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A Genetic Study of Male Sexual Orientation

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• Homosexual male probands with monozygotic cotwins, dizygotic cotwins, or adoptive brothers were recruited using homophile publications. Sexual orientation of relatives was assessed either by asking relatives directly, or when this was impossible, asking the probands. Of the relatives whose sexual orientation could be rated, 52% (29/56) of monozygotic cotwins, 22% (12/54) of dizygotic cotwins, and 11% (6/57) of adoptive brothers were homosexual. Heritabilities were substantial under a wide range of assumptions about the population base rate of homosexuality and ascertainment bias. However, the rate of homosexuality among nontwin biological siblings, as reported by probands, 9.2% (13/142), was significantly lower than would be predicted by a simple genetic hypothesis and other published reports. A proband's self-reported history of childhood gender nonconformity did not predict homosexuality in relatives in any of the three subsamples. Thus, childhood gender nonconformity does not appear to be an indicator of genetic loading for homosexuality. Cotwins from concordant monozygotic pairs were very similar for childhood gender nonconformity.

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During the past decade, there has been a resurgence of interest in biological explanations of sexual orientation.[1-4] This reflects several lines of scientific research, as well as sociological and historical factors.

First, several competitors to biological explanations have been tested and found wanting. The data testing the psychodynamic hypothesis that during childhood, male homosexuals tend to be distant from their fathers, show small effect size and are causally ambiguous.[5] Anthropologic observations reported by Stoller and Herdt[6] suggest that sexual orientation is not conditioned by sexual experiences in adolescence.

Second, a large literature on animal sexual behavior suggests that mating and other sex dimorphic behaviors are subject to the influence of sex steroid hormones acting on the brain during prenatal and early postnatal development. The sexual behavior of rodents can be altered by manipulating the testosterone level during sexual differentiation of the brain.[7,8] Prenatally androgenized female monkeys play in a manner more typical of the opposite sex,[9] as do human homosexuals in childhood.[5,10-12]

A "neurohormonal" theory of sexual orientation[1] has received direct support from at least four studies of humans. Ehrhardt et al[13] found that women who had been prenatally exposed to diethylstilbestrol, a synthetic estrogen that can exert androgenlike effects during brain differentiation, were more likely to report homosexual feelings than were unexposed controls. Similarly, Money et al[14] found that prenatally androgenized women had a higher incidence of homosexual feelings. Dörner et al[15] and Gladue et al[16] found that homosexual men showed a surge of luteinizing hormone in response to estradiol injections, intermediate to heterosexual women and men, which they interpreted as reflecting a partially female-differentiated brain in male homosexuals. Such research has led to the theory that human sexual orientation depends on variations in the degree of masculinization and behavioral defeminization of the brain that may occur during early periods of sexual differentiation.[17]

The neurohormonal theory of sexual orientation has received criticism on several grounds. For instance, the analogy between the feminized sexual behavior pattern of male rats deprived of testosterone and human homosexuals has been disputed.[18,19] The replicability and the interpretation of the luteinizing hormone findings have been questioned.[20-22] Nevertheless, to our knowledge, there is no current competing theory of sexual orientation that is equally well specified and influential.

A final factor that has increased interest in biological explanations of sexual orientation is the continuing tension between those who view homosexuality as an illness or a sign of moral weakness and those who see it simply as an alternative phenotype, without moral or pathological implications. It appears that one's etiological theory of homosexuality may contribute importantly to one's views on this larger issue. For instance, in American psychiatry, it has been those holding psychodynamic theories about the origin of homosexuality who have been most closely associated with the position that the homosexual is ill.[23] A 1970 survey found that 43% of Americans believed that frequently, "young homosexuals became that way because of older homosexuals."[24] Not surprisingly, that same survey found a high degree of intolerance toward homosexuals. A recent survey found that those who believed that homosexuals are "born that way" held significantly more positive attitudes toward homosexuals than

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subjects who believed that homosexuals "choose to be that way" and/or "learn to be that way."[25]

Given the general interest in and relevance of biological explanations of sexual orientation, it is somewhat surprising that very little work has been done in this realm from a behavior genetics perspective. The discipline of behavior genetics has helped illuminate individual differences in many other important psychological traits.[26-28] The dearth of such research is even more surprising given that several prior studies, though problematic, have each suggested that male sexual orientation has a substantial hereditary component. Unfortunately, almost all prior genetic research has focused exclusively on male homosexuality. Although we are in the process of a similar study of lesbian women, we restrict the remainder of our remarks to research on male homosexuality, as it is most pertinent to the study reported herein.

Pillard and Weinrich[29] demonstrated that male homosexuality is substantially familial. Brothers of male homosexuals were about four times more likely to be homosexual than were brothers of heterosexual controls, although this familiality could be due to genetic or shared environmental determinants.

In an early twin study of male homosexuality, Kallmann[30,31] reported a 100% concordance rate for 37 monozygotic (MZ) twin pairs compared with a 15% rate for 26 dizygotic (DZ) pairs. Kallmann's study has been criticized for methodological shortcomings, particularly the atypicality of the homosexual subjects, who were largely sampled from correctional and psychiatric institutions, the absence of an explanation of the zygosity diagnostic procedure, and its anomalous findings.[32] Results of several case studies and small twin series (reviewed by Pillard et al[33]) suggest that the true MZ concordance rate is substantially less than 100%, and probably nearer 50%. Largely because of this overestimation, Kallmann's results have been questioned.

