2004). Some pAIS individuals, raised as males, have later transitioned to live as women (Diamond and Watson, 2004).

22. Congenital Adrenal Hyperplasia (CAH) is a condition which causes a degree of virilisation of the genitalia; in an XX infant this may be obvious neo-natally. In these cases too, some infants have had their genitalia surgically modified to what might be regarded as a more cosmetically acceptable genital appearance. Occasionally CAH in 46,XX individuals is associated with later gender discomfort (Meyer-Bahlburg, *et al.*, 1996, Hines, 2004a) The condition is also associated with increased male-typical behaviour in children and a raised incidence of homosexual orientation in adults (Dittmann *et al.*, 1992; Ehrhardt *et .al.,* 1968; Money and Schwartz, 1977; Money *et al.,* 1984; Zucker *et al.*, 1996; Hines, 2004b).

23. Cloacal extrophy, is a condition in which the bladder and large bowel are poorly developed, intermingled, and lie outside the pelvic wall; all of the pelvic structures are abnormal. These have to be corrected surgically. There is often severe inadequacy of the genitalia, so males with this condition are typically raised as girls with their genitalia constructed within the first months of life, to appear female. Recent studies indicate that a significant number of those treated in this way are not comfortable with their gender of rearing. One such study involved twenty-nine (29) subjects all of whom had 46,XY chromosomes. Five (5) were raised male and continue to live as male, one individual dropped out and another died. Of the remaining twenty-two (22), thirteen (13) have declared themselves male, six of whom did so spontaneously without birth status information. All individuals raised female show moderate to marked male gender role preferences (Reiner, 2004; Reiner and Gearhart, 2004).

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24. These findings taken in conjunction with the evidence from the other histories of conditions involving anomalies of genitalia, indicate that gender identity often resolves independently of genital appearance, even when that appearance and the assigned identity are enhanced by medical and social interventions. It is, therefore, postulated that the brain is often the stronger factor in determining gender identity (Diamond, 1996, 1997; Reiner, 1997, 1999; 2001; Reiner and Gearhart, 2004).

25. However, faced with the distressing circumstances of an infant being born with ambiguous genitalia, many clinicians have accepted the hypothesis that genital appearance and unambiguous rearing in the gender role that was consistent with the surgically modified genitalia would inevitably lead to a congruent gender identity. This approach to treatment, however, has now been modified in accordance with the view that it is often better to wait and see how the child's gender identity develops before making irreversible changes (Diamond & Sigmundson, 1997; Beh & Diamond, 2000; Rangecroft *et al.,* 2001). Two factors, in particular, seem to have prompted this change of approach to treatment.

26. The first is the growing voice of those who, having been born with ambiguous genitalia, were surgically assigned a sex at birth regardless of karyotype. This practice was accompanied by a policy of secrecy (Preves, 1998; Groveman, 1998). It has only been as adults, on learning the truth about their condition, that the individuals affected have made public the damage they believe this practice has caused them. Many regard their surgery as a mutilation and some, though not all, are uncomfortable in the gender role imposed in accordance with the surgically created phenotype (Wilson and Reiner, 1998; Intersex Society of North America, 2003).

27. The second factor that had a significant impact on the understanding of the development of gender identity is the case of an individual known as John/Joan. John (pseudonym) was an infant who lost his penis owing to a circumcision accident. In an attempt to solve the resulting medical and social dilemma of being a boy without a penis, it was recommended that he be surgically assigned and raised as a girl (Joan). He was not told of his original sex/gender assignment as a male. This solution was initially presented as having been successful thus, apparently, confirming the overriding influence of rearing in determining gender (Money & Ehrhardt, 1972; Money, 1975).

28. This case was, for many years, believed to support the view that, in instances of ambiguity of genitalia at birth or their accidental damage shortly thereafter, a child's gender identity could be largely determined by rearing, so long as this was consistent with the external sex characteristics. Infants were regarded as psychosexually neutral up to the age of two (Money and Ehrhardt, 1972), so reassignment had to be achieved before that age. However, later follow-up revealed that the attempt to impose a female gender identity on John failed. Despite psychological treatment to make him more comfortable in the female role, Joan reverted to being John during adolescence; he

married and became step-father to his wife's children.[4] (Diamond & Sigmundson, 1997; Kipnis & Diamond, 1998, Colapinto, 2000).

