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Homosexuality, Type 1: An Xq28 Phenomenon

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Despite the absence of phenotypic manifestations in alternating generations characteristic of X-linked disorders, a thesis is presented that a major type of Kinsey grades 5 and 6 male homosexuality is determined by a gene in the Xq28 region. A total of 133 families in 78 kinships of male and female homosexual probands, in addition to 116 families (including those of 40 famous homosexuals) from the literature, revealed an unbalanced secondary sex ratio in the maternal generation of male, but not of female, homosexuals. On the maternal side, in this study, the ratio of all uncles to all aunts of 90 males homosexuals was 132/209, $\chi^2 = 8.52$, $p = 0.004$. *On the maternal side for the total of all sources, the ratio of uncles to aunts of male homosexuals was 241/367,* $\chi^2 = 13.20$; $p < 0.0001$. *The male/female ratio of the total number of maternal* sibships *bearing homosexuals (310/628: 0.491) was a measure of fetal wastage of the mothers' male sibs: 49%. This ratio was very close to that of the total number of children born to fathers affected with any one of nine Xq28-linked male semilethal conditions (255/508: ratio 0.556); for the difference between the two populations* $\chi^2 = 0.859$, $p = 0.354$. *The male/female ratio of the total number of children born to female carriers of any one of these same conditions (1,232/1,062: ratio 1.16),* $\chi^2 = 13.8$ $p \leq 0.0001$, *is close to that of the total number of children in homosexual sibships: 511/413,* $\chi^2 = 10.4$, $p = 0.005$. *Between the number of children born to Xq28 mothers and to those born of mothers of homosexuals* $\chi^2 = 0.581$, $p = 0.446$. *One may readily surmise that the maternal influence so often related to homosexuality may lie in the mother being a genetic carrier, with traits thereto associated. In this study, 65% of the mothers of homosexuals had no or only one live-born brother. Additional support for a genetic hypothesis is found in*

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[2]A limited number of long tables of data, and pedigree charts, which provide the details from which this paper was developed, may be obtained on paper or on disc from the author or, for a modest fee, from the Librarian, Health Sciences Center, State University of New York at Stony Brook, Stony Brook, New York 11794.

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the occurrence of multiple instances—almost exclusively among maternal relatives—of infertility, spontaneous abortions, miscarriages, stillbirths, remaining single past age 30, and suicide. Of 109 male and 43 female homosexual index cases in the present series there were 6 instances of brother/sister homosexual sibships. Instances of homosexual parent-to-homosexual child transmission occurred as follows: one father-to-son; one father-to-daughter; one bisexual father-son; one father/mother-to-2 sons; one of mother-to-son, and one of father-to-son and father-to-bisexual daughter. There were 16 instances of presumptive transmissions from heterosexual father-to-homosexual son and 5 of heterosexual father-to-homosexual daughter. A hypothesis is proposed: Homosexuality is due to a gene at Xq28 characterized by (i) elongated cytosine-containing trinucleotide repeats upstream to translation of a gene, (ii) elongated CpG islands upstream of the trinucleotides, and (iii) cytosine methylation of CpG islands and of the cytosine-containing trinucleotides.

KEY WORDS: homosexuality; sex ratio; genetic; Xq28; nucleotide repeats; methylation; pseudoautosomal.

INTRODUCTION

Despite a century of scientific study and debate, there is little agreement between those who support theories of environmental causation of homosexuality (Bieber *et al.,* 1962; Friedman, 1988; Byne and Parsons, 1993) and those who favor theories of biological causation of homosexuality (e.g., Diamond, 1965; Kenyon, 1968; Pillard *et al.,* 1981; Pillard and Weinrich, 1986; Dörner, 1988; Dörner *et al.,* 1991). Futuyma and Risch (1989) critically analyzed every proposed theory on the nature and genesis of homosexuality then current. They found the evidence faulty for each.

Heretofore, the strongest—and yet inadequate—supports for a genetic mechanisms in the etiology of homosexuality have been its familiality (e.g., von Römer, 1906; Hirschfeld, 1914; Kenyon, 1968; Pillard *et al.,* 1981; Pillard and Weinrich, 1986; Pillard, 1990) and the far higher concordance rate for homosexuality of monozygotic (MZ) than of dizygotic (DZ) twins (e.g., Bailey and Pillard, 1991; Diamond, 1993; Bailey *et al.,* 1993; Whitam *et al.,* 1993). The anatomical differences found in the brains of heterosexual and homosexual men (Swaab and Hofman, 1990; LeVay, 1991, 1993; Allen and Gorski, 1992; Pilgrim and Reisert, 1992; Swaab *et al.,* 1993; among others) have been offered as evidence for a biological, if not genetic, determination of homosexuality. Each and all of these lines of evidence have been discounted in a scholarly and detailed analysis by Byne and Parsons (1993), who upheld the view that homosexuality is of environmental origin.

There is now disclosed in this study a group of familial regularities of a genetic nature in a major proportion of homosexuals studied. This leads to an examination of genetic phenomena which takes what seemed to be a crucial flaw in the MZ twin concordance ratio and turns it into an instrument that may expose the possible mechanisms involved.

The impetus for the present study was provided by a psychotic woman who, in 1977, had talked about her homosexual brother and alcoholic father. Ten years later, in following up her illness, a homosexual man was questioned. He said, "There is no alcoholism in my family, but my mother has three sisters and no brothers. Could this be significant?" It seems that, aside from a brief abstract of a paper by Martensen-Larsen (1957), this question had never before been asked. It opened a new universe of discourse on the subject.

