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Neuroendocrine Mechanisms and the Aetiology of Male and Female Homosexuality

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Summary: Theories on the classification and aetiology of male homosexuality are reviewed, particularly recent hypotheses on the role of prenatal hormonal influences on brain sexual differentiation and subsequent sexual object chioce in the male. Female as well as male brain sexual differentiation may be hormonally determined, and so primary homosexuality in both sexes may be due to abnormalities in foetal exposure to hormones, leading first to physical mis-differentiation and later to homosexual behaviour in genetically and phenotypically normal men and women.

In spite of much effort, both psychoanalytically orientated workers and behaviourists have found great difficulty in creating a model which accounts acceptably for people whose sexual orientation is wholly homosexual (Money *et al*, 1957; McGuire *et al*, 1965; Money and Ehrhardt, 1972). Endocrine studies have in the main failed to establish a physiological basis for sexual behaviour and in particular they have failed to shed light on homosexuality and choice of sexual object in humans (Dewhurst, 1969; Bermant and Davidson, 1974). Similarly, transmission studies in single families have failed to indicate a clear genetic basis for homosexual preference (Ellis, 1963; Heston and Shields, 1968). The existence of monozygotic twins, reared together, completely discordant for sexual preference and behaviour (Feldman and MacCulloch, 1971; Zuger, 1976) suggests that the discordance in some cases at least must be explained in other than genetic and learning terms.

The failure to find clear biological or psychogenic causes for homosexual behaviour could result if biological and psychological factors make varying causal contributions in different individuals. Heterogeneity of the group of people displaying homosexual behaviour was suggested from the treatment of 73 mostly male homosexual patients by Feldman and MacCulloch (1971) who noted a very significant clinical division between patients without and those with prior heterosexual experience or interest. The first group, termed by them primary homosexuals, scored less than 20 on the female component of the Sexual Orientation Method (SOM) (Sambrooks and MacCulloch, 1973), were poorly motivated for treatment and resistant to aversive conditioning.

The second group, secondary homosexuals, had had some previous heterosexual interest or experience, scored more than 20 on the female component of the SOM, were well motivated for treatment by aversive techniques and responded well to treatment.

Although not all workers accept this dichotomy into primary and secondary homosexuals there is some preliminary biochemical evidence in line with it. Comparisons of serum testosterone levels between heterosexual and homosexual males produce differing results depending upon whether the homosexuals are integrated into a community with no desire for change (Brodie *et al*, 1974) or present themselves with a request for treatment to change their sexual orientation (James *et al*, 1977).

A Biochemical Theory of Male Homosexuality

A tentative formulation of a hormonal theory of male homosexuality (Feldman and MacCulloch, 1971) suggested that primary male homosexuals have sexually undifferentiated brains of the female pattern due to a lack of hypothalamic exposure to androgens in a critical period of intra-uterine life. The causal explanation for primary homosexuality in our monozygotic twin pair discordant for choice of sexual object was then that the homosexual twin had been differentially deprived of placental androgen during the critical period, leading to an undifferentiated (female) brain, whereas the other twin had developed in a male way.

Although the basis for the theory was clinically inspired to account for very puzzling observations on male homosexuals it drew heavily on the extensive animal literature on sexual dimorphism. By the early

1970's it was generally concluded that the inherent programme of sexual development in both sexes of mammals was female. Androgens at the critical periods of sexual differentiation organized both genetic males and genetic females to possess masculine reproductive organs (Jost, 1953), masculinize hepatic steroidogenic enzymes (DeMoor and Denef, 1968), and cause tonic (male pattern) hypothalamic control of gonadotrophin secretion (Pfeiffer, 1936; Wilson *et al*, 1941; Barraclough and Gorski, 1961) and also male sexual behaviour, (Grady *et al*, 1965). It was thought that an absence of either gonad during the critical developmental period allowed the expression of female characteristics which were thought to be inborn, (Pfeiffer, 1936; Jost, 1953; Grady and Phoenix, 1963; Harris, 1964; De Moor and Denef, 1968).

Dörner *et al* (1975) restated this hormonal theory for male homosexuality as follows: "An absolute or relative androgen deficiency in the first hypothalamic organization phase, i.e. intra-uterine, Leydig cell degeneration, results in a predominantly female brain differentiation. A normal or at least approximately normal androgen level during the second phase, i.e. post-pubertal Leydig cell generation, then exerts a sex non-specific activating effect on the predominantly female differentiated brain. Thus a genetic and somatic phenotypic male with a predominantly female differentiated brain is primarily sexually excited by another male".