More recent studies are also consistent with the possibility of a genetic influence on homosexuality. A report of two male MZ pairs from the Minnesota Study of Twins Reared Apart found one pair with similar homosexual orientations (Kinsey 6 and Kinsey 5) and the other of "problematic" classification (Kinsey 5 and Kinsey 2).[34] Buhrich et al[35] reported a twin study of sexual orientation and related behaviors using twins and multivariate model-fitting approaches. They found a strong familial resemblance, but had insufficient power to determine whether that correlation was due to genetic or environmental factors or both.

Given some evidence for genetic influence, there remains the question of what, exactly, is inherited. One possibility concerns childhood gender nonconformity (CGN),[10-12,36-38] which has been strongly linked to adult homosexuality. In childhood male homosexuals are frequently perceived as "sissies," and female homosexuals are frequently perceived as "tomboys." However, a substantial minority of male and female homosexuals deny a history of CGN. Bell et al[5(p200)] have suggested that homosexuals who were gender nonconforming as children may be more "constitutionally" homosexual than those who were more gender typical. A behavioral genetics translation of this hypothesis is that homosexuals with CGN should have a greater genetic loading, and hence should have a higher rate of homosexual relatives, or if twins, should be more likely to have homosexual cotwins.

The study reported below has two broad goals: first, to determine whether there is a genetic contribution to male sexual orientation; and second, to investigate the behavioral nature of this contribution. The study combines two methods from classical behavioral genetics: the twin method and the adoption method. Three groups of probands were recruited: male MZ twins, male DZ twins with same-sex cotwins, and male subjects with adoptively related brothers. We predicted that the rate of homosexuality would be higher for MZ than for DZ cotwins, and would be lowest for adoptive brothers of homosexual probands. We considered the degree to which ascertainment bias may have affected results. We then examined the possibility that CGN might be an indicator of genetic influence.

SUBJECTS AND METHOD

Subject Recruitment

Probands were recruited through advertisements placed in gay publications in several cities in the Midwest and Southwest. The ads specified that desired subjects were gay or bisexual men at least 18 years old with either (1) male cotwins or (2) adoptive or genetically unrelated brothers. The ads also stated the following: "We hope you will call regardless of the sexual orientation of your twin or adoptive brother." No mention was made of the possibility of the participation of cotwins or adoptive brothers. Potential subjects were instructed to call the laboratory, where they were asked clarifying questions. An additional criterion for the adoptive brother component was assessed at this point. Both probands and their adoptive brothers must have been no more than 2 years old when they entered the common rearing environment.

Subjects who met the inclusion criteria were scheduled for a 1- to 2-hour interview. The Family Studies Laboratory in Chicago, Ill, was the main interview site, but one of us (J.M.B.) traveled to several cities during the summer of 1990 to interview subjects. Subjects who lived within a reasonable distance of interview sites were interviewed in person. In a substantial number of cases (38%), a telephone interview was necessary. All interviews were conducted with informed consent. The session included questions concerning the proband's sexual orientation, siblings' sexual orientations (including twins and adoptive brothers), and CGN. After completion of the interview, each proband was asked for permission to contact his twin or adoptive brother. Probands inspected the questionnaire to be sent and were assured that the true nature of the study would not be divulged to the relatives.

The premise of the cover letter to relatives was that they were being asked to participate in a general behavior genetics study of personality, attitudes, and behavior. Five questions regarding sexual orientation were embedded within more than 100 other items about social attitudes, personality, and childhood behavior (including CGN items). Questionnaires were sent to consenting probands' twin or adoptive brothers. A follow-up reminder letter was sent 1 week later. If relatives had not responded within approximately 1 month, attempts were made to contact them by telephone. Efforts were halted to gain cooperation only if at least two mailings of the questionnaire were unsuccessful and (1) no telephone number was available for the relative, or (2) repeated telephone calls were unsuccessful, or (3) the relative was contacted and declined to participate.

Recruitment Results

This procedure resulted in 161 proband interviews: 115 probands with male twins and 46 probands with adoptive brothers. The group of twin probands included one triplet and both members of one twin pair, who called independently. Descriptive characteristics of the sample are included in Table 1. Probands ranged in age from 19 to 65 years, with a mean age of 33.2 years. The twins were somewhat older, on average, than the adoptive brothers (34.5 vs 29.9 years; $t=2.99$, $P<.01$).

Table 1.—Characteristics of Probands

	Twins (n=115)	Adoptive Brothers (n=46)	Combined (N=161)
Mean (±SD) age, y	34.5±6.4	29.9±6.3	33.2±9.1
Homosexual, No. (% of subsample)	111 (96.5)	39 (84.8)	**150** (93.0)
Bisexual, No. (% of subsample)	4 (3.5)	7 (15.2)	**11** (7.0)
Mean (±SD) Kinsey rating	5.4±0.88	5.3±0.87	5.4±0.87

Of the probands, 150 described themselves as "gay/homosexual," and 11 described themselves as "bisexual." Kinsey ratings[39] were obtained for adult fantasy and behavior, combined. The mean Kinsey rating, 5.4 (±.87), indicates a high degree of homosexual orientation for the sample as a whole. Individual Kinsey ratings ranged from 2 to 6. The three individuals who rated themselves "2" on the Kinsey scale all rated the idea of having sex with men as "very sexually exciting." There was a substantially higher proportion of bisexuality among the probands with adoptive brothers (seven of 46) than among the probands with male twins (four of 115; $\chi^2=7.1$; $P<.01$).