29. The outcome in the John/Joan case was consistent with the evidence derived from the intersex studies that seem, at least, to indicate that individuals are born with an innate sense of their gender identity, which does not necessarily accord with the genital appearance, and cannot necessarily be overridden by consistent socialisation supported by hormone administration (Diamond, 1965; Zhou *et al.,* 1995; Diamond, 1999; Kruijver *et al*., 2000**,** 2002; 2003**;** Swaab *et al***.,** 2003). However, it is acknowledged that one's upbringing and genital appearance, reinforced by hormone treatment, will have a significant impact on gender expression. A later similar case involved the reassignment as female of a seven month old XY infant. This individual appears to have accommodated to her imposed female role, albeit manifesting some typically masculine characteristics (Bradley *et al*., 1998).

30. Although intersex conditions are many and varied, they appear to have in common an association with atypical hormone environments and/or a malfunction of the endocrine system of the fetus itself, impacting on the process of sex differentiation; the brain is not immune from such hormonal effects. Reviewing some of the examples, given above, Cohen-Kettenis and Pfäfflin (2003) state that, though the evidence is not conclusive, "the existence of a wish to live as males, in (those) who have been reared as females suggests that prenatal androgen exposure may be a more important determinant of gender development than has long been believed" (Imperato-McGinley *et al*., 1979a). Much evidence is also derived from animal experimental data which suggest that the action of sex-steroid hormones causes permanent structural differences in the brain (Kawata, 1995). Some animal studies indicate a role for ovarian hormones in sex differentiation of the brain (Fitch and Denenberg, 1998; Beyer, 1999) although this has not been conclusively demonstrated in humans. It is more widely accepted that in all mammals, including humans, the presence or absence of testosterone is largely responsible for the virilisation, or not, of the brain and the body (Breedlove, 1994). Direct genetic effects on brain differentiation, which precede gonadal differentiation and the impact of fetal hormones, have not yet been demonstrated in humans, but cannot be ruled out (Dewing *et al*., 2003)*.*

31. Further support for a hormonal factor in predisposing to the condition is provided by a Green and Young study (2001). This analysed data of hand-preference in the performance of certain tasks. The study concluded that both trans women and trans men were more often non right-handed than were male and female controls. These results suggest a pattern of atypical laterality of cerebral hemispheric organisation in

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[4] *Sadly, during the preparation of this paper, John, whose real name was David Reimer, took his own life. Over the last two years he had suffered the death by suicide of his twin brother, the subsequent breakdown of his marriage and the loss of his job. The many difficulties endured by David during his childhood and adolescence, and his subsequent revolt against his upbringing, led to a greater understanding of possible influences on the psychological development of a male or a female identity, in the population generally. It is poignant to reflect that his pain and anguish were instrumental in bringing enlightenment to others, providing the springboard for change, albeit gradual, in the medical approach to treatment of infants with ambiguous or traumatised genitalia.*

trans individuals. The authors hypothesise that, "the association of atypical prenatal sex hormone levels and alterations in cerebral dominance…is consistent with the theory of an altered prenatal sex hormone origin for transsexualism." A separate large study (Zucker *et al*., 2001) also found that more left-handedness was found in 205 boys with gender identity disorder than in the control group. The same phenomenon was indicated in several other studies in adult trans individuals (Herman *et al.,* 1993; Orlebeke *et al*., 1992; Watson and Coren, 1992; Cohen-Kettenis *et al*., 1998).