Which population was to be investigated? Although alcoholism could be ascertained and variations on alcohol abuse defined by the criteria of DSM-III-R (American Psychiatric Association [APA], 1987), sexual orientation and behavior were another matter. Continua of sexual expression, orientation, and behavior have been described by many investigators (e.g., Ellis, 1936; Marmor, 1965; Saghir and Robins, 1973; Shively *et al.,* 1984). Buhrich *et al.* (1991) define sexuality in six dimensions. Freund *et al.* (1977), Berkey *et al.* (1990), and Coleman (1991) and others have attempted further dissections. These have offered so many variables as to obscure the central theme. Furthermore, since variations in sexual orientation and behavior suggest considerable heterogeneity, marked restriction is demanded. The criteria of Kinsey *et al.* (1948, 1953) were deemed suitable for the inquiry in mind. In this study the problem of asexuality ("Kinsey X": Kinsey *et al.,* 1948) came up three times. These asexual subjects were not counted, though their familial patterns were consistent with those presented for homosexuals. Transsexualism did not occur in this sample.

Without a positive personal statement, homosexuality in women is often difficult to establish (Foster, 1956; Wilbur, 1965; Hart and Richardson, 1981). Many who state that they are lesbians engage in heterosexual activity for a variety of personal, familial, social, and economic reasons. They may escape recognition through being discreet, celibate, bisexual, or married and mothers of children (Foster, 1956; Wafelbakker, 1975; Faderman, 1981). Previous professional experience had alerted the author to the fact that many women whose marital sex lives are "unpleasant" and regarded by them as "a duty," have some greater or lesser degree of sexual interest in other woman. In addition, there appears to be only one form of female bisexuality. In this form, for example, if a woman is married and has extramarital liaisons, she will have them with *both* sexes (unlike married

bisexual males). In this study, bisexuality was considered to be homosexuality if such liaisons were usually or always with same-sex partners.

Population geneticists have amply demonstrated that within any group defined by genetic criteria there are ranges of variation in the structure and biological consequences of almost any given gene (Wilson, 1975; Futuyma, 1986). These variations increase with time and changes in environmental factors. The worldwide and ancient occurrence of homosexuality would thus lead an investigator of this subject to expect to encounter heterogeneity. This point was made, for example, by Shively *et al.* (1984). The occurrence of homosexuality at a rate of 20% among women with congenital adrenal hyperplasia (MIM 201910: McKusick, 1992) is a case in point. It is a rare phenomenon (Dittman *et al.,* 1992) and not relevant to the present report. In the current study an effort was made to minimize variability by restricting the selection of probands and index cases to those who clearly met the criteria for Kinsey Grades 5 and 6 homosexuality (Kinsey *et al.,* 1948, 1953).

METHOD

All homosexuals known to the author from 50 years of practice were excluded from this study. The primary data derive from a personally and quite consecutively collected cohort of 133 families in 78 kinships identified by a Kinsey Grade 5 and Grade 6 homosexual (Kinsey *et al.,* 1948) male or female proband. The probands were identified by the letter "P" and the consecutive number in the collection. Though the cohort of families studied was collected without prior knowledge of the probands or families, rigorous criteria for random sampling (see Murphy, 1979) could not be met. Both method and data are readily replicable, as shown by agreement, on the one hand, between the families with male homosexuals only in the present study and those with male homosexuals only in the total literature and, on the other hand, agreement between the families with female homosexuals only in the present study and those with females only in the literature. (See Table I.)

The study began with the author asking friends, colleagues, and chance acquaintances met on trains, at parties, and at meetings: "Do you know, or know of, a homosexual person through whom I might obtain information regarding his or her family structure and family life?" Inquiry progressed only if it became clear from each informant that the proband met the criteria for K 5/6 homosexuality (Kinsey *et al.,* 1948, 1953); manifested uncoerced, present homosexual orientation and behavior; and if an assurance of correct knowledge of family relationships was provided. In the

Table I. Condensed Enumeration of Parental Sibships and Children in 133 Families with Male and/or Female Kinsey Grades 5/6 Homosexuals by Generation (G) and Identifying Number[a]

Kin	Locus	Sex	Paternal		Maternal		Sibship	
			Male	Female	Male	Female	Male	Female
P001A	GIV, 23	M	4	1	1	5	1^{G}	1
B	GIV, 35	F			1	5	0	3^{L}
C	GIV, 39	F			Same data		1	$2^{L\text{-}DZ,DZ}$
P030A	GIII, 6	M			0	2	4^{G}	2
B	GIV, 6	F			4^{G}	2	1	1^{L}
C	GIV, 8	F	1	0	Same data		1	1^{L}
P035		FM	2	1	0	2	1^{G}	3^{L}
P088		M	1	0	1	4	6^{G}	2
Sum, entire Table		152	230	119	132	312	244	198
78 kinships with 133 families having 111 male and 45 female index cases								
N of parents and homosexual + bisexual offspring			90			103	111	45
N of uncles (U), aunts (A) and heterosexual (HT) sibs			139	119	132	209	133	153
M/F ratio			1.17		0.63		0.87	
χ^2 between sexes			0.776		8.526		0.700	
p			0.379		0.004		0.403	
90 families with male homosexual probands only								
SUM			160	79	98	233	195	108
N of parents and homosexual + bisexual sibs			63			73	102 (include 1 BS)	0 (BS)
N of U, A and HT sibs			97	79	98	160	94	108
M/F ratio			1.24		0.61		0.86	
χ^2 between sexes			0.912		7.559		0.554	
p			0.340		0.006		0.457	