Probands had a total of 174 relatives of interest: 116 cotwins and 58 adoptive brothers. Three of these relatives were deceased. Permission was granted to contact 135 (78.9%) of the remaining relatives: 98 of the twins and 37 of the adoptive brothers. Questionnaires were returned by 127 relatives, representing 74.3% of the entire sample of living relatives and 94.1% of those whom probands consented to contact.

Assessment of Relatives' Sexual Orientation

The sexual orientation of relatives was assessed in two ways. First, probands were asked whether they believed their relatives' sexual orientation to be heterosexual, homosexual, or bisexual. Additionally, probands were asked how certain they were about their assessment, using the following scale: "completely certain" indicated that the relative had told the proband his orientation outright; "virtually certain" meant that the proband felt sure, but that this was based on behavior alone; "suspect, but not sure" meant that the proband had some reason for making a guess, but felt appreciable uncertainty; and "very uncertain" meant that the proband could do little more than guess. Additionally, those relatives who could be contacted were asked directly to rate themselves as "homosexual/gay," "heterosexual," or "bisexual." Relatives also gave their combined Kinsey fantasy and behavior ratings, and separately, their attraction to men and to women. Relatives' Kinsey ratings of sexual orientation closely conformed to the broader categories of self-assessment, ie, either "heterosexual" or "homosexual," where homosexual includes "homosexual/gay" and "bisexual." Because the broader categories are fewer in number and more readily understood, we have used them herein.

Relatives' self-ratings of sexual orientation were used when available. However, for a large percentage of relatives, these data were lacking. We had reason to believe, based on the family study of Pillard and Weinrich,[29] that probands would generally be accurate in assessing their relatives' sexual orientation, provided that the proband expressed a high level of confidence. This was, in fact, confirmed for those relatives for whom both ratings were available, as is evident in Table 2. In those 121 cases (of 127 total) where a proband was at least virtually certain about his relative's orientation, the prediction was 97.5% accurate for predicting heterosexuality and an identical 97.5% accurate for predicting nonheterosexuality (ie, either homosexuality or bisexuality). There were also six relatives about whom probands were less certain (ie, they merely "suspected," were "very uncertain" about, or in one case, would not even venture a guess). When probands were less certain, they were correct in both cases (two of two) in predicting heterosexuality. They were correct in half (one of two) the verifiable cases in predicting nonheterosexuality. (In an additional case in which a proband suspected a relative was not heterosexual, the relative failed to complete the sexual orientation items on the questionnaire. The final relative, for whom a proband did not offer a guess, was heterosexual.) Probands were not accurate in predicting whether a nonheterosexual relative would label himself "gay/homosexual" or "bisexual." However, the major distinction below is between heterosexual and nonheterosexual relatives, which probands made quite well.

Table 2.—Relatives' Sexual Orientation by Self and by Probands' Ratings*

Self-Rating by Relative	Rating of Relative by Proband		
	Heterosexual	Bisexual	Homosexual
Heterosexual	79	1	0
Bisexual	2	1	3
Homosexual	0	4	31

*Figures in this table represent those relatives who gave a self-rating of their sexual orientation and for whom probands gave ratings of at least virtual certainty.

Given the high degree of accuracy for confirmable cases when probands expressed a high degree of certainty, it was decided that without a relative's self-rating, the proband's assessment of his relative's sexual orientation would be used, provided the proband was at least virtually certain. If a relative's self-rating was unavailable and the proband was less confident, then that case was omitted from analyses of sexual orientation. This decision is supported not only by the aforementioned problematic results for the small number of relatives about whom probands were uncertain, but also by the results of Pillard and Weinrich. They found that when probands were asked to name siblings they merely suspected of being homosexual, they tended to be less accurate, overassessing homosexuality in their siblings. Sexual orientation ratings were thus available for 170 of the 174 relevant relatives, including 113 cotwins and 57 adoptive brothers.

In addition to twins and adoptive brothers, each twin proband was asked about the sexual orientation of nontwin brothers, in the manner described above. However, such brothers were not contacted directly. These data were not systematically collected for probands with adoptive brothers.

Diagnosis of Twin Zygosity

Zygosity was determined using the questionnaire developed by Nichols and Bilbro.[40] Similar in content to the majority of zygosity questionnaires, it contains items relating to physical similarity, past and present likelihood of twins being mistaken for each other, and twins' beliefs regarding their zygosity. Such questionnaires generally range in accuracy from 90% to 95%.[41-44]

Like most zygosity questionnaires, the Nichols-Bilbro questionnaire is intended to be answered by both twins of a pair, with both sets of responses entered into the diagnostic algorithm. Of the 95 pairs in which both twins completed the questionnaire (including one complete set of triplets), 50 were diagnosed as being MZ, 43 were diagnosed as being DZ, and two were undiagnosable. Because of the desirability of using data from incomplete pairs, as well as the likelihood that acceptable accuracy would be obtained using only one twin's responses, incomplete pairs were diagnosed using only the proband's responses. An additional six MZ pairs and 11 DZ pairs were classified in this manner.

To investigate the accuracy of this procedure, complete pairs were scored both ways, ie, using the information provided by both twins and then only the information provided by probands.

