Human Sexual Orientation

The Biologic Theories Reappraised

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• Recent studies postulate biologic factors as the primary basis for sexual orientation. However, there is no evidence at present to substantiate a biologic theory, just as there is no compelling evidence to support any singular psychosocial explanation. While all behavior must have an ultimate biologic substrate, the appeal of current biologic explanations for sexual orientation may derive more from dissatisfaction with the present status of psychosocial explanations than from a substantiating body of experimental data. Critical review shows the evidence favoring a biologic theory to be lacking. In an alternative model, temperamental and personality traits interact with the familial and social milieu as the individual's sexuality emerges. Because such traits may be heritable or developmentally influenced by hormones, the model predicts an apparent nonzero heritability for homosexuality without requiring that either genes or hormones directly influence sexual orientation per se.

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The origins of homosexuality have been a subject of intense debate ever since the concept of sexual orientation emerged from reconceptualizations of gender that occurred during the 18th century in northern Europe.[1] The term *homosexuality* first appeared in 1869 in a treatise by Benkert, writing under the pseudonym Kertbeny.[2] Despite nearly a century and a half of study and debate, there is still no universally accepted definition of homosexuality among clinicians and behavioral scientists[3(p3)]—let alone a consensus regarding its origins. The idea that it derives from moral degeneracy has long been discounted by scholars, many of whom have argued for the primacy of either biologic or psychosocial influences.[4(pp212-220)]

The biologic theories made headway during the 1970s as neurobiologists began to unravel the genetic, hormonal, and neurodevelopmental processes involved in the sexual differentiation of neural substrates integral to the regulation of reproductive behaviors in animals.[4,5] During this period, researchers at the Kinsey Institute for Sex Research, Bloomington, Ind, conducted a massive survey, subjected the data to path analysis, and concluded, perhaps erroneously, that there is no solid scientific support for any psychosocial explanation.[4] According to their final chapter, "Biology?" "a growing body of opinion posits biological factors as the *primary* [italics added] basis of sexual attractions," and recent evidence "is leading more and more scholars, including those who had previously rejected this possibility to believe that such a basis is likely after all."

As the influence of experience on brain development began to be better appreciated in the 1980s,[6-8] it became unfashionable to endorse either side of the nature/nurture debate, and a semblance of an interactionist approach emerged. Advocates for the primacy of biologic determinants might conclude, "the prenatal hormonal history is strongly implicated in the genesis and ultimate differentiation of a homosexual, bisexual, or heterosexual status,"[9] while advocates for the primacy of psychosocial factors would counter that "biological factors exert at most a predisposing rather than a determining influence."[10]

This uneasy truce was disrupted late in 1991 with the publication of LeVay's report in *Science*[11] that provided evidence of an anatomic difference in the hypothalamus of homosexual and heterosexual men. In the wake of that report, one might argue that replication studies would be more useful than literature reviews. In the past, however, replication studies have proved to be of little immediate value in settling disputes regarding possible biologic correlates of sexual orientation. For example, the idea that homosexuality equals a lack of male behavior, which in turn equals a deficiency of male sex hormones, persisted from the 1940s through the late 1970s despite the failure of hormone treatments to influence sexual orientation and despite the fact that most studies failed to find any association between adult hormone levels and sexual orientation. In fact, as reviewed by Meyer-Bahlburg,[12(pp376-377)] the relevant literature includes only three studies that suggested lower testosterone levels in male homosexuals, while 20 studies found no differences based on sexual orientation, and two reported elevated testosterone levels in male homosexuals. Similarly, in the related field of sex differences research, a report[13] that the splenium of the corpus callosum is larger and may, therefore, contain more interhemispheric fibers in women than in men has remained viable in the literature for more than a decade despite more than 20 replication attempts, all of which have failed.[14]

Owing to difficulties in obtaining suitable autopsy ma-

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terial, attempts to replicate the reported neuroanatomic correlates of sexual orientation may not be immediately forthcoming. Furthermore, if the studies of the corpus callosum serve as any example, such attempts may not provide definitive answers in the near future. And even if these findings are consistently replicated, we will not know whether the anatomic correlates are a cause or a consequence of sexual orientation. Thus, the theories of biologic influences on sexual orientation need reappraisal while replication studies are in progress.

Because experience can alter the physiology and structure of the brain,[6-8] the meaning of the word *biologic* is somewhat ambiguous. To the extent that sexual orientation, like other aspects of personality, must be represented in the brain in some relatively enduring manner, it is necessarily a biologic phenomenon. The interesting question, however, is not "Is sexual orientation in the brain?" but "How is it represented, and when and how does it get there?" Is it determined or appreciably influenced by genetic or hormonal factors, chemical or physical aspects of the intrauterine or postnatal environment, varied experiences in an individual's life that occur in a social and cultural matrix, or a combination of any or all of these factors? Furthermore, if there is a biologic predisposition toward one or another sexual orientation, is this predisposition at the level of sexual orientation per se, or is it at the level of some constellation of personality traits or drive states that influence the manner in which an individual and his or her environment interact as sexual orientation emerges developmentally? Historically, Western research aimed at describing the origins of sexual orientation has largely ignored the development of heterosexual orientation, assuming it to be a normal developmental end point. Instead, the emphasis has been on the development of homosexual orientation, which has traditionally been viewed as a deviation from that norm. Most of this research has been based on a number of questionable assumptions. The first of these is that homosexuals are intermediate between heterosexual men and heterosexual women along various continua or dimensions of sexual differentiation. This assumption is evident in the literature in the frequent equation of homosexual behavior in men with effeminacy. In the biobehavioral literature, this equation has led to the concept of homosexuality as "central nervous system hermaphroditism" and to the search in male homosexuals for "female mating centers," as well as for feminized cognitive and hormonal profiles and neuroendocrine responses.[12,15-18] The validity of this assumption is called into question by modern cultures in which homosexual behavior among adolescent boys has been viewed as essential to the attainment of strength and virility,[19(p126)] as well as by ancient cultures whose history, art, literature, and myths were filled with the homosexual exploits of archetypally masculine heroes, including Hercules and Julius Caesar.[20]

A second assumption is that homosexuality is a unitary construct that is culturally transcendent. However, a wealth of cross-cultural evidence points to the existence of numerous patterns of homosexuality varying in origins, subjective states, and manifest behaviors.[21] In fact, the pattern of essentially exclusive male homosexuality familiar to us has been exceedingly rare or unknown in cultures that required or expected all males to engage in homosexual activity.[19(pp125-145)]

A third assumption is that homosexuality results from some defect in either biologic constitution or socialization. Ford and Beach,[22] however, suggested that the existence of cultures that have required homosexual behavior of all males argues against the notion that such behavior necessarily arises within a pathologic context.

Of course, one must distinguish between homosexuality and homosexual behavior. As reviewed by Gadpaille,[23] both cross-species and cross-cultural evidence suggests a distinction between preferential homosexuality and all other expressions of homosexual activity at any period during one's life. We use the term *sexual orientation* to signify a cognitive identification and subjective emotional sense of oneself on a continuum of homosexual/bisexual/heterosexual identity.[3(p3)] This definition allows for a spectrum of thoughts and feelings and even for a discrepancy between one's actions and one's thoughts and fantasies. Furthermore, it allows for the possibility that one's sexual orientation may change over time.