Table I. Continued

Kin Locus Sex	Paternal		Maternal		Sibship	
	Male	Female	Male	Female	Male	Female
36 families with female homosexual probands only						
Sum	57	30	28	65	36	74
N of parents of homosexual + bisexual sibs	21			24	0	37
						(BS)
N of U, A, and HT sibs	36	30	28	41	35	37
M/F ratio		1.20		0.68		0.95
χ^2 between sexes		0.273		1.227		
p		0.601		0.269		identity
7 families with brother/sister homosexual probands						
Sum	13	9	4	15	11	15
N of parents and homosexual + bisexual sibs	6			5	7	7
N of U, A, and HT sibs	7	9	4	10	2	7
M/F ratio		0.62		0.40		0.02
N of U/A of families with male only probands + families with male/female probands	103	88	134	221	131	158
χ^2 between combined data by sex		0.588		10.81		1.262
		0.443		0.001		0.262
Study of Henry (1941) families with male probands only	60	60	48	72	36	41

Table I. Continued

Kin	Locus	Sex	Paternal		Maternal		Sibship	
			Male	Female	Male	Female	Male	Female
Families of 26 famous homosexual men								
			52	30	35	41	59	43
Families with male homosexual probands located in the literature								
			20	21	24	33	23	24
Σ of *N*			235	199	241	367	249	266
χ^2 between sexes			1.529		13.20		0.0280	
p			0.217		<0.0001		0.592	
Present study: 36 families with female homosexuals only (37 female homosexuals + 1 male bisexual)								
			36	30	28	41	35	37
N of paternal and maternal uncles and aunts and HT sibs of 21 female homosexuals of Henry (1941)								
			33	37	28	23	22	26
N of paternal and maternal uncles, aunts, and HT sibs of 14 famous women								
			35	35	31	23	21	21
N of paternal and maternal U and A, and HT sibs of homosexual women from pedigree charts in the literature								
			2	3	5	5	3	3
Σ of *N*			106	105	92	92	81	87
			identity		identity		0.106	
Compare data of all families having male probands with all families having female probands								
χ^2 between the two sets			0.1927		5.66		0.192	
			0.336		0.014		0.661	

Table I. Continued

Kin	Locus	Sex	Paternal		Maternal		Sibship	
			Male	Female	Male	Female	Male	Female
Total of all paternal and maternal U and A, and of all HT males and females in sibships, in families of homosexuals in the present study combined with the total literature								
			341	324	302	408	295	311
M/F ratio			1.05		0.74		0.95	
χ^2 between sexes			0.217		7.957		0.344	
p			0.642		0.005		0.531	

[a]Four examples from the complete list of families are shown. Superscripts[G] and [L]indicate male (gay) and female (lesbian) homosexual, respectively. "Same data" numbers are not added in.

[b]Piltz (1921); Wolf (1925), family 1; Hirschfeld (1936); Bakwin (1968); Pillard [GG,BS:LLL] (1990); Hamer et al. (1993), plus the same data for the first cousin of Mabel Dodge Ganson (a BS), and the two HS sons of Harold Nicolson and his wife, Vita Sackville-West (both famous homosexuals.

[c]Piltz (1921), Wolf (1925, family 2); Bakwin (1968).

course of professional consultations since 1988, 14 families with K 5/6 probands were identified. Every proband had "come out" to his or her family or to a primary informant, whether or not he or she had done so to others. It is certain that there were other homosexuals who were not known as such by their relatives, and others too young to be known to themselves. Their presence in a family would lead to a low population prevalence estimate, but would not result in omission of ancestors of a family already identified by a sibling. Heterosexual activity was reported to have occurred in the cases of many homosexuals of both sexes; among the men, it had largely occurred before age 25; among the women, largely before age 30. Family P024 was removed when the parental claim of homosexuality of a son had to be revised; he turned out to be a heterosexual transvestite with transsexual fantasies. Only five families were enlisted by ads placed in gay/lesbian publications, and even fewer from homosexual clubs and homosexual sections of professional organizations. Three probands dying of AIDS were presented by their attending physicians. Four index cases were lovers of enlisted probands. There was no response to appeals at gay bars in two cities. The probands were of varied provenance: wealthy and homeless; highly successful professionals; dancers, students, writers, garage employees, psychotic welfare recipients, and multiple drug abusers. They came from loving and from brutalizing families from a wide range of ethnic and racial groups. They were self-referred, or referred through a family member or friend, a clinic, or another homosexual. None were in prison or under any form of restraint or coercion. Many required repeated inquiries and reviews after family conferences.

Pedigree charts were constructed with identification on every known relative, supplemented with such data as could be obtained, then or later, on dates of birth, death, and marriage; results of pregnancies; usage of drugs or alcohol; psychiatric disorders; and family traits and illnesses. It was rarely possible to make a diagnosis of psychiatric disorders with the rigor required by the DSM-III-R (APA, 1987). In view of an initial indication that there might be a distinct form of homosexuality closely related to alcoholism, this concept played a large role in the first 4 years of the present investigation. It developed that alcoholism in a proband or first-degree relative, though frequently found, could not be shown to distinguish such families from those in which alcoholism was absent.

Observations on the first 20 families led the author to turn to the study of male homosexuals by Henry (1941) to test for consistency of data. Each case interview was first read and evaluated for Kinsey grade of homosexuality; only then was the pedigree chart examined. A year later Henry's female probands were studied. Again classification was made before examination of the pedigree charts. Further to enhance the breadth

of the study, a list of names of over 200 famous homosexuals (Rowse, 1977; Dynes and Johnsson, 1990; and others) was compiled. A scholar, to whom the author is greatly indebted, was engaged to search the literature to verify and amplify the author's endeavors. Over 150 volumes of biography, autobiography, letters, journals, essays, etc., were searched diligently for reliable and complete information. Data were provided for 40 appropriate families. (A separate bibliography is available from the author.) The scholar also aided greatly in resolving questions arising from the work of Henry (1941), and in providing additional information from the literature regarding other homosexuals and their family data.