Table 3.—Relatives' Sexual Orientation and Age

	Subsample		
	Monozygotic	Dizygotic	Adoptive Brothers
Homosexual, No./total (%)*	29/56 (52)	12/54 (22)	6/57 (11)
Homosexual (confirmed), No./total (%)†	25/50 (50)	11/46 (24)	6/31 (19)
Mean (±SD) age, y	33.8±7.8	34.6±11.0	30.0±10.6

*This figure includes relatives diagnosed as being either homosexual or bisexual according to the algorithm discussed in the text.
†This figure includes relatives who participated in the study and who gave their sexual orientation as either homosexual or bisexual.

Of the 90 complete pairs that could be diagnosed by probands' responses alone, 84 (93.3%) obtained the same diagnosis using both full and partial data. Thus, diagnosis of zygosity using only the proband's information appears to be nearly as accurate as diagnosis using information from both twins. The final twin relative subsample, including only those relatives whose sexual orientation and zygosity were diagnosable, consisted of 56 MZ twins and 54 DZ twins.

CGN

All probands and cooperating relatives completed the following three questionnaires of CGN. The Physical Aggressiveness Scale[45] consists of 12 items that comprise a retrospective self-report measure of boyhood aggressiveness. The scale's authors found that male heterosexuals recalled substantially more aggressive behavior than male homosexuals. The Sports subscale of the Childhood Play Activities Checklist[11] measures retrospectively reported childhood interest in 11 sports activities. The validity of the test as a measure of childhood gender atypical behavior was supported by the finding that male heterosexuals recalled significantly more interest in the sports activities than male homosexuals. The third scale, Childhood Effeminacy, consisted of 10 items from the Recalled Childhood Gender Behaviors Questionnaire[46] that ask retrospectively about attitudes and behaviors indicating effeminacy in male subjects (in contrast to the other questionnaires that concern typically masculine behaviors). For example, one item asks about the frequency with which the respondent was regarded as a sissy; another asks whether the respondent ever wished to be a girl. A sample of 66 male heterosexual college subjects scored significantly lower on the scale than did the homosexual probands in this study (college sample mean, 1.4±2.0; probands' mean, 6.6±4.3; $t=9.5$, $P<.001$).

For the sample of probands, correlations among the gender nonconformity scales were as follows: the Physical Aggressiveness Scale correlated .56 with the Sports subscale and −.52 with Childhood Effeminacy. The correlation between Sports and Childhood Effeminacy was −.32. To obtain a composite measure of CGN, the three measures were rescaled to unit variance with higher scores indicating greater gender nonconformity (ie, less masculine or more effeminate behavior), and then summed. The composite will be referred to as CGN. Using the correlations among the three scales and the Spearman-Brown Prophecy Formula,[47(p211)] the internal consistency reliability of the composite was estimated as .72.

RESULTS

Rates of Homosexuality in Relatives

The rates of homosexuality (including bisexuality) among MZ cotwins, DZ cotwins, and adoptive relatives of probands are given in Table 3. Fifty-two percent (29/56) of the MZ cotwins were either homosexual or bisexual, using the algorithm for the assessment of sexual orientation described above, compared with 22% (12/54) of the DZ cotwins and 11% (6/57) of the adoptive brothers. The proportion of bisexuals and homosexuals was significantly greater for MZ cotwins than for either DZ cotwins ($\chi^2=10.3$; $P<.001$) or adoptive brothers ($\chi^2=22.5$; $P<.001$). The proportion of homosexuals and bisexuals was greater for DZ twins than for adoptive brothers; however, the difference was only marginally significant ($\chi^2=2.8$; $P<.10$).

Focusing on those relatives for whom we have complete data, ie, confirmation by self-report, the picture was similar for the twin comparisons. The proportion of homosexuals among MZ cotwins exceeded that for DZ cotwins (25/50 vs 11/46; $\chi^2=7.0$; $P<.005$). Similarly, the rate of homosexuality in MZ cotwins remained greater than that rate for adoptive brothers (6/31; $\chi^2=7.6$; $P<.005$). However, the rate of homosexuality among DZ cotwins was no longer significantly greater than that for adoptive brothers ($\chi^2=0.2$; $P>.60$). This was primarily due to the decreased likelihood that a proband with a heterosexual adoptive brother would consent to have him contacted: consent was given to contact 30 of 51 heterosexual adoptive brothers; for heterosexual cotwins, this figure was 59 of 67 ($\chi^2=13.4$; $P<.001$). There was a high degree of cooperation in both groups when relatives were homosexual: twins allowed contact for 37 of 40 such cases; adoptive brothers allowed this in all six cases. Evidently, adoptive probands were particularly unwilling (or twins particularly willing) to involve their heterosexual adoptive brothers. The cooperation pattern was similar (uniformly high) for MZ and DZ twins: MZ probands authorized contact for 93% (25/27) of their heterosexual cotwins and 93% (26/28) of their homosexual cotwins; the corresponding figures for DZ twins were 85% (34/40) and 92% (11/12).