32. Other studies also support the hypothesis that there are psychoneuroendocrinological links in the development of transsexualism, that is, that the endocrine environment impacts on the neural organisation of potentially sex dimorphic areas of the brain; these, in turn, influence the psychological identification as male or female (Gooren, 1990; Swaab and Hofman, 1995; Zhou *et al.,* 1995; Diamond, 2002; Kruijver *et al.,* 2000**;** 2002; 2003). Sex differentiation of the mammalian brain has been shown to be initiated during fetal development and continues after birth (Phoenix *et al*, 1959; Kawata, 1995; Chung *et al.,* 2002).   It is also postulated that the hormonal effects on the brain occur at several critical periods of sex differentiation during which gender identity may be established. So, at present, although the exact mechanism is incompletely understood, it is hypothesised that an atypical hormone environment at a critical time in the organisation of the fetal brain may be associated with an inconsistent gender outcome (Kruijver, 2004).

33. It is postulated that, in those who experience severe gender dysphoria, the sex differentiation of their brains has not followed the pattern usually predicted by the earlier steps in the differentiation process (such as the chromosomes, genitalia and gonads) "but has followed a pattern typical of the opposite sex in the final stage of that differentiation process" (Gooren, 1999; Gooren and Kruijver, 2002). This hypothesis is substantially supported by two important studies on post-mortem brains, including those of trans individuals (Zhou *et al*., 1995; Kruijver *et al*., 2000).

34. These studies followed others that found several sex-dimorphic nuclei in the hypothalamic and other areas of the brain (Allen & Gorski, 1990; Le Vay, 1993; Swaab *et al*., 2001). Of particular interest, in regard to transsexualism, is the sex-dimorphic region called the central subdivision of the bed nucleus of the stria terminalis (BSTc). This nucleus appears to become fully volumetrically sex differentiated in the human brain by early adulthood. In human males the volume of this nucleus is almost twice as large as in females and its number of neurons is almost double (P <0.006) (Zhou *et al*.,1995; Kruijver *et al*., 2000; Chung *et al.*, 2002). The Kruijver *et al.* study found that in the case of trans women (n=7), the size of this nucleus and its neuron count was in the same range as that of the female controls (n=13) and, therefore, women in the general population. When all the subjects were included, the neuronal differences between the groups were found to be highly significant. In the only available brain of a trans man, the volume and structure of this nucleus was found to be in the range of the male controls (n=21) and, therefore, men in the general population. The latter is not a significant result, but in the context of the overall findings, it leads to the hypothesis that this male-like BSTc will be present in other trans men as well.

35. In the 42 human brains collected for the Kruijver study, the BSTc was found to have a structure concordant with the psychological identification as male or female. It is inferred that the BSTc is an important part of a sex-dimorphic neural circuit, and that it is involved in the development of gender identity (Kruijver *et al*., 2000; 2002; 2003). These findings were independent of sexual orientation and of the use of exogenous sex hormones. No depression of neuron numbers in the BSTc was noted in association with estrogen administration, anti-androgen treatment and orchidectomy, in either trans women or in male controls. A high, male neuron number was found in the BSTc of the female to male trans individual. The 83 year old individual who had identified strongly throughout life as female in contradiction to both karyotype and phenotype, and who had undergone no feminising treatment of any kind, had a BSTc fully in the female range.

36. A 31 year old man who suffered from a feminising adrenal tumour, resulting in high estrogen levels (577 779 pmol/L), nevertheless, had a BSTc neuron count in the normal male range. In a female control with high serum testosterone (26.82nm/L) and androstenedione levels (48.0ng/mL) the neuron count had not been driven up but remained in the lower female range. Also, two untreated post-menopausal female controls with low endogenous estrogens levels, as well as the Turner syndrome patient with ovarian hypoplasia, did not show any increase in neuron numbers. Two males in the reference group had been orchidectomised for prostate cancer. In one case, this was done three months before death and on the other case, two years before death. The BSTc of both these men was in the male range. The first was close to the mean; the second, who had also taken anti-androgens for two years, had the highest observed number of neurons. Analysis of the total number of neurons in the human BSTc in individual patients with highly different hormone levels gave no indication that changes in sex hormone levels in adulthood affect the neuron numbers (Kruijver *et al.,* 2000).