The statistical tool employed in this work was χ^2 with 1 degree of freedom, two-tailed, uncorrected. Values less than 5.41 ($p = 0.02$) were considered nonsignificant. However, low values were added when it was shown that the populations in question did not differ significantly from one another.

RESULTS

Figures 1 and 2 exhibit some of the major features of familiality in what the author proposes to designate Homosexuality, Type I. This type is marked by a highly significant excess of maternal aunts over maternal uncles, by occurrence of further instances of homosexuality—almost exclusively among maternal relatives—and by multiple instances of infertility, spontaneous abortions, miscarriages, stillbirths, remaining single past age 30, and sui-

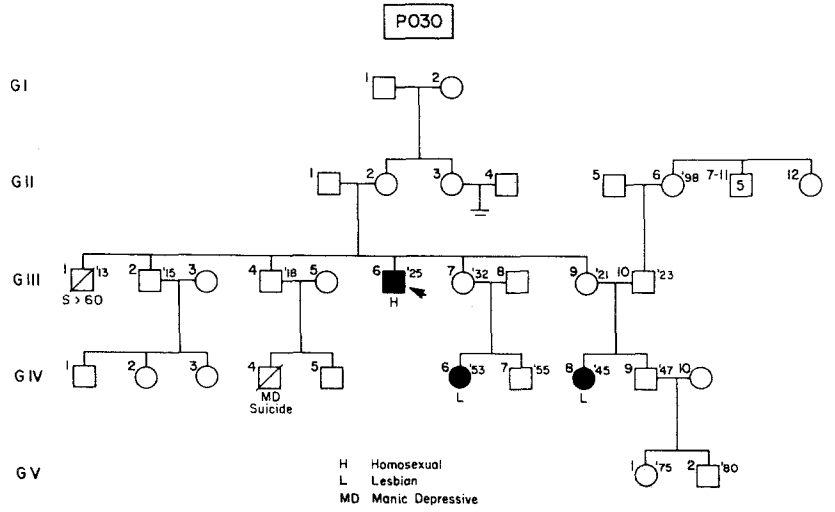

Fig. 1

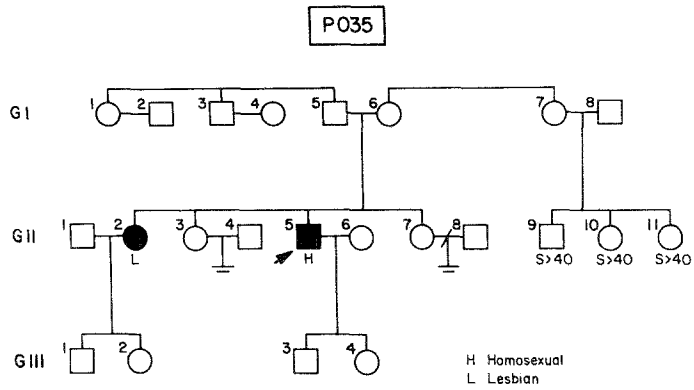

Fig. 2

cide—also chiefly among maternal relatives. The results of the present study, in condensed form, are provided in Table I. The data of Henry (1941), as well as other data from the literature, are summarized at the bottom of Table I.

Among the personally studied cohort of 133 families in 78 kinships, there were 243 sons (109 homosexual and 2 bisexual) and 195 daughters (43 homosexual and 1 bisexual). In 90 families the homosexual probands were male; in 36 they were female. In 7 families the index cases were brothers and sisters. There were 103 *paternal* uncles (U) and 87 *paternal* aunts (A) of male + female homosexuals: $\chi^2 = 0.675$, $p = 0.0412$. There were 134 *maternal* uncles and 262 *maternal* aunts of male + female homosexuals (U/A ratio = 0.51): $\chi^2 = 10.81$, $p = 0.001$. In the sibships there were 131 heterosexual males and 158 heterosexual females. In six families there were 2 homosexual brothers and in two families there were 3 brothers who constituted the index cases. Only once were 2 sisters the index cases. In six families the index cases were 1 brother and 1 sister. In one family the index cases were 3 brothers and 1 sister; only 1 other sister was heterosexual. Data on 3 asexuals, 1 heterosexual transvestite, and 1 severely obsessional man of unknown sexual orientation, whose maternal U/A ratios were consistent with those of the homosexuals, were not included in calculations.

The same results held for families of 34 male probands and index cases of Henry (1941). The maternal U/A ratio, 48/101 yielded $\chi^2 = 9.765$, $p = 0.002$, virtual identity with the present study. Combining the data of the maternal generation of male homosexuals from the two sources, there were 182 maternal U to 293 maternal A: $\chi^2 = 13.14$, $p < 0.0001$ To these numbers were added: (i) those of the maternal U and maternal A of 26 famous male homosexuals; (ii) those of 15 male homosexual probands and

index cases in 10 pedigrees found in or constructed from the literature (Piltz, 1921; Wolf, 1925; Hirschfeld, 1936; Bakwin, 1968; Pillard, 1990; Hamer *et al.,* 1993); (iii) that of the male + homosexual maternal first cousin of Mabel Dodge Ganson (a bisexual); and (iv) those of the two homosexual sons of the homosexual Harold Nicolson and his homosexual wife, Vita Sackville-West, resulted in a total maternal U/A ratio, 241/367, $\chi^2 = 13.20$, $p < 0.0001$.