Although most homosexuals have accepted their orientation by age 18 years, a substantial minority have not.[5(p99)] Because the sample of relatives included individuals as young as 18 years old, a few relatives who currently identify themselves as heterosexual may eventually have development of a homosexual orientation. Consistent with this possibility, the mean age of homosexual and bisexual relatives was higher than the mean age of heterosexual relatives within both MZ cotwins (36.0±8.1 vs 31.4±6.8; $t=2.3$, $P<.05$) and adoptive brothers (38.8±10.4 vs 28.9±8.5; $t=2.2$, $P<.05$), but not among DZ cotwins (33.8±8.6 vs 34.8±11.7; $t=-0.27$, $P>.70$). Because the mean age of the adoptive brothers was significantly lower than that of the twins ($t=2.5$, $P<.05$), it is possible that the difference in rates of homosexuality between cotwins and adoptive brothers has been overestimated slightly.

The distribution of sexual orientation among cotwins of the MZ probands appeared to be bimodal. The most frequently endorsed category was Kinsey 0 (n=21), which represents exclusive heterosexuality, followed by Kinsey 5 and 6 (n=9 each), which represent, respectively, a primarily homosexual orientation with (at least one but not more than) an occasional heterosexual fantasy or contact, and a completely homosexual orientation with no heterosexual fantasy or contact. The categories 2 through 4, which represent significant bisexuality, totaled only seven individuals, significantly fewer than the 18 in the primarily homosexual categories 5 and 6 (testing via the normal approximation to the binomial distribution, $z=2.0$, $P<.05$), and the 25 cotwins with primarily heterosexual scores of 0 or 1 ($z=3.0$, $P<.01$). This bimodality is even more dramatic if one considers the distribution of MZ cotwins' responses to two items: (1) whether the idea of sex with other men is sexually exciting, and (2) whether the idea of sex with women is sexually exciting. Only four cotwins gave positive ratings (ie, at least "moderately sexually exciting") to both items, compared with 20 who gave positive ratings to the male item only and 24 who gave positive ratings to the female item only. The proportion of cotwins admitting only homosexual feelings was significantly greater than those admitting both homosexual and heterosexual feelings ($z=3.3$, $P<.001$).

Table 4.—Proband-Relative Correlations, and Heritability and Environmentality Estimates Under Several Sets of Assumptions

Assumptions*		Tetrachoric Correlations†			Parameter Estimates‡		
B_1	P_h	r_{MZ}	r_{DZ}	r_A	e^2	h^2	c^2
1.0	.10	.76	.31	.02	.26	.74	.00
1.0	.04	.83	.50	.25	.17	.60	.23
2.0	.10	.54	.08	−.17	.52	.48	.00
2.0	.04	.68	.30	.08	.34	.62	.04
3.0	.10	.40	−.04	−.26	.69	.31	.00
3.0	.04	.50	.19	−.01	.34	.54	.00

*B_1 indicates the ratio of the likelihood of ascertaining a proband if his relative is homosexual vs heterosexual; P_h, the base rate of homosexuality in the general population.
†r_{MZ}, r_{DZ}, and r_A are the respective tetrachoric correlations for monozygotic (MZ) twins, dizygotic (DZ) twins, and adoptive (A) brothers.
‡e^2, h^2, and c^2 are the proportions of phenotypic variance explained by, respectively, nonshared environmental differences, additive genetic differences, and shared environmental differences.

Heritability of Sexual Orientation

Results of the preceding analyses suggest that genetic factors are important in determining individual differences in sexual orientation. However, the mere finding that the rates of homosexuality in different types of relatives are consistent with some genetic influence does not provide an estimate of the *magnitude* of that influence.[48,49] Assuming a multifactorial model of transmission (ie, genetic influence is polygenic and environmental events are many with each of small effect[26]), one can calculate heritabilities from rates of homosexuality in relatives, provided that one has an estimate of the base rate of homosexuality in the general population.[48,49] Unfortunately, a wide range of estimates has been cited. The two most commonly mentioned figures, however, are 4% at the low extreme[50,51] and approximately 10% at the high extreme.[52(p34)] Finally, the accuracy of a heritability estimate depends on assumptions about sampling. If, as is generally the case in volunteer twin samples, relatives who are most similar to each other are most likely to be ascertained,[53] this may bias heritability estimates (although the direction of the bias may vary).

Heritability estimates were computed using the data from Table 3 (ie, the relatives for whom a sexual orientation assessment was available) as follows: first, tetrachoric correlations were computed for the three groups of relatives under six sets of assumptions, which depended on two parameters, P_h and B_1. The parameter P_h, which represents the base rate of male homosexuality in the general population, was assumed to be either 4% or 10%. The second parameter, B_1, represents the ratio of the likelihood that a proband will be ascertained if his relative is homosexual to the likelihood that he will be ascertained if his relative is heterosexual. Thus, if $B_1=2$, then a proband with a homosexual relative is twice as likely to be ascertained as a proband with a heterosexual relative. Subsequent estimates were computed for three values of B_1: 1.0 (no differential ascertainment), 2.0, and 3.0. When B_1 was set to 3.00, the corrected rate for homosexuality among adoptive brothers was 4%, the most frequently mentioned lower bound population base rate, and thus 3.0 seemed a reasonable upper bound for B_1.