37. In line with the hypothesis outlined above, that the fetal hormone milieu is critical to the sex differentiation of the brain, it is suggested that a number of factors may contribute to an altered environment at the critical moments in its early development. These factors might include genetic influences (Money and Pollitt, 1964; Benjamin, 1966; Buhrich and McConaghy, 1978; Landén, 1999; Henningsson *et al*., 2005; Coolidge *et al*, 2002) and/or medication, environmental influences (Diamond *et al.,* 1996; Dessens *et al.,*1999; Whitten *et al*., 2002), stress or trauma to the mother during pregnancy (Ellis and Cole-Harding, 2001; Ward *et al.,* 2002*;* Swaab *et al*., 2003; Kaiser *et al*., 2003).

38. Evidence of genetic effects were discussed in a doctoral thesis (Landén, 1999) which analysed the possible impact of three particular genes on the development of transsexualism. The genes targeted were: a tetra nucleotide polymorphism of the aromatase gene, a CAG nucleotide repeat sequence in the first exon of the gene coding for the androgen receptor, and a CA repeat polymorphism of the estrogen receptor beta gene. Results of the research supported "the notion that gender identity is related to the sex-steroid driven sexual differentiation of the brain, and that certain

genetic variants of the three genes critically involved in the process, may enhance the susceptibility for transsexualism" (Landén, 1999; Henningsson *et al*., 2005). As mentioned earlier, the raised incidence of atypical gender development in those with 47,XXY and 47,XYY karyotypes supports the hypothesis that genetic and endocrine influences may be involved in the atypical gender development (Money and Pollitt, 1964; Buhrich and McConaghy, 1978; Diamond and Watson, 2004).

39. A study on the heritability of gender identity disorder in a child and adolescent twin sample found a statistical significance in the results of 314 twins responding to a DSM-IV based gender identity disorder scale. The investigators report that "the results support the hypothesis that there is a strong heritable component in gender identity disorder" (Coolidge *et al*., 2002). In another recent study, Diamond and Hawk (2003) also found a high concordance for gender identity disorder among monozygotic twins where one twin transitioned, and a strong, but lesser concordance, among dizygotic twins. The effect was more noticeable among males than females.

40. In addition to the twin study just mentioned, transsexualism in one or both twins, some monozygotic and some dizygotic, as well as concordance for transsexualism in siblings have been the subject of a number of studies (Ancherson, 1956; Green and Stoller, 1971; Stoller and Baker, 1973; Hore *et al.,*1973; Sabalis *et al.,* 1974; McKee *et al.,* 1976; Hyde and Kenna, 1977; Ball, 1981; Broadbent, 1996). Family co-occurrence of gender dysphoria in ten sibling or parent-child pairs is discussed in a further study, in which it is suggested that such co-occurrences, viewed in the light of the relative rarity of transsexualism, are unlikely to be random (Green, 2000).

41. Research has also indicated a significantly greater number of maternal aunts versus uncles in the families of trans women; no differences from the expected parity were found for trans men. One posited explanation for this phenomenon is a genetic effect occurring over three generations (Green and Keverne, 2000).

42. Evidence of a mechanism that can alter the fetal endocrine milieu is reported by Dessens *et al.* (1999). They found a raised incidence of transsexualism in children of mothers exposed to anti-epileptic medication during pregnancy. In laboratory conditions, diethylstilbœstrol (DES) has been shown to affect sex differentiation in mice and rats, producing effects such as hypospadias, hypogonadism and cryptorchidism. Findings that the human fetus is similarly affected by chemicals crossing the placenta are inconclusive, however there is some evidence of this. DES is described as an 'endocrine disrupter' (Gorski, 1998, McLachlan 2001; McLachlan *et al.,* 2001), having anti-androgenic and possibly estrogenic effects, which are capable of altering the human fetal environment when administered to a pregnant mother (Toppari and Skakkebaek, 1998; Berkson, 2000). Beyer explains that it crosses the placental and blood-brain barriers, bypassing the feedback system which would normally suppress the body's production of estrogen (Beyer, 2003; Gorski, 1998). DES, therefore, may have the potential to impact on the sex-differentiation of the central nervous system. It was widely administered to pregnant women from the 1950s through to the 1980s to prevent miscarriage. A number of defects of sex differentiation occurred in the children born of these pregnancies (Klip *et al.,* 2001).