Examination revealed a significant difference in the U/A ratios of the maternal generation of male and of female homosexuals. In the present study: the maternal U/A ratio for males was 98/160, $\chi^2 = 9.946$, $p = 0.002$; for females the ratio was 28/41, $\chi^2 = 1.221$, $p = 0.269$, χ^2 for the difference was 0.155, $p = 0.694$. In Henry's (1941) study of female homosexuals, the maternal U/A ratio was 28/23. The data on 14 famous female homosexuals disclosed the U/A ratio to be 31/23. The four miscellaneous pedigrees of female homosexuals found in the literature revealed a maternal U/A ratio of 5/5. In sum, the maternal U/A ratio for female homosexuals was 92/92, identity. This is relevant to the view of Pillard (1990) that female homosexuality is genetically transmitted in a manner different from that of male homosexuality.

A homosexual father in P025 sired a homosexual son (GIII,12); in P076 the homosexual father had a homosexual daughter (GIII,2). In P084 both the father *and* the mother were K 5/6 homosexuals. In P019 (GIV,1) the father was bisexual, his son was homosexual and one of his two daughters bisexual. In this series there was one instance (P083,GIII,12) of lesbian mother-to-homosexual son transmission. In Henry's study (1941), there was no instance of homosexual father-to-homosexual son transmission. This, however, occurred in the family of Thomas Mann. In the family of Harold Nicolson and Vita Sackville-West (*both* homosexual) their two live-born children (sons) were homosexuals. The author believes that Christopher Isherwood's father, who had 2 homosexual brothers, was a "closet" homosexual. Finally, in one of the two pedigrees of Wolf (1925), there was one instance of lesbian mother-to-homosexual son transmission.

If homosexuality is genetically transmitted, at least one parent must be a carrier. For example, in this study heterosexual (carrier) father-to-homosexual son transmission occurred in 16 cases (9.5% of all sons), and carrier father-to-homosexual daughter transmission occurred in 5 cases (3.3% of all daughters). In one kinship (P040) two heterosexual men were born to a woman with 5 sisters and no brothers. The wife of one brother had miscarriages before bearing 2 gay sons. His brother's wife gave birth to a lesbian daughter and a gay son. This leaves 83.6% of carrier (sometime homosexual) mother-to homosexual-child transmissions.

In this study the ratio of paternal uncles to paternal aunts was 103/87 for families of male probands, and 36/30 for families of female probands.

In Henry's (1941) study the ratio was 60/60 for males and 33/37 for females. In the families of famous homosexual men the ratio was 52/30 and 35/35 for females. In sum, the paternal U/A ratio for families of male homosexuals was 205/177, $\chi^2 = 1.243$, $p = 0.265$. For the families of female homosexuals the ratio was 104/102, identity.

Relevant to a biological, and specifically genetic, theory for the etiology of homosexuality is the fact that in the present study, 28% of mothers of homosexuals had no live-born brothers and a further 37% had but one apiece. In only nine families were there more males than females in the maternal sibship. The numbers are too small to permit statistical comparison with the data of Geissler (Edwards, 1958), which were based on 4 million births. However, for 1–4 women, Table I of Edwards (1958) shows 3.97% having no brothers, and 7.49% having one brother apiece.

To be noted among first- and second-degree relatives of mothers, in this study and in the literature, are the reported high frequencies of single or multiple spontaneous abortions, of miscarriages, of stillbirths, and of infertility without known cause. Conditions of information collection did not provide secure, quantifiable data with regard to these events. However, in this study the differences are impressive between the numbers of first- and second-degree relatives of fathers of homosexuals, and the relatives of mothers of homosexuals, who were infertile or had multiple failure to bear surviving concepti (MM). So also are the same differences in the numbers for those who remained single past age 30, and for the occurrence of suicide.

Paternal 1°–2° Relative				Maternal 1°–2° Relatives			
Infertile	MM	Single >30	Suicides	Infertile	MM	Single >30	Suicide
8	0	5	3	67	17	13	14

In this summation no correction has been made for the number of families for which there was complete information on the paternal sibship (93, or 70%) and those for which there was complete information on the maternal side (116, or 87%). Some, but not all, of the differences may be attributable to incomplete information on the relatives of the fathers. However, the first kinships obtained alerted the author to the high incidence of infertility and miscarriage in the maternal side of homosexual index cases. The high incidence of suicide in homosexuals and their families has long been known (Hirschfeld, 1914; Schneider *et al.*, 1989; Erwin, 1993), but its significance for a theory of the genesis of homosexuality is unclear at this time.

Table II. The Number of Males and Females Born to Fathers and to Mothers in Families with Semilethal Xq28 Disorders Wherein at Least 5% of the Males have Offspring[a]

MIN No.[b] Genetic condition	Paternal *n*	Maternal *n*
300100 Adrenoleucodystrophy (Addison's disease)	6/14	48/50
303800 Color blindness, RCP (deutan color blindness)	56/92	173/143
304800 Nephogenic diabetes insipidus	41/54	106/113
305900 G-6PD deficiency	23/47	37/33
306700 Hemophilia A, mild form	57/104	216/158
309550 Fragile X, mar Xq28	21/39	415/352
310300 Emery-Dreifuss muscular dystrophy	45/83	188/180
310440 Myopathy/autophagia	3/1	4/0
310460 Myopia, bornholm type	13/35	45/33
Σ of all *n*	255/508	1232/1057
M/F ratio	0.502	1.17
χ^2 between sexes	83.7	13.8
p	<0.0001	<0.0001

Table II. Continued

Number in paternal and maternal sibshipps and offspring in all homosexual families							
		Paternal		Maternal		Offspring	
	Families	Male	Female	Male	Female	Male	Female
This study	133	230	119	132	312	244	198
Henry	55	140	97	76	144	99	93
Literature	21	41	25	28	47	51	32
Famous	40	127	65	66	102	114	82
Σ	249	538	306	302	605	507	413
M/F ratio		1.783		0.494		1.237	
χ^2 between sexes		32.5		52.0		4.81 ($p = 0.029$)	

χ^2 between sexes for Σ of children born to Xq28 fathers and Σ of males + females in the maternal generation bearing homosexual offspring: 1.082, $p = 0.229$.