GENETIC STUDIES

Perhaps the most frequently cited study of the genetics of sexual orientation is that of Kallmann,[24] in which he reported a concordance rate of 100% for sexual orientation among monozygotic (MZ) twins. However, Kallmann[25(p259)] subsequently conjectured that this perfect concordance was an artifact, possibly due to the fact that his sample was drawn largely from mentally ill and institutionalized men. Some subsequent studies have failed to find any concordance for homosexual orientation in men[26,27] or women,[28] while others have found concordance rates between 10% and 50%.[28-31] Unfortunately, these studies either have involved very small numbers of twin pairs or have studied twins who were raised together from birth, making it difficult to determine the relative contributions of genetics and environment. Similarly, Pillard and Weinrich[32] investigated the prevalence of homosexuality in the families of homosexual and heterosexual male probands. Compared with heterosexuals, homosexuals were about four times more likely to report having a homosexual brother. Because the brothers were raised together, this study could not determine whether the observed familiality was due to genetic or environmental factors.

The largest twin study published to date is the study by Bailey and Pillard,[30] which recently received considerable attention from the news media. This study, which included 56 homosexual male probands with MZ cotwins and 54 homosexual probands with dizygotic (DZ) cotwins, found the probandwise concordance rate to be significantly greater for MZ (52%) than DZ (22%) twins.[30] The higher concordance rate in the MZ twins compared with the DZ twins would be consistent with a role of heritable factors. However, the concordance rate for homosexuality in nontwin biologic brothers was only 9.2%—significantly lower than that required by a simple genetic hypothesis, which, on the basis of shared genetic material, would predict similar concordance rates for DZ twins and nontwin biologic brothers. Furthermore, the fact that the concordance rates were similar for nontwin biologic brothers (9.2%) and genetically unrelated adoptive brothers (11.0%) is at odds with a simple genetic hypothesis, which would predict a higher concordance rate for the biologic siblings. On the basis of a previous study that found homosexuality or bisexuality in 22% of the biologic brothers of predominantly homosexual probands, Bailey and Pillard[30] suggested that the 9.2% concordance rate for nontwin brothers in their study may be artifactually low due to random sampling fluctuations. However, if we rely only on the data presented in their study, we must at least consider the possibility that the higher concordance rate for homosexuality in DZ twins compared with nontwin biologic brothers is due to increased similarity of the trait-relevant environment in the former. This is because DZ twins and full biologic siblings share the same proportion of genetic material. Thus, any differ-

ence in the true concordance rates would be attributable to environmental rather than genetic factors.

A more recently published study by King and McDonald[31] found similar concordance rates for MZ and DZ twins. Of 20 male and female homosexual probands with MZ twins, two, three, and 15 of the cotwins were homosexual, bisexual, and heterosexual, respectively. Similarly, of 25 homosexual probands with DZ twins, two, one, and 22 of the cotwins were homosexual, bisexual, and heterosexual, respectively. Thus, the concordance rates for MZ twins would be 10% or 25%, depending on whether or not the bisexuals were included with the homosexuals, while the rates for the DZ twins would be 8% or 12%. These rates are significantly lower than those reported by Bailey and Pillard[30]; in a comparison of the MZ concordance rate, including bisexuals (25%), with the comparable figure from Bailey and Pillard (52%), $\chi^2=4.02$, $df=1$, $P=.045$. Furthermore, if the concordance rate is similar for MZ and DZ twins, the importance of genetic factors would be considerably less than that suggested by Bailey and Pillard. The Bailey and Pillard study appears to have been methodologically superior to that of King and McDonald in that it involved a larger number of subjects, all of the same sex, and most of whom were interviewed. Not only did the latter study have fewer subjects, it relied solely on questionnaires and included probands of both sexes (38 men and eight women). The presentation of data does not allow one to calculate the concordance rates separately for each sex. This is unfortunate in the absence of evidence that the concordance rates for homosexuality in twins are similar for men and women.

Interpretation of the studies of Bailey and Pillard and of King and McDonald is hampered by technical flaws that are difficult to avoid in this area of research. First, the validity of both studies rests on the veracity of the assumption that the trait-relevant environment is equal for MZ and DZ twin pairs. While available research supports the accuracy of this "equal environments assumption" for intelligence and certain personality traits,[33(chap 12)] there is no direct evidence that it holds for sexual orientation. It is possible that, compared with the traits for which data are available, sexual orientation is significantly influenced by more idiosyncratic aspects of the familial environment. If the trait-relevant environment were more similar for MZ than DZ twins, the conclusions of Bailey and Pillard would be called into question.

Second, neither study employed a systematically ascertained sample of twins. Subjects in both studies were recruited through advertisements placed in homosexual-oriented periodicals and, therefore, may not be typical of the homosexual population at large. While there is no reason to suspect that the heritability for homosexuality would differ between consumers and nonconsumers of homosexual-oriented periodicals, it is plausible to ask whether these two groups might differ in their motivations for participation in such a study. Such a difference would have an unpredictable effect on ascertainment bias. While the heritability estimates of Bailey and Pillard remained statistically significant under a range of assumptions about the degree of ascertainment bias, including the assumption that a proband was up to three times more likely to be ascertained if his cotwin were homosexual, the true degree of such bias remains unknown.

Third, unless the equal environments assumption can be shown to hold for those aspects of the environment pertinent to sexual orientation, no study of twins reared together will be able to tease apart and quantify the differential contributions of genetic and environmental factors. What is lacking in this literature are studies similar to the Danish Adoption Study of schizophrenia, in which biologic relatives of schizophrenic adoptees were found to have an increased prevalence of schizophrenia and schizophrenia "spectrum" disorders relative to controls.[34] A study of this sort would provide strong evidence of a genetic contribution if it were to demonstrate that the prevalence of homosexuality in biologic relatives of homosexual adoptees exceeds that of the population at large.

Fourth, the finding of a nonzero heritability does not specify the intervening pathways between genes and sexual orientation. For example, if a gene influenced some factor, such as temperament, in a manner that would increase the probability of homosexual development in a particular environment, that gene could be called a gene for homosexuality with reduced penetrance. Such terminology, however, would minimize the overriding importance of environment in such a scenario.

Finally, what is most intriguing about the studies of Bailey and Pillard and of King and McDonald is the large proportion of MZ twins who were discordant for homosexuality despite sharing not only their genes but also their prenatal and familial environments. The large proportion of discordant pairs underscores our ignorance of the factors that are involved, and the manner in which they interact, in the emergence of sexual orientation.

HORMONAL STUDIES

Since the turn of the century, there has been much speculation concerning a possible role of hormones in sexual orientation. The belief that sexual orientation is determined by adult hormonal constitution, which was popular until the middle to late 1970s, has now fallen into disfavor because sensitive hormonal assays have failed to demonstrate a correlation between sexual orientation and adult hormonal constitution.[12,35] Furthermore, hormonal therapies have failed to influence sexual orientation in adults,[36] and there is also no evidence that sexual orientation has shifted in adults as a consequence of changes in androgen or estrogen levels induced by gonadal neoplasm, trauma, or surgical removal.[37] However, peripheral hormonal levels per se are of limited value in the absence of some measure of end-organ sensitivity, such as brain steroid receptor density and postreceptor mechanisms. Currently, data pertaining to possible neurochemical differences between homosexual and heterosexual individuals are lacking.