This theory predicted that a positive oestrogen feedback effect, characteristic of the normal female, should be present in primary homosexual males. In a critical experiment, Dörner *et al* (1975) demonstrated such an effect in 13 out of 21 primary homosexual males, who showed a biphasic luteinizing hormone (LH) effect similar to that seen in normal women (Van der Wiele *et al*, 1970; Nillius and Wiede, 1971; Tsai and Yen, 1971); by contrast only 2 out of 25 25 secondary homosexuals or heterosexuals showed this response. This led MacCulloch and Feldman (1977) to predict that (1) primary male homosexuals would show the most feminine LH response curves and be most resistant to treatment and (2) the secondary homosexual groups would consist of subjects with a masculine LH response. Secondary homosexuality may arise more from psychosocial influences acting in accordance with learning theory (McGuire *et al*, 1965; Feldman and MacCulloch, 1971; MacCulloch and Feldman, 1977).

Female Homosexuality

Lesbians present at clinics less frequently than do male homosexuals, but there is some clinical evidence that they also can be divided into primary and secondary homosexual groups (Feldman and MacCulloch, 1971). Recent animal studies, which assert that mammalian brains are sexually neutral prior to their exposure to different hormones which subsequently render them dimorphic, suggest a mechanism for the etiology of primary female homosexuality.

Phoenix *et al* (1959) injected androgen into pregnant guinea pigs to produce some female pseudohermaphrodite offspring and investigated the offspring's sexual responses to male and female hormones, after ovariectomy to eliminate endogenous gonadal hormone. They found that female hormones provoked even less female sexual behaviour than before, usually increasing mounting and male sexual behaviour. After the injection of male hormones, however, male sexual behaviour was seen, like that following the injection of male hormones in previously castrated males. They concluded that at a crucial stage in the growth of the nervous system abnormally high androgen levels will produce neural circuits capable of organizing male sexual behaviour in the female. These experiments showed how a genetic female could be masculinized by androgens, and paradoxically, male behaviour induced by oestrogen.

Shapiro *et al* (1976a, b) tested genetically male, androgen insensitive, pseudohermaphroditic rats for male and female sexual behaviour following gonadectomy and subsequent oestradiol and testosterone treatments. There was a complete absence of any form of sexual behaviour. The absence of female behaviour was at variance with the concept that female differentiation is inherent and independent of hormonal imprinting. Shapiro *et al* (1976a) suggested that foetal hormones, possibly progesterone, may be necessary for female as well as male brain organization, and their results are consistent with the failure of androgen-insensitive male pseudohermaphroditic rats to show the cyclic gonadotrophin secretion characteristic of the female phenotype (Goldman *et al*, 1975).

In further studies Shapiro *et al* (1976b) showed that newborn female rats have a markedly higher level of serum and adrenal progesterone than newborn males; these serum progesterone levels could be further increased by exogenous gonadotrophins. It is known that the female brain can be masculinized by both androgen and oestrogen (Jost, 1953; Barraclough and Turgeon, 1975). As Dorfman (1967) has demonstrated that progesterone has both anti-oestrogenic and anti-androgenic activity, this clearly suggested that raised serum progesterone in the newborn female rat might function both to cause feminization of the brain and as a hormone antagonist to protect the developing female brain from the masculinizing effect

of both androgen and oestrogen (Shapiro *et al*, 1976a, b).

As an hormonal hypothesis for lesbianism we suggest that a reduction of progesterone in the hypothalamus of the developing human foetus might result in failure to initiate feminization and to protect the non-differentiated hypothalamus from the masculinizing effect of androgen and oestrogen. Thus a genetically female brain would be differentiated as functionally male, with subsequent homosexual behaviour (choice of female sexual object). This leads to the prediction that primary homosexual females will show a male LH response and that the response will be normal in secondary female homosexuals.

To date there is little direct evidence that the brain is sexually differentiated by endocrine experience in humans. However, endocrine abnormalities such as the adrenogenital syndrome (Ehrhardt *et al*, 1968a, b; Ehrhardt and Baker, 1974; Money *et al*, 1967), androgen insensitivity (Money *et al*, 1968), and Turner's syndrome (Ehrhardt *et al*, 1970) all show that both gender-related behaviour and genital morphology are subsequently affected by levels of steroid hormones present during pre-natal development.