For each set of assumptions, three parameters were estimated using the relatives' frequencies of homosexuality, tetrachoric correlations, and the model-fitting program MX[54] (which specifically fits multifactorial threshold models): the heritability, h^2, or the proportion of phenotypic variance explained by additive genetic differences; c^2, the proportion of variance explained by those features of the environment shared by siblings; and e^2, the proportion of variance explained by the environment that siblings do not share. Genetic model fitting capitalizes on the fact that phenotypic correlations between different types of relatives will reflect different degrees of genetic and/or environmental similarity. For example, MZ cotwins share all their genes, DZ cotwins share half (identical by descent), and adoptive brothers share none. Because all three types of relatives studied herein were reared together, they are all perfectly correlated for shared environment. Nonshared environment, by definition, must be uncorrelated for all types of relatives. As a result, a genetic model with additive genetic, shared environmental, and nonshared environmental parameters is specified as follows: for MZ cotwins, their genetic, shared environmental, and nonshared environmental correlations are 1.0, 1.0, and 0.0; for DZ cotwins, these correlations are 0.5, 1.0, and 0.0; and for adoptive siblings, the correlations are 0.0, 1.0, and 0.0. Further details regarding the model-fitting procedure can be obtained from one of us (J.M.B.). (For the theoretical rationale behind the computation of heritabilities for threshold characters, see Gottesman and Carey.[49])

Results are presented in Table 4. Heritability estimates (h^2) ranged from .31 ($P_h=.10$, $B_1=3.0$) to .74 ($P_h=.10$, $B_1=1.0$). Thus, estimated heritability remained substantial under a wide variety of assumptions. The estimate of variance attributed to shared environment (c^2) ranged from 0 (for four models) to .23 ($P_h=.04$, $B_1=1.0$), and was in every case smaller than the estimated heritability. Estimated nonshared environmental variance (e^2) ranged from .17 ($P_h=.04$, $B_1=1.0$) to .69 ($P_h=.10$, $B_1=3.0$). Although the primary purpose of these analyses was to examine the magnitude of heritability estimates under different assumptions regarding the base rate and degree of ascertainment bias, rather than to test hypotheses, we note that for every model h^2 was significant. In contrast, c^2 was significant in none.

The Rate of Homosexuality in Nontwin Brothers

Twin probands reported 142 nontwin brothers about whose sexual orientation they were at least virtually certain. Of these, 13 (9.2%) were thought to be homosexual or bisexual. This percentage is considerably less than one would expect, given a simple model with only additive genetic, shared environmental, and nonshared environmental factors. Specifically, the rate of homosexuality and bisexuality in nontwin brothers was significantly less than the 22% rate found for DZ cotwins ($\chi^2=6.0$; $P<.05$). Furthermore, this rate failed to exceed the analogous rate for adoptive brothers. Finally, the rate of homosexuality in nontwin brothers was significantly less than that found by Pillard and Weinrich[29] (22%; $\chi^2=6.6$; $P<.05$).

CGN

If homosexuals who were gender nonconforming as children are more constitutionally homosexual, and if "constitutional" is taken to mean "heritable," then the twin probands who were most gender nonconforming should be most likely to have homosexual cotwins. Translated into the measures of our study, this hypothesis predicts that for both the MZ and DZ subsamples, probands with homosexual cotwins should have higher scores on the CGN composite than should probands with heterosexual cotwins. If such a pattern occurred due to genetic (and not shared environmental) factors, then there should be no difference in the CGN scores between probands with homosexual adoptive brothers vs those with heterosexual adoptive brothers. Table 5 shows that contrary to the hypothesis, probands with homosexual relatives were not significantly distinguishable from probands with heterosexual relatives on the basis of CGN in any of the three subsamples: for MZ, DZ, and adoptive probands, respectively, $t=-0.52$ ($P>.60$), $t=1.31$ ($P>.10$), and $t=-0.45$ ($P>.60$). Thus, we found no evidence that the presence of gender nonconformity increases the likelihood of finding homosexual relatives.

A second question concerns the extent to which the different

Table 5.—Childhood Gender Nonconformity (CGN): Means and Correlations Between Probands and Relatives, by Relatives' Sexual Orientation

	Monozygotic (MZ) Twins	Dizygotic (DZ) Twins	Adoptive Brothers
Mean (±SD) CGN			
Probands with homosexual relatives	0.58±2.5	1.98±2.1	0.67±2.5
Probands with heterosexual relatives	0.92±2.3	1.02±2.3	1.02±1.7
Homosexual relatives*	0.49±1.6	0.67±1.5	0.92±2.8
Heterosexual relatives†	−2.19±1.4	−2.39±1.2	−2.56±2.1
Correlation			
Between probands' and homosexual relatives' CGN*	.76‡	.43	−.26
Between probands' and heterosexual relatives' CGN†	.10	−.02	−.06

*Associated Ns for MZ and DZ twins and adoptive brothers are, respectively, 25, 11, and 6.
†Respective associated numbers are 25, 32, and 25.
‡$P<.0001$.

types of relatives resemble each other for CGN. For instance, do heterosexual cotwins of gender-nonconforming MZ probands also report having been gender nonconforming as children? Are homosexual MZ cotwins similar to their proband twins with respect to CGN? Table 5 also contains the correlations between probands' and relatives' CGN, separately for homosexual and heterosexual relatives. The only significant correlation was for MZ probands with homosexual cotwins. This correlation ($r=.76$) exceeded the lower-bound reliability estimate of the composite scale. Thus, if twins were both homosexual, they reported a very similar degree of CGN. This contrasted with the correlation ($r=.10$) between MZ probands and their heterosexual cotwins, which is significantly lower ($z=4.2$; $P<.001$). Thus, the CGN of MZ cotwins depended on the interaction between their own sexual orientation and the probands' CGN.