At present, the major impetus for speculation on a constitutional basis for homosexuality comes from work showing that, in laboratory animals, sexually dimorphic reproductive behaviors are organized in early development (prenatally or perinatally, depending on the species) by gonadal steroid hormones.[5,38]

The Prenatal Hormonal Hypothesis

According to this hypothesis, the intrinsic pattern of mammalian brain development is female, and the production of androgens by the male fetus is necessary for differentiation of the male brain. This is analogous to somatic sexual differentiation: the genetic constitution determined at conception (XX or XY) determines whether the gonadal anlagen develop as a testis or an ovary. In males, testicular hormones then direct the differentiation of male genitalia. In the absence of these hormones, development of female genitalia ensues.[39(p283)] Unlike differentiation of the external genitalia, in which a bipotential structure loses its female characteristics in the process of acquiring male characteristics (eg, fusion of the labioscrotal folds obliterates the labia as it forms the scrotum), during sexual differentiation of the brain the loss of female characteristics and the acquisition of male characteristics are largely independent. Furthermore, these processes of defeminization and masculinization occur during different but overlapping periods of early development and may involve different neural substrates as well as different hormonal metabolites.[5]

Evidence suggests that in some species testosterone exerts some of its influences on brain development by interaction with androgen receptors, while other effects require that androgen be converted to estrogen by aromatase enzymes within the brain.[40] After this conversion, brain-derived estrogen exerts its effects by interaction with estrogen receptors.[40] Defeminization, which includes suppression of both female-typical reproductive behavior and the ability of the hypothalamus to regulate the ovarian cycle, involves the aromatization pathway of testosterone.[38,41] Female fetuses of some species are possibly protected from defeminization by ovarian estrogen by an α-fetoprotein that binds estrogen in the peripheral circulation and precludes it from entering the brain.[42] The hormonal requirements for masculinization appear to vary across species. While the aromatase pathway may

be required for brain masculinization in some species, masculinization in others occurs independent of this pathway or involves a combination of central estrogenic and androgenic activity.[38,41]

The prenatal hormonal hypothesis of human sexual orientation holds that male heterosexuality and female homosexuality result from prenatal exposure to high levels of testicular hormones, while homosexual males and heterosexual females are exposed to lower levels and thus retain a female pattern of brain organization.[4(p216)] This hypothesis is based on the observation that "one can produce 'homosexual' mating behavior, e.g., lordosis [a female sexually receptive posture] in males by experimentally inducing a deficiency of androgenization during a critical phase."[16(p315)] Conversely, mounting, a male-typical mating behavior, is displayed with increased frequency in female rats that were exposed to androgens in early development.[5]

The enduring effects of hormones on the developing brain are often referred to as "organizational effects" to distinguish them from the reversible or "activational effects" that hormones may have on inducing or supporting particular behaviors in adulthood. For example, a female-organized brain will support the display of lordosis when activated by ovarian steroids, while androgens activate the display of male-typical behaviors in a male-organized brain.[5] While the distinction between organizational and activation effects remains a useful concept, it is now clear that a rigid dichotomy does not actually exist.[43]

Because of the tremendous influence that rodent models of behavioral and brain sexual differentiation have had on current thinking concerning the possibility of parallel phenomena in humans, it is necessary to explore these models in some depth.

Lordosis.—Lordosis is a posture that a sexually receptive female rodent displays on appropriate tactile stimulation, such as being mounted by another rodent or the touch of the researcher's hand. The lordosis posture allows a mounting male to achieve successful intromission and subsequent ejaculation. A complete description of the organization of the lordosis reflex was given by Pfaff[44] but is beyond the scope of this review. However, it is important to note that some of the structures integral to the organization of the lordosis reflex, such as the ventromedial nucleus, are anatomically[45,46] and neurochemically[44,47] sexually dimorphic. In rats, lordosis is displayed only by female rats or by genetic males that were castrated perinatally, and is strictly dependent on gonadal hormones. In fact, lordosis can be activated in the female rat by intracranial implantation of estrogen into the ventromedial nucleus.[48,49]

During the rat estrous cycle, the ovarian hormones, estrogen and progesterone, act in concert to coordinate female sexual behavior with ovulation. Twenty-four hours before ovulation, a rise in plasma estrogen levels induces an increase in both plasma progesterone and luteinizing hormone (LH) levels,[50] which occurs several hours before the appearance of reproductive behavior and ovulation. Progesterone initially activates proceptive behaviors, such as soliciting and ear wiggling, which are thought to alert the male to the presence of a sexually receptive female in the environment.[51-53] Progesterone also facilitates sexual receptivity, as measured by the frequency and quality of the lordosis posture.[54,55] Ovulation follows, and reproductive behavior disappears several hours later. The activation of lordosis in the female rat is paralleled by an increase in the synthesis of progestin receptors in the hypothalamus.[47,56] Thus, estrogen-induced progestin receptors in the brain may serve to tie sexual receptivity with the fertile period of the estrous cycle.

Mounting.—In rodents, the ability of the brain to support male-typical reproductive behavior requires exposure to androgens or their metabolites in early development. For example, mounting, the most easily studied male mating behavior, is displayed with increased frequency in female rats that were exposed to androgens in early development.[5,38] Mounting can be activated by implanting androgens into the preoptic and anterior portions of the hypothalamus of castrated male rats, while, conversely, mounting can be abolished by lesions in this region.[57,58] Although a prominent sexually dimorphic nucleus has been described in this region, lesion studies have failed to demonstrate that it participates in the regulation of any sexually dimorphic function.[59]

Limits of Extrapolation.—The problems inherent in extrapolating from mating behaviors and postures in rodents to psychological processes in humans are complex. Nevertheless, procedures that increase lordosis in male rodents are sometimes viewed as models for the origins of homosexuality in men, while procedures that increase mounting behavior in female rodents are viewed as potential models for the origins of homosexuality in women.[15,60-62(pp139-140)] In these laboratory situations, the neonatally castrated male rat displaying lordosis when mounted by another male is considered the homosexual. It is important to note that the animal that initiated the contact—the mounter—is considered the heterosexual and escapes scientific scrutiny and labeling, as does the female that displays lordosis when mounted by another female.

If we apply such reasoning to our own species, then we would be forced to conclude that there is only one homosexual when two individuals of the same sex are engaged in sexual intercourse and that the homosexual individual is obvious from the position he or she assumes. Thus, in these rodent models, "homosexuality" is defined by the particular behavior displayed and not the sex of the partner, whereas in humans, sexual orientation is defined on the basis of sexual fantasies and the sex of the preferred sex partner. Furthermore, homosexual activity in humans is thought to be a motivated behavior, whereas the best studied rodent model of homosexual behavior in men—lordosis—is hardly more than a reflex exhibited in response to appropriate tactile stimulation, whether it be delivered by another rat or by a nonsexual stimulus, such as the touch of the researcher's hand.

Proceptive behaviors, which have been less well studied than the lordosis response, appear to be less reflexlike and, in this regard, superficially appear more similar to sexually motivated behaviors in humans.[51-53,63] However, the expression of proceptive as well as receptive sexual behaviors in rodents is under rigid neuroendocrine control.[54,55] In fact, the appearance of proceptive behaviors is preceded by the appearance of progestin receptors in the nuclei of hypothalamic cells,[54,56] and both proceptive behaviors and the lordosis reflex can be blocked by inhibiting postreceptor mechanisms.[47,54,56] Motivated sexual behaviors in humans are unlikely to be under such rigid endocrine control. Thus, the suitability of proceptive behavior in rodents as a model for motivated sexual behavior in humans is questionable. Furthermore, the rodent model equates androphilia in homosexual men with androphilia in heterosexual women, and, similarly, gynephilia in homosexual women is equated with gynephilia in heterosexual men. The validity of these equations regarding the motivational aspects of partner selection have not been adequately addressed.

