

Sexual orientation, handedness, sex ratio and fetomaternal tolerance-rejection

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ABSTRACT

Fraternal birth order (FBO) appears as a prenatal cause of 15% of homosexual males (gays) through mnemonic maternal anti-male factors. Non-right-handed men seem to be protected from homosexuality. Four hypotheses are proposed: (1) androgenic factors of non-right-handedness neutralize anti-male factors; (2) non-right-handedness and homosexuality are lethal or produce mental impairment; (3) non-right-handed male embryos are insensitive to anti-male factors; (4) mothers of non-right-handed fetuses do not produce anti-male factors. Studies of the sex ratio (SR) of older and younger siblings show: (1) a significant heterogeneity in the SR of siblings of right or non-right handed heterosexual men and women; (2) lesbians are born among siblings with high SR; (3) siblings of right-handed gays show a higher SR than non-right-handed gays that present a low SR. Based on our discovery of maternal tolerance-rejection processes, associated with genetic systems (ABO, Rh), where zygotes or embryos different from their mother induce better pregnancy and maternal tolerance than do those that share antigens with their mothers, I propose a new explanation for sexual relationships, sexual orientation, handedness and sibling SR. Lesbian embryos could induce tolerance from mothers with anti-female factors. Non-right-handedness could induce maternal tolerance, or change the maternal compatibility of "gay" embryos. Alternatively, gay embryos could be poor inducers of maternal tolerance towards male traits.

Key terms: homosexuality, handedness, sex ratio, birth order, fetomaternal tolerance, genetic distortions

INTRODUCTION

The biology and genetics of psychosexual differentiation has remained unknown for a long time. This has also been the case with the heterogeneity of the sex ratio (SR) or male proportion (MP) in human populations. A difficulty for these studies is the lack of sharply defined psychosexual phenotypes. We proposed a phenotype dissection of neuro-psychic human sexuality into: sexual identity, sexual orientation (which we consider rather as the configuration of sexual appetite or dia-morpho-philia), sexual psychomotor form, sexual somatic connection, genital connection, and sexual integration in the whole personality (Valenzuela, 1993, 2006). In the last 20 years, two lines of study have found a reliable basis for understanding the biology of human psychosexual development and SR heterogeneity: (1) Human mutants of "sexual" hormones or their metabolism point to the prenatal role of androgens conditioning maleness of the brain, sexual identity and sexual orientation (Hines, 2004; Rahman, 2005; Bocklandt and Vilain, 2007). (2) There is a consistent association among the number of older biological brothers (fraternal birth order, FBO), handedness, SR of siblings and male homosexual orientation (Blanchard and Bogaert, 1996; Zucker et al., 1997; Cantor et al., 2002; Blanchard, 2004, 2006; Blanchard and Lippa, 2006, 2007). The present study analyzes this second line of research.

The influence of FBO on male sexual orientation was attributed to mnemonic maternal anti-male immune factors originated by previous pregnancies with male fetuses; female fetuses would not have such an effect. The FBO effect appears similar to fetomaternal Rh incompatibility, but here the H-Y antigen could induce anti-male factors in the mother. Around 15% of homosexuality is due to FBO; only

biological brothers, reared together or apart from the index homosexual case, are responsible for FBO effect. The probability of being homosexual increases as the number of older brothers increases. Handedness interacts with homosexuality and the SR of siblings; homosexuality, due to FBO, affects non-right-handed men less (Blanchard, 2001, 2004; Blanchard and Bogaert, 1996; Cantor et al., 2002; Bogaert, 2003, 2005, 2006), a relationship explained hypothetically by four prenatal mechanisms (Blanchard and Lippa, 2006, 2007; Blanchard et al., 2006; Blanchard, 2008): (1) androgenic factors associated with non-right-handedness could cancel maternal anti-male factors leading to homosexuality; (2) homosexuality and non-right-handedness together may lead to death, neuro-psychic impairment or any condition that confers a low probability of being ascertained; (3) non-right handed fetuses may be insensitive to maternal anti-male factors; (4) mothers of non-right handed fetuses do not produce anti-male factors. The FBO was found also in transsexuals whose sexual identity, rather than their sexual orientation, is altered (Green, 2000). These hypotheses are in contradiction with the fact that non-right-handedness is more frequent in homosexual men (gays) and women (lesbians) than in heterosexuals (Lalumiére et al., 2000; this study). A hypothetical reconciliation of these contradictory facts was presented by Blanchard (2008). The authors (of the FBO hypothesis, FBO Authors hereafter) thought that if their hypothesis were true, it would predict a higher SR in older siblings. Significant contradictions with the FBO effect were found in a huge Danish sample (Frisch and Hviid, 2006; Blanchard, 2007; Frisch and Hviid, 2007), in which a higher or the highest SR of older siblings was found in lesbians and not in gays; siblings of non-right-handed gays showed a low SR instead, and handedness were more