χ^2 between sexes of differences of total number of children born to Xq28 mothers and total number of children in sibships of homosexuals: 0.936, $p = 0.344$.

[a]Nine such disorders are dealt with. The total number of children born to fathers in these families is compared to the total number of males + females in the maternal generation bearing homosexual offspring; and the total number of children born to mothers in these families is compared to the total number of children in the sibships of homosexuals.

[b]MIM No. is number in McKusick, 1992. *References:* #30100: Catrufo *et al.,* 1987; Davis *et al.,* 1979; Fanconi *et al.,* 1964; Holmberg *et al.,* 1991; O'Neill *et al.,* 1981, 1985; Willems *et al.,* 1990. #303800: Drummond-Borg *et al.,* 1989; Rinaldi *et al.,* 1978. #304800: Cannon, 1955; Carter and Simpkiss, 1956; Kambouris *et al.,* 1988; Knoers *et al.,* 1988. #305900: Boyer and Graham, 1965; Childs *et al.,* 1958; Eber *et al.,* 1985; Ishwad and Naik, 1984; Howell *et al.,* 1972; Nakashima *et al.,* 1977; Veregnes *et al.,* 1981. #306700: Bond, 1962; Boyer and Graham, 1975; Graham *et al.,* 1953; Howard *et al.,* 1988; Pola and Svojitka, 1957; Robertson and Trueman, 1964. #309550: Brown *et al.,* 1985; Opitz *et al.,* 1984. #310300: Consalez, 1991; Dickey *et al.,* 1984; Emery and Dreifuss, 1966; Hopkins, 1985; Mawatari and Katayama, 1973; Merlini *et al.,* 1986; Sulaiman, 1981; Waters, 1975. #309550: Brown *et al.,* 1985; Opitz *et al.,* 1984; Richards *et al.,* 1991; Zoll *et al.,* 1988. #310460: Bartsocas, 1981; Haim, 1988; Schwartz, 1990; Wold, 1949. Others in *References of* this paper: #303800: Hurvich, 1983; Jaeger and Schneider, 1976; Kinnear *et al.,* 1976; Neuhann *et al.,* 1976; Roberts and Pembrey, 1985; Went and deVries-deMoi, 1976; Nathans *et al.,* 1993. #306700: Ramgren, 1962; Roberts and Pembrey, 1985 #309550: Anvret *et al.,* 1988; Buchanan *et al.,* 1987; Dunn *et al.,* 1963; Nordstrom *et al.,* 1992. #310300: Emery and Dreifuss, 1961.

Azoospermia as the cause of infertility was found in two families and raised a question as to its role in the infertility of marriages of relatives of homosexuals. There seems to be no literature dealing with this matter in connection with homosexuality.

All of the above data indicate the occurrence of male fetal wastage in families having homosexual offspring. Indeed, the maternal U/A ratio is a direct measure of this. In this study the overall maternal U/A ratio, (140/335) means that in this cohort 58.2% of the males conceived in the maternal generation died before or without sex determination. The complete data in this paper point to a 36% excess of deaths of male concepti over that of female concepti.

For clarification of the significance of this degree of male fetal wastage, sex ratios were ascertained for parents and their offspring afflicted with each of nine distinct disorders resulting from genes in the Xq28 region (Freije *et al.,* 1992; McKusick, 1992). Each of the nine conditions permits some males to reproduce. This type of condition is commonly referred to as male semilethal. Those dealt with here are among a larger number cited and referenced in McKusick (1992), by MIM number (Table II). They are adrenoleukodystrophy (Addison's disease; MIM 300100); color blindness, RCP (deutan color blindness; MIM 303800, Hurvich, 1981; Jaeger and Schneider, 1976; Kinnear *et al.,* 1976; Nathans *et al.,* 1993; Neuhann *et al.,* 1976; Roberts and Pembrey, 1985; Went and deVries-de Moi, 1976), nephrogenic diabetes insipidus (MIM 304800); G-6-PD deficiency (MIM 305900); hemophilia A, mild form (MIM 306700, Ramgren, 1962, Roberts and Pembrey, 1985); fragile X, mar Xq28 (MIM 309550, Anvret *et al.,* 1988; Buchanan *et al.,* 1987; Dunn *et al.,* 1963; Nordstrom *et al.,* 1992); Emery-Dreifuss muscular dystrophy (MIM 310300 Emery and Dreifuss, 1966); myopathy/autophagia (MIM 310440), and myopia, Bornholm type (MIM 310460). References in McKusick (1992) are cited in Footnote[b] in Table II, as are those not in McKusick.

For male carriers of Xq28 male semilethal disorders, in the paternal generation, there were 255 sons and 508 daughters: χ^2 between sexes = 83.7, $p < 0.0001$ (43% male fetal wastage). The *total* numbers of males and females in the maternal generation, of this study and all others sources of data, bearing homosexual offspring (310/628: χ^2 between sexes = 107.8) differed from these by $\chi^2 = 0.859$, $p = 0.354$. For female carriers of Xq28 disorders there were 1232 sons and 1057 daughters: χ^2 between sexes was 13.8, $p < 0.0001$. Between these and the numbers of male and female children of mothers of homosexual sons and daughters (511/413) $\chi^2 = 0.581$, $p = 0.446$.