A final but salient objection to the prenatal hormonal hypothesis of human sexual orientation must be addressed. One of the most striking aspects of the organization of reproductive behaviors in rodents is the stereotypic nature of proceptive behaviors, the lordosis reflex, and the mounting response. In fact, while other factors are undoubtedly involved, the frequency with which a female rat displays lordosis in response to a male is correlated with the level of estrogen-induced progestin receptors[47,54,56] in her hypothalamus. It is difficult to imagine that the gamut and plasticity of human sexual behavior can be reduced to factors as simple as this. One striking finding of the work of Kinsey et al[64] was the continuum of the human sexual response, which can even involve a dissociation between sexual fantasy and behavior. Individuals who engage exclusively in heterosexual behavior may differ considerably in the homosexual content of their sexual fantasies. Thus, what is supposedly organized by prenatal hormonal exposure—thoughts and fantasies and/or manifest behaviors? Furthermore, how does the prenatal hormonal theory of homosexuality allow us to understand the plasticity and complexity of the human sexual response, including changes in erotic imagery and preferred modes of sexual expression over time?

Prenatal Hormonal Status and Sexual Orientation

As suggested by Meyer-Bahlburg,[12] if the prenatal hormonal hypothesis is correct, then one might expect to find homosexuality in a large proportion of males with syndromes involv-

ing prenatal androgen deficiency or insensitivity, and also in females with syndromes involving androgen excess. However, extensive reviews of the literature suggest that this is not the case.[12,65] However, some of these studies have been interpreted as providing evidence consistent with the prenatal hormonal hypothesis.[4,5(p79),66]

Androgen Insensitivity.—A number of syndromes have been described in which target cells are unable to respond fully to normal or even elevated levels of androgens. This insensitivity, which may be partial or complete, may result from either a deficiency of androgen receptors[67] or a defect in other intracellular mechanisms.[68] Some authors have speculated that 40% of men referred for evaluation of infertility secondary to low sperm counts have some degree of androgen insensitivity.[69] In the absence of studies showing an increased incidence of homosexuality in men with partial androgen insensitivity, these syndromes do not at present provide evidence in favor of the prenatal hormonal hypothesis.

A more complete form of androgen insensitivity is sometimes referred to as the syndrome of testicular feminization (Tfm).[4,5,39(p286)] In this sex-linked condition, the testes are normal but there is a congenital reduction of androgen receptors. Although affected individuals are genetically male and have abdominal testes, they have normal-appearing female external genitalia and are reared as girls.[70(p203)] In the absence of androgen receptors, breast development and female fat distribution occur at puberty in response to estrogen of testicular origin. Unless the testes become prominent within the labia, they are usually left in place until after puberty so that secondary sex characteristics can develop without the need for hormonal replacement therapy.[70] Often these individuals do not come to medical attention until after puberty, when they present with complaints of amenorrhea and infertility.[70]

Because humans with Tfm are not deficient in their levels of androgens, aromatase enzymes, or estrogen receptors,[5,68] one would predict, on the basis of the rat model, that they would have defeminized and at least partially masculinized brains. However, psychosexual assessments of these individuals suggest that they are indistinguishable from heterosexual genetic females in terms of sexual arousal and erotic imagery.[61]

Some authors have conjectured that the "complete absence of masculine tendencies" in these individuals "suggests a primary role for androgen receptors in human brain sexual differentiation."[5(p79)] These authors fail even to address the possibility that the absence of "masculine tendencies" might have resulted from the individuals' female appearance and rearing. Rather than challenging the assumption that rodent and human brains are similarly sexually dimorphic, they suggest instead that the metabolic requirements of sexual differentiation differ between rodents and humans, with the aromatization pathway playing a crucial role in the former but not the latter. Some authors have even suggested that because individuals with Tfm have a male genetic constitution, they can technically be considered homosexuals.[4(p215)] Because individuals with Tfm are reared as females, this syndrome clearly cannot provide unequivocal evidence favoring a major role of hormones in the development of psychosexual orientation.

5-α-Reductase Deficiency.—This disorder leads to a profound deficiency of the hormone dihydrotestosterone. Human males with this deficiency are born with severe genital ambiguity and are sometimes assumed to be female. However, if the condition is untreated, masculinization occurs at puberty: the voice deepens, the phallus enlarges, the testes descend into the unfused labialike scrotum, and a muscular habitus develops.[71-73] Imperato-McGinley and collaborators[71,72] studied a familial form of this disorder in the Dominican Republic. In their initial article, they reported that the affected individuals had been raised as girls, yet after their somatic masculinization at puberty, they assumed a male gender role and erotic interest in women. It soon became doubtful, however, that the affected individuals had been raised unambiguously as girls, since most of them came from interrelated families.

In a follow-up study, Imperato-McGinley and her collaborators[72] studied a cohort of 33 affected individuals, 18 of whom seemed to have been raised unambiguously as girls. Of these, 16 assumed a male gender identity and male gender role during or after puberty. The authors concluded that the sex of rearing was not nearly as important as particular hormonal events. However, Benderly[73(p23)] speculated that the outcome with regard to affected individuals in the Dominican Republic may be due to the low status their society affords to women. Consistent with this interpretation are case studies showing that, outside the Dominican Republic, most individuals with this syndrome choose to live as females.[74] One plausible explanation for this discrepancy is that the disorder occurs sporadically outside the Dominican Republic and the affected individuals are thus more likely to be raised unambiguously as girls. However, Imperato-McGinley et al suggested that the discrepancy in outcome may be because affected individuals in the Dominican Republic are left gonadally intact, whereas elsewhere they are generally gonadectomized before puberty. That is, they suggest that in addition to prenatal androgen exposure, androgen exposure at the time of puberty may be important for the evolution of male gender identity.[72]

Hormonally Treated Pregnancies.—Beginning in the 1940s, synthetic progestogens were administered to women to prevent miscarriage.[19,75] Progesterone-related progestogens may have androgenic or antiandrogenic properties, depending on their chemical formulas. As reviewed by Ehrhardt and Meyer-Bahlburg,[76] three studies of the offspring of treated pregnancies had been published before 1981. One showed decreased physical activity in boys and decreased "tomboyism" in girls; one found no significant effect; and the third detected no effect in boys, but decreased activity and increased feminine interests in girls. All three studies suffered from inadequate control groups. The overall impression from these and more recent studies[77,78] is that the data do not preclude the possibility that progesterone-related compounds have a demasculinizing effect on the developing human brain; however, there are no solid data to suggest that these hormones affect future sexual orientation.[37,76-78]

Prenatal exposure to the very potent estrogenic progestogen diethylstilbestrol has not been found to influence sexual orientation in men.[37,79,80] Because this compound inhibits androgen synthesis by the testes, exposed men might be expected to have been exposed to lower than normal levels of testosterone during development. Two studies have found no effect of diethylstilbestrol exposure on the future sexual orientation of women.[79,81] A third study found an increased incidence (25%) of bisexuality and homosexuality in exposed female subjects.[77] The notion that increased estrogen exposure would increase homosexuality in women is at odds with what is known about sexual development in the syndrome of Tfm. As discussed above, the latter syndrome suggests that if sexual differentiation of the human brain occurs at all, masculinization and defeminization of sexual behavior and orientation are not mediated by estrogen (ie, they appear to be independent of the aromatase pathway).