According to self-reports, there appears to be a raised incidence of gender dysphoria experienced by the sons in this group (DES Sons' International Research Network). It is thus thought that there may possibly be a link between this condition and the prenatal exposure to DES of those sons. This remains a plausible, but unproven hypothesis.

43. Further evidence of chemicals crossing the placenta derives from atypical sex differentiation in animals which appears to be associated with environmental pollutants, especially 'estrogen-mimics'.   Not only mammals, but also the reproductive systems of reptiles and fish have been found to be affected by pollutants (Pollution, Arctic, 2002).

44. In sum, gender identity, whether consistent or inconsistent with other sex characteristics, may be understood to be "much less a matter of choice and much more a matter of biology" (Coolidge *et al.,* 2000). The scientific evidence supports the paradigm that transsexualism is strongly associated with the neurodevelopment of the brain (Zhou *et al.,* 1995; Kruijver *et al.*, 2000). It is clear that the condition cannot necessarily be overcome by "consistent psychological socialisation as male or female from very early childhood" and it is not responsive to psychological or psychiatric treatments alone (Green, 1999). It is understood that during the fetal period the brain is potentially subject to the organising properties of sex hormones (Kruijver *et al.*, 2000; 2001; 2002; 2003). In the case of transsexualism, these effects appear to be atypical, resulting in sex-reversal in the structure of the BSTc, and possibly other, as yet unidentified, loci (Kruijver, 2004). The etiological pathways leading to this inconsistent development almost certainly vary from individual to individual, so no single route is likely to be identified. Different genetic, hormonal and environmental factors, acting separately or in combination with each other, are likely to be involved in influencing the development of the psychological identification as male or female. Psychosocial factors and cultural mores are likely to impact on outcomes (Connolly, 2003).

45. Finally, over and above any discussion already presented, it is imperative to emphasise that attention to the needs of trans people should be extended on the basis of human rights, justice and equality. Medical and scientific findings are often amended and clarified, but the right of individuals to appropriate care and respect remains.

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Authors to this paper are:

Professor Michael Besser, DSc, MD, FRCP, FMedSci. (UK)
Dr Susan Carr, MPhil. MFFFP. DDRCOG. (UK)
Professor dr Peggy Cohen-Kettenis PhD. (The Netherlands)
Dr Pamela Connolly PhD. (USA)
Professor dr Petra de Sutter, PhD. (Belgium)
Professor Milton Diamond , PhD. (Chair) (USA)
Dr Domenico Di Ceglie, FRCPsych., DIP. PSICHIAT. (Italy) (Child Section) (UK)
Dr Yuko Higashi, Ph.D. (Japan)
Dr Lynne Jones, MP, PhD. (UK)
Dr Frank Kruijver, MD., PhD. (The Netherlands)
Dr Joyce Martin, MRCGP, MB, ChB, D.Obst.RCOG. (UK)
Professor Zoe-Jane Playdon, BA(Hons), PGCE, MA, MEd, PhD, DBA, FRSA. (UK)
Mr David Ralph, MBBS, BSc, FRCS, MS. (UK)
Mrs Terry Reed, JP, BA(Hons), MCSP, SRP, Grad Dip Phys. (UK)
Dr Russell Reid, MB, ChB, FRCPsych. (UK)
Professor William Reiner, MD. (USA)
Professor Dick Swaab , MD, PhD. (The Netherlands)
Mr Timothy Terry, BSc, MB, BS, LRCP, FRCS (Urol), MS (UK)
Dr Philip Wilson, DPhil MRCP MRCPCH FRCGP. (UK)
Dr Kevan Wylie, MB, MmedSc, MD, FRCPsych, DSM. (UK)