DISCUSSION

The genetic theory of the etiology of male and female homosexuality presented here rests upon four major lines of clinical evidence. The first is the pattern of familiarity: In the families of male and female homosexual probands there is a clustering of other homosexuals, chiefly among the maternal relatives. The second consists of the much higher rates among maternal than among paternal relatives of: (i) remaining single past age 30; (ii) infertile marriages and single or multiple spontaneous abortions, miscarriages, and stillbirths; and (iii) suicide. The third line is the much higher concordance rate for homosexuality among MZ than among DZ twins. The fourth line is the distorted sex ratio in the maternal generation bearing male and female homosexuals, matched closely by the numbers of children born to fathers carrying one of eight Xq28-linked disorders. This also reveals the suspected gene for homosexuality to lie in a pseudoautosomal region of the X and Y chromosomes: Xq28/Yq11.

The first and second lines of evidence are somewhat vulnerable to alternative explanations. Yet the numerous occurrences of homosexuality among second- and third-degree relatives of the probands are found almost exclusively among relatives of the mothers of the probands. The large numbers of relatives of homosexuals who remain single or whose marriages are infertile have never constituted a matter for inquiry in the literature dealing with sexual orientation from *any* standpoint. Which social, educational, or other experiences could cause these to occur far more frequently in the maternal than in the paternal extended kinships of homosexuals? As for suicide, there is too little firm knowledge about it with regard to homosexuality to consider it further at this time. Nothing in the literature on prenatal or postnatal environmental factors provides anything like the *consistency* of experience that would be necessary to produce these patterns of familiality.

With regard to the third line of evidence, it is first necessary to consider the failure of MZ twins to be 100% concordant for homosexuality. One of the arguments against genetic, and in favor of environmental factors, in the etiology of homosexuality as presented, for example, by Byne and Parsons (1993), is the fact in both male and female MZ twins the concordance rate for homosexuality is far below an expected 100% (see e.g., Bailey and Pillard, 1991; Bailey *et al.*, 1993; Diamond, 1993; Whitam *et al.*, 1993). Such an argument is simply invalid. In a number of well-defined, genetically determined anatomical and biochemical disorders, MZ twins exhibit much less than 100%—even as little as 50%—concordance. Some of the genetic and other biological mechanisms responsible for this lack of concordance have been reviewed by Vogel and Motulsky (1979)

and by Turner (1994). Indeed, this phenomenon actually calls to attention *the high probability that an unaffected sib or other relative may carry the gene, but in inactive form, as that carried by the affected individual in an active form.* Such inference is relevant to the apparent 9.5% carrier father-to-son transmission of a gene for homosexuality in this study. One may readily surmise that the maternal influence so often related to homosexuality may lie in the mother being a genetic carrier, with traits thereto associated.

The fourth line of evidence, that of a distorted sex ratio in the maternal generation bearing homosexuals, has hitherto never been examined. Could it be shown that the ratio obtained in the present study was faulty? It was specifically to deal with this possibility that the work of Henry (1941), the literature on famous homosexuals, and each and every suitable report in the literature, were examined. Comparing the 90 families in the present study with *male* homosexuals only for (i) their paternal U/A ratio, (ii) their maternal U/A ratio, and (iii) their male heterosexual (HT) sib/female HT sib ratios, with those of the 72 families in the total literature with *male* homosexuals only, the three χ^2 values obtained between the sexes ranged from insignificant ($p > 0.2$) to identify. In like manner, comparing the 36 families in the present study with *female* homosexuals only with the 35 families of *female* homosexuals only from the entire literature, the three χ^2 values obtained between sexes also ranged from insignificant to identify (see Table I). The difference between maternal U/A numbers (241/367) of the combined families with male probands only, and the combined data on families with female probands only (U/A ratio 92/92) strikes they eye forcibly.

For the slight but significant excess of paternal uncles over paternal aunts in families with male index cases, the author has at this time no plausible theory.

Fetal wastage is universal and frequent. Most occurs in the first few weeks after conception, and affects males more than females (Dömötöri, 1966; Roberts and Lowe, 1975; Smart *et al.,* 1982; Byrne *et al.,* 1985). The X chromosome is more involved in this than any other (Stevenson and Bobrow, 1967; Naeye *et al.,* 1971; Jacobs *et al.,* 1974; Hassold, 1986). This distorted sex ratio (302/610, M/F ratio = 0.495), which involves a high rate of male fetal wastage, corresponds very closely to that of the offspring of fathers in families having male semilethal Xq28 disorders, as described above. Further, the ratio of all children born to the mothers of these Xq28 corresponds almost exactly with the ratio of those children born to mothers of homosexuals.

Consider the data of Table II. It appears conceptually as if the mothers bearing homosexuals offspring were derived from the previous paternal generation with male semilethal Xq28-linked (pseudoautosomal) conditions

exhibiting the Sherman paradox (Sherman *et al.,* 1984, 1985; Fu *et al.,* 1991). The relevant gene residing in unaffected male carriers may be modified as it passes through an unaffected female carrier such that when it is passed to the third generation it becomes manifest. Only some males or some females of this third generation will be affected. If this applies to homosexuality, then a significant proportion of relatives of homosexuals who remain single or who are infertile may be carriers of a gene for homosexuality, Type 1.

Is there a well-defined genetic condition that may serve as a model consonant with the data on homosexuality described here? Recently attention has been drawn to some potential candidates. Duchenne and Becker muscular atrophies (C. R. Richards *et al.,* 1990), myotonic dystrophy (Harley *et al.,* 1993), spinal and bulbar muscular atrophy (Riggins *et al.,* 1992), and fragile X syndromes (FraXA to FraXF) (Sherman *et al.,* 1984; Pembrey *et al.,* 1985; Verkerk *et al.,* 1991; Yu *et al.,* 1992; Loesch *et al.,* 1993; Reiss *et al.,* 1993; Kruyer *et al.,* 1994, among others).

An exposition of relevant genetics is called for at this point, to introduce some factors that lead to deviations from classical Mendelianism. Here it is not a matter of a mutation from one nucleotide to another, frame shifts, deletions, etc. (although they also play their parts), but rather of the effects of a variation in length of di- and trinucleotide sequences and of cytosine methylations in inactivation of the gene downstream.