Congenital Virilizing Adrenal Hyperplasia.—Exposure of females to virilizing hormones also occurs in a genetically recessive condition called congenital virilizing adrenal hyperplasia.[61] Reviewing the studies of congenitally virilized girls in 1980, Ehrhardt (as cited by Goy and McEwen)[5(p89)] concluded, "the outcome of prenatal virilization . . . is not homosexuality." Subsequently, evidence has been provided for an increased incidence of homosexuality in women with congenital virilizing adrenal hyperplasia.[61] While the authors concluded that this was due to masculinization of the brain, little attention was given to the impact of having been born with masculinized genitalia or the subject's knowledge that she had been prenatally virilized. Of the 30 subjects with congenital virilizing adrenal hyperplasia, 21 had had corrective surgery up to age 3 years and one at age 9 years. In another study, the authors did recognize the importance of socialization, but only to the extent that it may overcome a biologic predisposition. In fact, they suggested that the majority of prenatally virilized women develop heterosexual interests because "society limits the full expression of their biological predisposi-

Table 1.—Somatic and Brain Sexual Differentiation in Rodents and Humans

Event	Days (Approximate)		
	Rat	Guinea Pig	Human
Conception	0	0	0
Fetal testis becomes active	16[5]	25[5]	63[70]
Genital differentiation	16-20[5]	25-40[5]	77-112[70]
Hormone receptors in brain	18[5,86]	28[35]*	After 140[87]†
Behavioral defeminization	20-25[5]	33-37[5]	May not occur[38]
Defeminization of estrogen feedback‡	20-25[5]	33-37[5]	Probably does not occur
Behavioral masculinization‡	18-25[5]	28-37[5]	Conflicting interpretations[76,82,83]
Hypothalamic anatomy	18-28[88]	28-37[85]	Conflicting data§
Birth	22-23	63-68	270-280

*Presence of receptors inferred from ability of hormones to influence anatomy at this time.
†Single uncorroborated report.
‡Stated period refers to the period of maximal sensitivity to the organizational effects of androgens. In the guinea pig, similar effects on endocrine function and behavior can be achieved with testosterone administered on gestational days 38 to 65.[85]
§Data and references summarized in text.

tion toward lesbianism."[66] The existence of such a predisposition is purely speculative. Furthermore, it would not be possible to demonstrate the existence of such a predisposition in heterosexual women. The studies of women who were exposed prenatally to virilizing hormones have been thoroughly reviewed and critiqued by Bleier[82] and Fausto-Sterling.[83] Perhaps an equally plausible alternative is the speculation by Bleier that the adaptations of congenitally virilized women grow out of an ambiguous situation: having boylike genitalia and being told you are a girl. "Gender must seem a fragile and arbitrary construct if it depends upon plastic surgery."[82(p101)]

Postnatal Correlates of Early Hormonal Exposure

Another strategy in trying to establish a link between prenatal hormonal exposure and sexual orientation has been to examine presumed correlates of such exposure in known homosexual and heterosexual individuals. The most obvious correlates would be hypogonadism and ambiguous genitalia, since in laboratory animals there is a close temporal association between the onset of fetal gonadal activity and sexual differentiation of both the brain and genital structures[5,84] (Table 1).[85-88] Thus, in laboratory species for which data are available, exposure to aromatizable androgens during the period of genital sexual differentiation is usually accompanied by some degree of behavioral masculinization.[5] Although castration of male rats after the completion of genital differentiation may result in normal female levels of lordosis responding, they nevertheless exhibit high levels of mounting behavior.[5] Thus, the existence of exclusive homosexuality in men with normal genitalia is difficult to reconcile in terms of animal models. In the absence of evidence that anomalies of gonadal function or genital differentiation are more common in homosexuals than in heterosexuals, researchers have looked elsewhere for correlates of prenatal androgen exposure. Rodent studies have suggested two possible correlates as alternatives: (1) the positive feedback of estrogen on LH release and (2) neuroanatomic sexual dimorphisms.

Hormonal Feedback Mechanisms

After an extensive review of the literature in 1984, Meyer-Bahlburg[12] concluded that studies on hormonal feedback mechanisms provided the strongest evidence in support of a biologic basis for sexual orientation. The rationale for investigating hormonal feedback as a possible correlate of sexual orientation was derived by extrapolating from rodent studies of hypothalamic organization. In adult female rodents, estrogen acts on the hypothalamus where it exerts both negative and positive feedback on the release of LH.[89] Immature follicles secrete low levels of estrogen, which act on the medial basal hypothalamus to inhibit LH release (negative feedback). In contrast, mature follicles secrete high levels of estrogen, which act on the preoptic hypothalamus to initiate a surge of LH release (positive feedback) that triggers ovulation. In normal adult male rodents, estrogen exerts only negative feedback on LH release. In rats, estrogen administration will elicit an LH surge from normal adult females and adult males that were castrated at birth, but not from females that were treated with aromatizable androgens perinatally or males that were castrated as adults (Table 2). Thus, the concept emerged that, in addition to the organizational effects of androgens on reproductive behavioral repertories, androgens have an organizing action on the developing brain, abolishing the ability of estrogen to exert positive feedback on LH release.[89,90] Some have assumed that if male homosexuality is associated with a deficiency of prenatal androgenization, then homosexual men should show a stronger positive feedback effect than heterosexual men do.[4,12,17,91] Two groups have claimed that this is indeed the case.[17,91]

The studies making these claims have a number of flaws, some of which have been discussed elsewhere.[37] Most troubling is the authors' failure to cite any data pertaining to the brain's regulation of LH release in primates. Instead, they implicitly assumed that this mechanism displays the same sexual difference in humans as in rats. The primate hypothalamus, however, may not be sexually dimorphic with respect to its role in LH secretion (Table 2). Evidence of the lack of sexual dimorphism includes the following observations: (1) human[92] and rhesus monkey[5,93] females exposed to high levels of androgens prenatally and born with masculinized genitalia have cycles; (2) while ovarian tissue fails to cycle when transplanted into male rats castrated as adults,[89] it continues to cycle when transplanted into male monkeys castrated as adults[94]; (3) laboratory evidence suggests that estrogen exerts positive feedback on LH secretion in male primates, including marmosets,[95] rhesus monkeys,[93] and humans[96-99]; and (4) clinical research evidence suggests that the positive feedback mechanism matures during adolescence in human males as well as females.[98]

If there is no neurologic sex difference in the feedback mechanism in humans, then one would not expect (even from a culture-bound perspective) homosexual men to exhibit feminized feedback responses. Thus, it is not surprising that other studies have failed to demonstrate a correlation between sexual orientation and the magnitude of the feedback effect of estrogen.[96,97,99] The most convincing of these studies were carried out by Gooren.[96,97] First, he tested the feedback effects of estrogen on LH release in male and female transsexuals before any hormonal therapy or sex reassignment surgery, and in heterosexual male and female controls. The transsexuals showed exactly the same

Table 2.—Ability of Brain to Mediate Positive Feedback of Estrogen and Regulate Ovarian Cyclicity*

Species and Sex	Treatment	Can Brain Regulate Ovarian Cyclicity?†
Rat		
F	None	Yes
F	Early androgen	No
M	None	No
M	Early castration	Yes
M	Adult castration	No
Monkey		
F	None	Yes
F	Early androgen	Yes
M	Early castration	Yes
M	Adult castration	Yes
Human		
F	None	Yes
F	Early androgen	Yes

*All references given in text.