In 23 girls with adrenogenital syndrome, Ehrhardt *et al* (1968b) described masculinization of childhood behaviour and a 50 per cent incidence of homosexual imagery in adolescence. In a study of girls with Turner's syndrome, however, Money and Ehrhardt (1972) concluded that there was an unequivocal feminine gender identity and neither oestrogen nor androgen could be involved in the differentiation of a female brain. This is not inconsistent with the suggestion of Shapiro *et al* (1976a, b) that it is progesterone which femininizes the previously sexually-undifferentiated brain when androgen is not present to excess. Where it is in excess we would expect the previously undifferentiated brain to be masculinized.

As it is unclear whether exogenous hormones administered to pregnant women pass through the placenta in unchanged form, it is difficult to draw firm conclusions about the effects of parenteral preparations on foetal brains. However, Ehrhardt and Money (1967) described high IQ and excessive tomboyish behaviour in 10 girls born to mothers treated pre-natally with synthetic progestins. Similarly, Yalom *et al* (1973) described less aggression, less assertiveness and less athletic skills in the sons of mothers treated pre-natally with diethylstilboestrol.

More specifically, Wilkins *et al* (1958) describe the occasional incidence of male external genitalia in girls born to mothers treated prenatally with male hormones. These females have almost always been raised as boys and have themselves preferred to continue in this way even when increased ovarian activity at puberty has begun to induce secondary feminine characteristics. This syndrome is suggestive of male brain differentiation in the human female, following prenatal exposure to abnormally high levels of male sex hormones that are sufficient to overcome the normal protective effect of progesterone against normally occurring amounts of androgen, and is consistent with our theory of female homosexuality.

The In Utero Defect

Clearly there is an explanatory gap between the results of animal experiments which withhold the effects of hormones when they are normally present and include them when they should be normally absent, and a model of human sexual developmental deviation. It is not immediately clear in most cases how these abnormal hormonal conditions might come about during foetal life. An important animal study offers a possibly insight. Bidlingmair *et al* (1977) have described how an immune reaction to testosterone in the pregnant rabbit could alter the sexual development of male offspring. They produced pregnant female rabbits whose serum contained antibodies capable of neutralizing the biological activity of testosterone; the male offspring of these rabbits had elevated serum testosterone levels and developed a reproductive system like that of a normal female rabbit. This experiment demonstrated that antibodies to testosterone can pass the placental barrier and that developing sex organs can be deprived of the effect of the hormone, despite a feedback-induced increase in absolute testosterone level, leading to changes in morphogenesis similar to experiments on testicular atrophy in other species. The spontaneous production of antibodies to hormones is known in the human (e.g. auto-immunizing thyroiditis, Hashimoto's disease) and human antibodies can pass through the placenta from the mother to the foetus (Bell *et al*, 1968). If auto-antibodies to testosterone were produced in a woman pregnant with a genetically male foetus one might hypothesize that they would reduce the biological activity of the testosterone leading to a female brain differentiation and subsequent primary homosexual behaviour. As in the rabbits a feedback-induced raised level of circulating biologically inactive testosterone might also appear, and it is interesting that Brodie *et al* (1974) found significantly elevated serum testosterone levels in young primary male homosexuals. It is true that many other workers have failed to find such raised serum levels of testosterone (James *et al*, 1977; Kolodny *et al*, 1971; Tourney and Hatfield, 1973; Dorner *et al*, 1975), but we argue that a clinically heterogeneous group contains both primary and secondary homosexuals and any high values in the primary cases would be

lost amid the normal or low values of the secondary cases.

In primary female homosexuality, mothers might show spontaneous generation of antibodies to progesterone with a consequent increase in biologically inactive serum progesterone levels in their offspring. But this is a speculation so far without any serum measurements either to support or to deny it. However these ideas give rise to some predictions capable of experimental testing.

(1) Mothers of primary male or female homosexuals should have had a previous normal male or female child. (2) Mothers of primary male and female homosexuals may have abnormal titres of testosterone or progesterone antibodies respectively. (3) Young primary male and female homosexuals may show abnormally high levels of serum testosterone and progesterone respectively, and this should not be shown by their respective secondary homosexual counterparts. (4) They may also show abnormally high titres of antibodies to testosterone or progesterone.

If this antibody production hypothesis were to prove to be incorrect, we would mention one other animal study where Gandelman *et al* (1977) have shown that intra-uterine position can bring about masculinization of female foetuses. It may be possible that foetal position and contiguity with amniotic membranes can subtly influence circulating hormone levels *in utero* and hence induce sexual mis-differentiation in the foetus.

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