COMMENT

Ascertainment Bias

The sampling method employed in this study falls short of the ideal genetic epidemiological study, which would involve systematic sampling from a well-specified population. In particular, although all recruiting advertisments stated that probands were desired regardless of the sexual orientation of their relatives, there is no guarantee that volunteers heeded this request. Consider two broad categories of sampling bias: type 1 or concordance dependent[55] bias, in which the probability of ascertaining a proband depends only on the degree of similarity between proband and relative for the trait of interest; and type 2 bias, in which ascertainment probability depends on the combination of proband-relative similarity and the type of relative. Type 1 bias, which was examined as B_1 in the above analyses, does not affect the validity of inferential tests. Concluding that sexual orientation is partially heritable based on different patterns of MZ and DZ twin concordance is equally valid whether or not type 1 bias occurred. Estimates of parameters, such as heritability, are sensitive to type 1 bias, but the analyses presented in Table 4 show that estimated heritability of sexual orientation remains appreciable over a wide range of values representing type 1 bias. In contrast, type 2 bias can lead to spurious findings of heritability. Type 2 bias would require that a proband's participation depend not only on his relative's sexual orientation, but also on how closely related he is to the relative. For example, if discordant MZ twins were less likely to participate than discordant DZ twins, this would inflate the difference in concordance rates between MZ and DZ twins and could lead to a significant difference in observed concordance rates even if there were no true difference in the population.

To our knowledge, no available data address this issue directly. However, there is an indirect indicator of proband cooperation: whether the proband consented to have his relative contacted. As noted above, probands with heterosexual adoptive brothers were significantly less likely to consent than probands with heterosexual twins; cooperation did not differ notably if relatives were homosexual. If similar factors affect probands' decisions regarding (1) allowing their relatives to be contacted and (2) their initial participation in the study, then our results would suggest that the proportion of heterosexual relatives was underestimated in the adoptive brothers, compared with the twin subsamples. This would lead to an *underestimation* of heritability and decreased power for genetic tests. As noted above, the pattern of cooperation (in allowing relative contact) was similar for MZ and DZ twins; thus, there is no evidence that the difference between MZ and DZ concordance rates was due to a type 2 cooperation bias. However, this possibility cannot be ruled out definitively with the available data.

Implications for the Genetics of Sexual Orientation

Results of this study confirm the view that Kallmann's finding of perfect concordance for homosexuality for MZ pairs is too high.[30,31] The 52% rate was similar to both the 50% rate estimated by Pillard et al[33] and the 40% rate found by Heston and Shields,[56] who reported the only systematically ascertained sample of homosexual twins to date. Nevertheless, the pattern of rates of homosexuality by type of relative was generally consistent with substantial genetic influence, with the exception of nontwin brothers, whose rate was lower than that of DZ cotwins and approximately equal to that of adoptive brothers. Furthermore, the rate of homosexuality among nontwin brothers was significantly less than that found by Pillard and Weinrich,[29] who obtained a rate remarkably close to the figure we obtained for DZ cotwins. One possible explanation for this finding concerns the fact that the probands in the present study who gave information regarding nontwin siblings were twins, while the probands of Pillard and Weinrich included only one (DZ) twin. Perhaps the rate of homosexuality in nontwin brothers differs according to whether the proband is a twin. This could occur if the causes of homosexuality in twins and singletons were different, ie, if a special twin environment contributes to the development of sexual orientation. On the other hand, the low rate could merely be due to sampling fluctuations. Therefore, we emphasize the desirability of replicating the finding of lower than expected rates of homosexuality among nontwin brothers of twin probands.

Heritability varied according to assumptions regarding the base rate of homosexuality and the degree of ascertainment bias. However, all heritability estimates accounted for a substantial proportion of phenotypic variance. It is not clear that attempts to narrow the heritability estimates within the broad range of estimates obtained should be given high priority. Heritability is not informative regarding the development of sexual orientation (or, for that matter, of any trait). That is, given any heritability estimate, there are a variety of possible developmental mechanisms. For instance, these data are consistent with heritable variation in prenatal brain development or in some aspect of physical appearance that, by way of differential parental treatment, leads to differences in sexual orientation.

Nevertheless, there are at least two ways in which the finding of substantial heritability is important. First, the present study provided some support for the view that sexual orientation is influenced by constitutional factors. This contrasts with previous attempts to test psychodynamic and psychosocial theories, which have largely yielded negative findings,[5] and emphasizes the necessity of considering causal factors arising within the individual, and not just his psychosocial environment.

Second, the demonstration of nonzero heritability for sexual orientation raises the question of how genes for homosexuality could persist despite presumed strong evolutionary counterselection. Bell and Weinberg,[57] for instance, found that adult male homosexuals reported about one fifth the number of children as male heterosexuals. There have been a number of attempts to explain how genes for homosexuality might be maintained in the population gene pool.[58-60] Although these attempts have hypothesized behavioral mechanisms such as kin selection, there may be nonbehavioral benefits of genes for homosexuality, eg, immunity against certain diseases. In any case, the illumination of the genetic diathesis, ie, what exactly is inherited, would both suggest and constrain plausible hypotheses.