†If the brain can mediate the ovarian cycle, it can also mediate the positive feedback effects of estrogen on luteinizing hormone release.

feedback responses as their genetic and gonadal sex control groups (ie, gonadally intact male-to-female transsexuals responded the same as heterosexual male controls). After sex reassignment surgery and hormonal therapy, however, male and female transsexuals demonstrated responses consistent with their newly assigned sex. Gooren concluded that the type of feedback response elicited is determined by the hormonal status of an individual at the time of the estrogen challenge rather than genetic sex or sexual orientation.[97]

If homosexual and heterosexual men do not differ in their hypothalamic organization, could the previously observed differences in LH responses to estrogen have resulted from differences in testicular function? As reviewed by Gooren,[37] that could be the case, since a number of factors affect testicular functioning, including aging, viral infections, and alcohol and other drug use. Gooren carefully matched homosexuals and heterosexuals for such variables and found no sexual orientation–associated differences. Unfortunately, the descriptions of subjects in the studies that report differences associated with sexual orientation have not been detailed enough to determine if such matching was adequate.

Ironically, as discussed by Gooren,[37] it is unlikely that any study has actually exhibited positive feedback in gonadally intact men. This is because testosterone would inhibit the positive feedback response. To demonstrate positive feedback unequivocally, it is necessary to test LH responses to the hypothalamic hormone gonadotropin releasing hormone. In the case of positive feedback, the LH response to gonadotropin-releasing hormone would be greater after exposure to estrogen than before.[100] When this test was given to homosexual and heterosexual subjects who had LH responses to estrogen that resembled positive feedback, it was found in every case that the LH responses to gonadotropin-releasing hormone decreased after estrogen exposure, suggesting that true positive feedback responses cannot be elicited in gonadally intact men.[97]

In summary, compelling evidence suggests that the hypothalamus of primates, including humans, is not sexually dimorphic with respect to the potential to regulate the feedback effects of estrogen on LH release. Thus, reports of sexual orientation–associated differences in the LH response to estrogen possibly reflect experimental artifacts or differences in testicular function rather than brain differences. The studies of Gooren,[96,97] in which subjects were carefully matched for factors that might influence testicular function, did not detect differences in the feedback mechanism associated with sexual orientation.

Neuroantomic Studies

Animal Studies.—During the past decade and a half, neuroanatomic sexual dimorphisms of various types have been described in the medial preoptic–anterior hypothalamic region of several laboratory rodents.[101] The significance of these findings lies in the fact that this area participates in the regulation of a number of behavioral and neuroendocrinologic functions that, in rodents, undergo sexual differentiation in response to sex differences in exposure to androgens or their metabolites in early development. The neuroanatomic sex differences in rodents are, therefore, thought to be the signature of the organizational action of androgens on sexually differentiated brain functions.

The initial reports of sex differences involved the fine structure of the rodent brain. Electron microscopic studies revealed sex differences in the synaptic organization of a portion of the preoptic area of the rat.[102] Golgi-stained material revealed sex differences in dendritic branching patterns in the preoptic area of the hamster[103] and rat,[104] while electrophysiologic studies in the rat suggested sex differences in the convergence of synaptic inputs to the preoptic area and anterior hypothalamus.[105]

The best-studied anatomic sex difference in the rodent hypothalamus involves a cell group that was first described by Gorski and his collaborators[106] in the rat, where it is five to eight times larger in males than in females. Gorski et al designated this cell group the "sexually dimorphic nucleus of the preoptic area" (SDN-POA). Shortly after the initial description of the SDN-POA, Bleier et al[101] examined the hypothalamus of several rodent species and discovered that the SDN-POA is only one component of an extensive complex of sexually dimorphic nuclei extending from the lamina terminalis to the bed nucleus of the stria terminalis. The most rostrally placed sexually dimorphic nucleus is the anteroventral periventricular nucleus (also known by several other names[85]), which is larger in females than in males in all species examined, including guinea pigs, rats, hamsters, mice, and voles.[85,101,107,108] This nucleus is thought to regulate the positive feedback effects of estrogen on LH secretion,[85] a function that is sexually dimorphic in rodents but unlikely to be so in primates.[93-97,99] Thus, researchers have not sought to demonstrate a comparable sex difference in this nucleus in humans.

Human Studies.—*Hypothalamus.*—Speculation that the SDN-POA may be involved in the regulation of reproductive behavior in male rats has stimulated considerable interest, and some authors have conjectured about the existence of a comparable nucleus in humans.[11,109,110] (Interestingly, anatomists have been unable to demonstrate an SDN-POA in mice.[101,111]) In 1984, Swaab and Fliers[109] presented evidence that a cell group in the human anterior hypothalamus is larger in men than in women. On the basis of its location and purported sexual dimorphism, they suggested that this cell group (which had been previously described as the intermediate nucleus[112]) is comparable with the SDN-POA in the rat, and they redesignated it as the sexually dimorphic nucleus. They subsequently provided evidence that the dimorphism develops postnatally after the age of 4 years and that its size does not vary with sexual orientation.[113]

Two subsequent studies in other laboratories have failed to find a sex difference in the size of this nucleus.[11,110] Each of these studies, however, described three nuclei that were designated as interstitial nuclei 2 through 4 of the anterior hypothalamus (INAH2, etc). The nucleus formerly called the intermediate nucleus was redesignated as the first interstitial nucleus (INAH1). The initial study suggested that INAH2 and INAH3 are sexually dimorphic,[110] while the second study found only INAH3 to be dimorphic.[11]

The second study, which was the highly publicized study carried out by LeVay[11] at the Salk Institute, La Jolla, Calif, provided evidence that the size of INAH3 also may vary with sexual orientation, being as small in homosexual men as in heterosexual women. On the assumptions that (1) INAH3 is comparable with the rat's SDN-POA and (2) the lordosis posture in male rats is comparable with homosexual orientation in men, LeVay conjectured that INAH3 would be small in individuals who were sex-

ually attracted to men.[11] In support of this speculation, he cited work showing that in male rats the size of the SDN-POA correlates positively with the frequency of mounting behavior displayed, and that lesions in the region of the SDN-POA disrupt mounting behavior. However, lesions restricted to the SDN-POA do not impair mounting or any other sexually dimorphic mating behavior or endocrinologic function.[59] The effective lesion site within the anterior hypothalamus for disrupting mounting behavior lies above, not within, the SDN-POA.[59] Thus, the SDN-POA does not play a critical role in male-typical behavior in male rats, and the correlation between its size and mounting frequencies clearly does not reflect a causal relationship. While the possible role of the INAH3 in sexual orientation in humans is ultimately a question independent of its homology with the SDN-POA in rats, evidence derived from studies of the SDN-POA do not be used to support the notion that the INAH3 is crucial to the "generation of male-typical sexual behavior."[11]

LeVay's study can be faulted for a number of technical flaws, such as a variable method of tissue fixation, inadequate sexual histories, and small sample sizes (19 homosexual men, all of whom died of acquired immunodeficiency syndrome [AIDS]; 16 presumed heterosexual men of unknown sexual history, six of whom died of AIDS; and six women presumed to have been heterosexual). Although it is unlikely that variations in fixation could account for a selective reduction in the volume of INAH3 in the homosexual men, one can hypothesize a plausible mechanism by which human immunodeficiency virus infection could do this. This is because significant reductions of testosterone levels have been documented in end-stage human immunodeficiency virus infection,[114] and in some mammals, the volume of a cell group presumed to be comparable with INAH3 is dependent on adulthood testosterone levels.[115] To account for the fact that the heterosexual men with AIDS had larger nuclei than the homosexual men with AIDS, one could propose that the heterosexual men had a different disease course or died at an earlier stage of infection than did the homosexual men. This does not seem unlikely, because the major AIDS risk factor for heterosexual men in the United States is intravenous drug abuse, and compared with such men homosexuals tend to have superior health care. Alternatively, a differential incidence of AIDS-related opportunistic fungal infections between the homosexual and heterosexual subjects might have influenced the results, as some antifungal agents decrease testosterone levels when administered systemically.[114] Unfortunately, the medical histories available in the LeVay study are not adequate to test this hypothesis.