In a variety of genetic conditions, what is called a CpG island (for CpG, read "cytosine-guanine pair," Josse *et al.,* 1961) follows a chain of trinucleotides of variable length just downstream of the beginning of the translation site (McConkie-Rosell *et al.,* 1993; Snow *et al.,* 1993). A disorder consequent to expression of a relevant gene involves varying degrees of methylation of cytosines in either the CpG island and/or the trinucleotide repeats (van der Ploeg and Flavell, 1980; Monk, 1986; Sapienza *et al.,* 1987).

FraX shall be used here as a "paradigm" for homosexuality because it exemplifies the variations which may be involved in sexual orientations. The gene for FraX lies at the Xq27/28 margin (McKusick, 1992). A CpG dinucleotide island of variable length follows a specific trinucleotide repeat $p(CGG)_N$; that is, "polyrepeats of CGG of variable number." In FraX, when the chain of CGG repeat is no longer than about 50, the disorder is not manifested. The longer the chain—which may run up to 4000 repeats—the greater the likelihood of manifestation, the more severe, and the earlier the age of onset disorder. Pembrey *et al.* (1985) called the longer unmethylated repeats "premutations," which alone do not lead to inactivation of the gene. These may be transmitted through more than one generation unnoticed. When the cytosines of the CpG islands, or the extended

trinucleotide repeats, are methylated—as occurs chiefly in passage through the female—they give rise to genetic disorders, parallel in degree to the degree of methylation (Verkerk *et al.,* 1991; Yu *et al.,* 1992; McConkie-Rosell *et al.,* 1993, among others). There extended chains and their methylations are unstable, not only in sperm or ova but also in the somatic cells. Indeed, it appears that discordance between MZ twins is often the result of postzygotic mitotic crossing over (Loesch *et al.,* 1993). A specific example of the effect of methylation is given by Kruyer *et al.* (1994). They described MZ twins discordant for FraX thus:

> in one family, two affected MZ brothers differed in the number of CGG repeats, demonstrating *in vivo* mitotic instability of the CGG repeat and suggesting that the transition to the full mutation occurred postzygotically. In the second family, two MZ sisters had the same number of repeats, but only one was mentally retarded. When the methylation status of the FMR-1 CpG island was studied, we found that the majority of normal chromosomes had been inactivated in the affected twin, thus leading to the expression of the fragile X phenotype. (p. 437)

This instability and variability may lead to apparent failure of transmission, to incomplete penetrance, to extreme or lethal manifestation, or to what appears to emerge as a new mutation (Brook, 1993; Reiss *et al.,* 1993). It is noteworthy that Sherman *et al.* (1984) reported that 44% of the carriers of FraX could not be detected clinically; that "over one-half of carrier females are fresh mutants"; and that "normal brothers have a 17% chance of carrying the gene." How close this is to data reported above!

Unstable premutations may explain variations in expressivity or penetrance of the gene responsible for other disorders, as is the case for incontinentia pigmenti (Traupe and Vehring, 1994), also Xq28-linked. Variation in numbers of repeats affects males more than they do females. The fact that females carry two X chromosomes may be only one of the reasons why homosexuality occurs in females at a rate half that of homosexuality in males; another reason might be that females carry a shorter, or unmethylated, premutation (Hunt and LeMaire, 1992). All these differences, taken together with the relative insensitivity of females to increased length of trinucleotide repeats, may explain the usual carrier state of women in this connection, and conform with the view of Pillard (1990) that the genetics of female homosexuality differs from that of male homosexuality. Why does expression of the gene require fewer maternal aunts than is required in males?

CpG islands and specific trinucleotide sequences are scattered over the entire genome (Gardner-Garden and Frommer, 1989). Wilkie (1993) noted that "The telomeric regions of chromosomes are rich in both genes and hypervariable minisatellite sequences and may be particularly prone to cryptic breakage events (p. 688)." Depending upon the length of di- and trinucleotide

repeats and the locus of methylation, might not the genetic source of homosexuality be transmitted unrecognized, without phenotypic manifestation, through repeated generations? However, the high male fetal wastage involved and the low reproductive rates of male and female homosexuals, given the various estimates of the worldwide prevalence of homosexuality—even if the lowest estimate is employed—would require an appreciable and not inconsiderable mutation rate. Failure to recognize this contributes heavily to the belief that environmental factors produce homosexuality.

These matters are now under intense scrutiny. R. I. Richards and Sutherland (1992), wrote, "The properties of heritable unstable elements come with their own set of rules. Finding out exactly what these rules are, and the circumstances under which these rules contribute to genetic disease and variations, represents a new and unexpected challenge in molecular genetics." Brook (1993) observed: "One year on, the challenge remains much the same." The challenge now is to learn precisely how human sexuality, in both orientation and intensity, is determined by a gene at Xq28; how and why variations occur at different ages: and by what mechanisms homosexuality both of men and of women can arise from a base in common.

In the interval between the original submission of this work in 1990 and April 1994 two papers and numerous commentaries dealing with a possible locus for male homosexuality in the long arm of the X chromosome have appeared. The first (Hamer *et al.,* 1993) revealed a linkage between male homosexuality and DNA sequences in the Xq28 region. The second (Macke *et al.,* 1993) found no linkage to DNA sequences associated with the androgen receptor gene at Xq11.2-12. The paper by Hamer *et al.* (1993) has been criticized by Baron (1993), Fausto-Sterling and Balaban (1993), and by Risch *et al.* (1994). It is interesting that no one has commented on the exclusive inheritance of male homosexuality from the mothers in the report by Hamer *et al.* (1993).

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