The distribution of sexual orientation among MZ cotwins appeared to be bimodal. Although bimodality is sometimes accepted as evidence for a major gene, this need not be the case. The analysis of MZ cotwins is less potentially informative in this respect than the analysis of ordinary siblings of probands. A bimodal distribution among the latter may represent the differentiation of those who share a major gene with the proband from those who do not.[61(p174)] But MZ cotwins share all the proband's genes, and so cannot be informative in this respect. Moreover, one assumption of the heritability analyses presented above is that there are no major genes for homosexuality, and that any discontinuity is at the phenotypic level. This is a multifactorial threshold model.[48,49,61] One alternative to a major gene as an explanation for the bimodality is a developmental process in which factors that cause attraction to female subjects simultaneously inhibit the development of attraction to male subjects. Distinguishing between these possibilities will require further data.

Implications for the Development of Sexual Orientation

Contrary to prior speculation, we found no evidence that homosexuality associated with CGN is more heritable. Homosexuals who behaved like typical boys during childhood do not appear to have been influenced particularly by external events during and after childhood compared with homosexuals who behaved atypically from an early age. Monozygotic pairs concordant for homosexuality tended to be concordant for the degree of childhood gender nonconformity. This suggests that among homosexuals, individual differences in development are largely determined by genetic and/or shared environmental factors. To determine which of these factors is more important for the expression of CGN, it will be useful to study pairs of homosexual relatives, such as homosexual brothers, to see if they report similar levels of CGN. Furthermore and more generally, it would be desirable to focus more attention on the differences between homosexuals who report a history of CGN and those who do not.

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Oxygen Radicals and Neuropsychiatric Illness

Some Speculations

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• Free radicals are reactive chemical species with an unpaired electron that are produced through a variety of physiologic and pathologic processes. Free radicals have been implicated in a variety of neuropsychiatric conditions, many of which are marked by the gradual development of psychopathologic symptoms and movement disorder. There is evidence that radical-induced damage may be important in Parkinson's disease, tardive dyskinesia, metal intoxication syndromes, and Down's syndrome, and possibly also in schizophrenia, Huntington's disease, and Alzheimer's disease. Although some of this evidence is highly speculative, it may offer an avenue for further understanding and treatment of these conditions.

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Free radicals are highly reactive chemical species that have an unpaired electron in an atomic or molecular orbital. In biologic systems, most of the important free radicals are based on oxygen. Molecular oxygen readily gains an electron to form superoxide anion radical, symbolized $O2^{-\bullet}$. Other important oxygen radicals can also be formed during the four-electron reduction of molecular oxygen to water, and these can be produced in many different ways. In the presence of free transition metals, such as iron, copper, or manganese, hydrogen peroxide can be split to yield the hydroxyl radical ($^{\bullet}OH$), the most reactive oxygen radical known. For example, when iron is mixed with hydrogen peroxide, the Fenton reaction can occur: $Fe^{2+}+H_2O_2 \longrightarrow Fe^{3+}+{}^{\bullet}OH+OH^-$. In the presence of superoxide radical, transition metals can function as catalysts of the Haber-Weiss reaction, also producing hydroxyl radicals:

$$O2^{-\bullet} + Fe^{3+} \longrightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$$

$$O_2{}^{-\bullet} + H_2O_2 \longrightarrow O_2 + {}^{\bullet}OH + OH^-$$

Because free radicals are potentially toxic, organisms have developed efficient ways to deactivate them. The enzyme superoxide dismutase (SOD) catalyzes the dismutation of superoxide radical to hydrogen peroxide and oxygen: $2O_2{}^{-\bullet}+2H^+ \longrightarrow H_2O_2+O_2$. Superoxide dismutase occurs in two main forms: SOD-1, also called copper-zinc SOD, located in the cytoplasm, and SOD-2, or manganese SOD, which is found in mitochondria. The hydrogen peroxide formed through these and other reactions can be reduced to water by the enzymes glutathione peroxidase (GPx) or catalase, although in the brain, GPx is the more important enzyme.

In addition to free radical deactivating enzymes, free radical scavengers exist, which detoxify radicals by capturing an extra electron, becoming themselves less toxic radicals. Important scavengers include vitamin C (ascorbic acid), perhaps the most critical water-soluble scavenger,[1] and vitamin E (α-tocopherol), probably the most important lipid-soluble scavenger.[2]

Free radical metabolizing enzymes, scavengers, and other substances that prevent radical formation or increase radical removal are often referred to as antioxidants. The different antioxidant defense systems appear to exist in a controlled and balanced state.[3] For example, an increase in SOD would be expected to be protective by decreasing the amount of superoxide radical. In the face of decreased GPx or increased free iron, however, the hydrogen peroxide produced through the action of excess SOD may result in hydroxyl radical formation and increased radical damage. Hydroxyl radicals are much more reactive than most other radicals, reacting virtually at the site of their formation.

Free radicals can attack most cellular constituents, including proteins and nucleic acids, but membranes are particularly vulnerable. This is because of the lipid peroxidation cascade, a chain reaction in which one free radical can cause the production of many more radicals, resulting in lipid peroxide formation and widespread membrane changes. The major chain-breaking substance appears to be vitamin E,[2,4] which is inserted in the membrane. Membranes that contain large amounts of polyunsaturated fatty acids, such as those found in the brain, are especially susceptible to free radical attack. The formation of lipid peroxides in the membrane can alter membrane characteristics, causing changes in membrane potential,[5,6] decreased membrane fluidity,[7,8] and formation of peroxide pores,[9] which may allow calcium and

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