There has also been a report that the size of another hypothalamic nucleus, the suprachiasmatic nucleus (SCN), varies with respect to sexual orientation in men.[116] Specifically, evidence has been presented that the SCN is larger in homosexual than heterosexual men. Again, however, this study has not been corroborated, and few studies of this sort have proved to be replicable in the past. But even if corroborated, this finding would not support the prenatal hormonal hypothesis, because in humans the size of the SCN does not vary with sex.[116] Furthermore, existing evidence does not suggest a primary role for the SCN in the regulation of sexual behaviors. The SCN does, however, participate in regulating the temporal patterns of hormonal secretion, which in turn modulate the expression of particular reproductive behaviors in laboratory rodents.[117]

The positioning of cells within the hypothalamus (ie, formation of nuclei) is only part of the process of hypothalamic sexual differentiation.[102-105] For example, in the guinea pig[84] the sexually dimorphic nuclei are the only hypothalamic cell groups in which neurogenesis continues after the onset of fetal gonadal activity. Gonadal steroids may, therefore, influence many developmental processes in sexually dimorphic regions, including neurogenesis, cell migration, synaptogenesis, and selective cell death. Furthermore, the administration of androgens to female guinea pig fetuses can masculinize behavioral and endocrinologic functions of the hypothalamus after cytoarchitectonic patterns (ie, positioning of cells) have been determined.[85] More simply put, one can experimentally produce genetic female animals that behave as males despite having female-typical hypothalamic cytoarchitecture. Subsequent organizational effects might involve neuronal connectivity or hormonal receptor mechanisms. Thus, even if sexual orientation in humans were prenatally determined by hormones, one would not necessarily expect a simple relationship between hypothalamic cytoarchitecture and sexual orientation.

Brain Commissures.—In addition to the hypothalamus, researchers have begun to examine the commissures of the human brain for possible sex and sexual orientation dimorphisms. These studies and their rationale are discussed more fully elsewhere.[14] Briefly, a recent report by Allen and Gorski[118] provides evidence that the anterior commissure (A) is larger in women and homosexual men than in heterosexual men. This study requires replication as the only other laboratory to examine the AC for sex differences found a tendency for it to be larger in men than in women ($P<.05$).[119] Even if the recent study by Allen and Gorski proves replicable, the size of the AC alone would tell us nothing about an individual's sexual orientation because the overlap of AC size between homosexual and heterosexual men was tremendous (ie, the size of the AC of 27 of 30 homosexual men fell within the range established by 30 heterosexual men). Because these authors relied heavily on the brains of subjects with acquired immunodeficiency syndrome and provide little clinical history, their study is subject to many of the same interpretive difficulties as LeVay's study of the hypothalmus.

There has also been recent speculation that the morphology of the corpus callosum may be found to be female-typical in homosexual men (LeVay. *New York Times.* October 7, 1991:letter). Such speculation is premature as the 23 studies that have sought sexual dimorphism in the corpus callosum have yielded conflicting results. Although the initial study based on a postmorten analysis of nine male and five female brains concluded that the splenium of the corpus callosum is larger ($P=.08$) and more bulbous in women than in men,[13] none of the 22 subsequent studies replicated the sex difference in splenial size.[14] Furthermore, while some researchers did replicate the finding of a more bulbous splenium in women, others found it more bulbous in men and still others found no sex difference.[14] As described by Byne,[14] some of the negative studies have been unfortunately misinterpreted as successful replications. Even if the prenatal hormonal hypothesis of sexual orientation was correct, in the absence of unequivocal evidence for sexual dimorphism in the corpus callosum there would be little rationale for hypothesizing that callosal morphology should be characteristic of the opposite sex in homosexuals.

In summary, three as yet uncorroborated reports suggest that the size of three different brain structures may vary with sexual orientation in men. These reports must be viewed cautiously while replication studies are pending.

WHY LOOK TO BIOLOGY?

Four lines of reasoning are prominent in the literature that attempts to delineate biologic factors contributing to sexual orientation. First, it has been suggested that despite the position of humans in the animal kingdom, they are nevertheless mammals. According to Meyer-Bahlburg,[12] "throughout the mammalian class there appear to be marked similarities in the anatomical structures of the genitals as well as of sex-behavior-related brain regions and in the role of sex hormones in the differentiation and development of these structures." He suggested that it is "unlikely that such brain regions as the preoptic area and ventromedial nucleus in humans should differ fundamentally from those in subhuman mammals."[12(p390)] There are, however, marked differences in hypothalamic anatomy[101] and in the localization of functions[85] within the hypothalamus even among rodents. For example, intact connections between the preoptic and medial basal regions of the hypothalamus are necessary for the positive feedback effects of estrogen in rats, but not in guinea pigs or primates.[120]

Furthermore, it is not clear that the concept of sexual orientation is applicable to animals, and as noted previously, reproductive postures and behaviors in animals are poor models of sexual orientation in humans.

Second, some seem to suggest that the most reliable predictor of adult sexual orientation, childhood gender nonconformity, appears so early in development that it must be inborn.[4,121] For instance, Bell et al[4] conjectured that "the familial factors commonly thought to account for homosexuality may themselves be the result of a prehomosexual son or daughter being 'different' to begin with." In their study, homosexual men were more likely than heterosexual men to have displayed some degree of gender nonconformity in childhood, as measured by the following: a fear of injury in childhood (75% vs 46%), avoidance of physical fights (89% vs 55%), avoidance of baseball (84% vs 38%), or a preference for girls as playmates (33% vs 10%). As reviewed by Friedman,[3] more than a dozen other studies have also found some degree of childhood gender nonconformity associated with the emergence of homosexual orientation in men. However, to conclude that childhood gender nonconformity is inborn ignores the fact that boys and girls are differentially socialized from the moment of birth.[122(p32-34)] Convincing evidence suggests that gender identity is established by the age of 3 years largely in response to social factors (sex assignment and rearing).[76] The concept of gender constancy is acquired somewhat later and appears to influence whether a child models its behavior after males or females.[122,123] Therefore, it is not unreasonable to consider the possibility that the degree of gender conformity may largely reflect social factors.

A third line of evidence is the resistance of sexual orientation to change.[4(p217),12(p380)] Resistance to change, however, does not imply that a behavioral phenomenon is innate. Vocal learning in bullfinches serves as an illustrative example. These birds can only learn their native call during a restricted period of brain development. If they are allowed to hear only the call of another species during that period, they will learn it instead.[124] While the bird's call seems to be "hard wired" into its brain, it is clearly learned by experience and not innate. That is, the bird's song is determined by experience, whereas biology defines the crucial period during which that experience must occur. This example is not meant to imply that sexual orientation in humans is learned by simple mimicry. Instead, it seems reasonable to suggest that the stage for future sexual orientation may be set by experiences during early development, perhaps the first 4 years of life. This is not only the period during which gender identity is established,[76] but also a period of tremendous brain development.[82(pp64-68)] In fact, the human brain quadruples in size after birth, and the major expansion of its synaptic network occurs during the first 2 years after birth.[82]

A fourth line of reasoning is that "biological theories enjoy widespread acceptance" by behavioral scientists "dissatisfied with the status of psychosocial explanations."[12(p380)] For example, the path analysis model of Bell et al[4] accounted for only 23% of the variance in childhood gender nonconformity in men. The fact that 77% of the variance was not correlated with the social factors included in the model may reflect the simple nature of the included social variables (ie, strong mother, weak father) rather than a primary role for biologic factors. The inadequacies of present psychosocial explanations do not justify turning to biology by default—especially when, at present, the biologic alternatives seem to have no greater explanatory value. In fact, the current trend may be to underrate the explanatory power of extant psychosocial models. For example, as reviewed by Van Den Aardweg,[125] the literature suggests that many, perhaps a majority, of homosexual men report family constellations similar to those suggested by Bieber et al[126] to be causally associated with the development of homosexuality (eg, overly involved, anxiously overcontrolling mothers, poor father-son relationships). This association has been observed in nonclinical as well as clinical samples.[3,4]

Finally, political arguments have been offered in favor of biologic causation.[4] It has been suggested that if sexual orientation is largely a biologic phenomenon, "society would do well to reexamine its expectations of those who cannot conform"[4(p219)]; and, writing in the "Opinions and Editorials" pages of the *New York Times* (December 17, 1991:19), Bailey and Pillard stated: "If true, a biological explanation is good news for homosexuals and their advocates." However, political arguments have no impact on biologic realities, including the extent of genetic or hormonal influences on the emergence of sexual orientation. Furthermore, one might question if an innate inability to conform is a humane criterion by which society should decide which of its nonconformists will be granted tolerance. Surely, tolerance granted on such a basis would fall short of genuine social acceptance. Furthermore, history suggests that it is unrealistic to expect any protections to be conferred on the basis of alleged biologic causality. For example, the undisputed innateness of skin color does not appear to have a mitigating influence on racism. Moreover, within the biologically deterministic literature, theories pertaining to homosexuality are almost invariably expressed in pejorative terms, such as hormonal "deficiency," "failure," "abnormality," "defect," or "aberration."[5(p72),16(p317),127(p223)] The danger here lies in the fact that states perceived as undesirable and of biologic origin have traditionally been assigned to the medical domain. In the past, physicians have attempted to "cure" homosexuality not only with psychoanalysis and aversion therapies but also with hormones, neurotropic drugs, and brain surgery.[128-130(pp129-208)] More recently there has been discussion of amniocentesis to detect potentially correctable androgen deficiencies in male fetuses to prevent homosexuality.[5(p71)] It is imperative that clinicians and behavioral scientists begin to appreciate the complexities of sexual orientation and resist the urge to search for simplistic explanations, either psychosocial or biologic.

AN INTERACTIONIST MODEL

Conspicuously absent from most theorizing on the origins of sexual orientation is an active role of the individual in constructing his or her identity. For example, Bailey and Pillard[30] suggested that their twin data "are consistent with heritable variation in prenatal brain development" or "in some aspect of physical appearance which, by way of differential parental treatment, leads to differences in sexual orientation." According to these schemes, the individual is passive and sexual orientation is thrust upon him or her either by constitution or by parental treatment. While most authors have recognized the possible importance of both biologic and experiential factors,[3,12] too little attention has been given to the manner in which these factors may interact. We propose an interactional model in which genes or hormones do not specify sexual orientation per se, but in-

stead bias particular personality traits and thereby influence the manner in which an individual and his or her environment interact as sexual orientation and other personality characteristics unfold developmentally. Such a mechanism would allow for multiple developmental pathways leading to homosexuality and would account for the high concordance rate for homosexuality among identical twins reared together,[30] as well as for the failures of various psychosocial theories that have focused exclusively either on personality traits of individuals or on various environmental factors, but not on the interaction of the two.[4]

Consider the following hypothetical scenario, similar to that posed by Stoller and Herdt.[131] Two boys had absent fathers and overly protective mothers who disparaged sports. One of these boys enthusiastically participated in baseball and developed a heterosexual erotic orientation, while the other shunned baseball and developed a homosexual orientation. This scenario (which is not intended to perpetuate cultural stereotypes) illustrates the failure of simple explanations in which parenting styles determine sexual orientation. However, would the explanation be so simple as that the prehomosexual boy had a feminized brain (ie, small INAH3) as the result of a prenatal androgen deficiency that may have been genetically programmed?

Research into the heritability of personality variants suggests that some personality dimensions may be heritable, including novelty seeking, harm avoidance, and reward dependence.[132] Applying these dimensions to the above scenario, one might predict that a boy who was high in novelty seeking, but low in harm avoidance and reward dependence, would be likely to disregard his mother's discouragement of baseball. On the other hand, a boy who was low in novelty seeking, but high in harm avoidance and reward dependence, would be more likely to need the rewards of maternal approval, would be less likely to seek and encounter male role models outside the family, and would be more likely to avoid baseball for fear of being hurt. In the absence of encouragement from an accepting father or alternative male role model, such a boy would be likely to feel different from his male peers and as a consequence be subject to nonerotic experiences in childhood that may contribute to the subsequent emergence of homoerotic preferences. Such experiences could include those described by Friedman[3] as being common in prehomosexual boys, including low masculine self-regard, isolation, scapegoating, and rejection by male peers and older males, including the father.

While most studies suggest that a greater proportion of homosexual men than heterosexual men exhibited some degree of childhood gender nonconformity, they also indicate that a significant proportion of heterosexual men also exhibited such behavior, while a significant proportion of homosexual men did not.[3(pp33-48),4,125] Any model for the development of sexual orientation must be able to account for these exceptions. For the sake of the model, one could speculate that in the context of the average expectable environment, boys who were high in novelty seeking and low in reward dependence, in contrast to the above scenario, might be more likely to make choices culminating in a nonconformist life-style or identity. This is not meant to imply that one consciously decides one's sexual orientation. Instead, sexual orientation is assumed to be shaped and reshaped by a cascade of choices made in the context of changing circumstances in one's life and enormous social and cultural pressures.

The above model is clearly limited; however, it illustrates how genetic factors can be conceptualized as indirectly influencing the development of sexual orientation without supposing that they either directly influence or determine sexual orientation per se. Similarly, one could imagine that prenatal hormones influence particular personality dimensions or temperamental traits, which in turn influence the emergence of sexual orientation. In this regard, the model is similar to that proposed by Coates[133] for the ontogenesis of boyhood gender identity disorder. The validity of the model is not contingent on the validity of any particular set of proposed heritable personality traits. Instead, it rests on the validity of the assumptions that (1) some temperamental traits and personality dimensions influence the manner in which an individual's sexual orientation emerges and (2) at least some of these temperamental and personality factors are developmentally influenced by either hormones or heredity. As Lewontin et al[134] succinctly stated, in a world in which such complex developmental interactions are always occurring between an individual and his or her environment, "history becomes of paramount importance. Where and how an organism is now is not merely dependent upon its composition at this time but upon a past that imposes contingencies on the present and future interactions of its components."[134(p11)] In assuming that sexual orientation emerges from an interaction between the environment and personality characteristics of the individual, such as temperament, one must also assume that it is a higher-order psychological phenomenon. We view such processes as likely to be primarily cortical rather than primarily hypothalamic in nature and to reflect, like all mental functions, a complex mosaic of biologic, psychological, and social/cultural factors.

Since this review was accepted for publication, Bailey and his collaborators have completed a study suggesting that homosexuality is comparably heritable in men and women.[135] Thus King and McDonald,[31] cannot account for the discrepancies between their findings and those of Bailey and his collaborators.[30,135] While the probandwise concordance rates for female homosexuality in the recent study by Bailey et al[135] are consistent with a role of heritable factors (MZ twins [48%], DZ twins [16%], adoptive sisters [6%]), the study is subject to the same interpretative difficulties as the male study of Bailey and Pillard.[30]

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