related to SR distortions than to sexual orientation (Blanchard and Lippa, 2006, 2007, Valenzuela, 2008); among Korean transsexuals, a significant excess of sisters instead of brothers was found (Zucker et al., 2007); the hypothesis of the maternal "antiboy antibody" resulted untenable under new theoretical and data analyses (Whitehead, 2007). Authors seem immune to these refutations and added auxiliary hypotheses to sustain their theory (Blanchard, 2008). The aim of the present study is: (1) to show that there are sufficient contradictions to conclusively refute the standard version of the FBO hypotheses; (2) to propose a new theory that considers, not only distortions (of SR or others) related to gays, but all the distortions and phenotypes, and to give a comprehensive vision of the human SR, in relation to genetic markers and biotic processes of development, within an evolutionary approach. In a previous article, I presented the contradictions of the FBO hypothesis and a new explanation based on fetomaternal tolerance-rejection mechanisms (Valenzuela, 2008). In the present work, I extend the theory with evidence of the SR of older and younger siblings connecting it to organic evolution. I present this theory now, (it is more than 25 years old) because its core is only in Spanish (Valenzuela, 1985; 1987; 2008).

BREVIA ON SEX RATIO (SR)

Present researchers use SR as the ratio of the number of males per 100 females in a population [(number of males)/(100 females)]. Previous studies considered SR as the proportion of males (MP) in the whole population [(males)/(males + females)]. Here, MP is used as SR to be consistent with previous studies. The reader can easily transform MP to SR and vice versa. MP distributes binomially and allows direct tests by the reader; which does not occur with SR.

The primary SR is given by the X-Y chromosome segregation that leads, after fertilization to XX and XY zygotes; we assume that primary SR is 0.5 and binomially distributed. Complex theoretical analyses to explain the factual SR found in populations introduce several non-demonstrated assumptions (James, 2000) that are not used here. We shall be strictly attached to data, X-Y chromosome segregation, and Mendelian, Hardy-Weinberg and elementary statistical distributions, rather than to undemonstrated theoretical assumptions. Studies of SR at birth have revealed that: (1) SR is universally higher than 0.5 (in favor of males). In the USA population (Mathews and Hamilton, 2005), it was 0.512459 in 231,809,422 newborns, between 1940 and 2002; it is similar in Hungary, Venezuela, Canada, Denmark, Italy and in all the assessed large samples (Rex-Kiss, 1991; Chacon-Puignau and Jaffe, 1996; Allan et al., 1997; Jacobsen et al., 1999; Biggar et al., 1999; Ulizzi et al., 2001; this study); (2) There is a universal decay of SR with the birth order; in the USA, SR decayed from 0.51386 among first live newborns to 0.50763 among the 8th or more babies (Biggar et al., 1999; Mathews and Hamilton, 2005; Jacobsen et al., 1999; this study). In grand grand multiparous women, SR may decay to under 0.5 (in favor of females, Juntunen, Kvist, and Kauppila, 1997; Almagor et al., 1998); (3) there is a significant heterogeneity of SR among countries, ethnic groups, maternal age (related to birth order), socioeconomic and cultural variables, environmental stress, time and

several other conditions (Mathews and Hamilton, 2005). Two other universal conditions that affect or alter the SR of siblings deserve a particular analysis: (4) FBO, and eventually (at least by default of FBO) sister birth order (SBO, Zucker et al., 2007) are universal conditions among human siblings; (5) SR is strongly affected by several genetic systems among mother-newborn pairs.

FRATERNAL BIRTH ORDER (FBO) IS A UNIVERSAL CONDITION

Biggar et al. (1999) studied SR in Danish newborns (1,403,021) from 1960 to 1994. They found a universal SR of over 0.5 and its decay with birth order. They also found "Of first births, 51.2 percent were male ... However, the probability of having another boy increased to 51.5, 51.6, 52.4 and 52.2 percent for families with one, two, three, or four prior boys, respectively (p for trend = 0.0007) ... The probability of a newborn being male was greater if the child born immediately before was also male rather than female (p<0.0001)". They summarized this result as: "families with boys were significantly more likely than expected to have another boy (biologic heterogeneity)" This result contradicts the immune FBO hypothesis. They attributed this heterogeneity to biotic factors "It is somewhat surprising that such a basic biologic effect has not been long known ... However, the increasing likelihood of having boys following the birth of prior boys remains an enigma". FBO authors disregarded the article of Biggar et al. (1999) performed on a national sample; otherwise, they could not insist on the exclusivity of the FBO effect on gays (and on the anti-male antibody condition). The FBO effect is a trait of any human sibling (Biggar et al., 1999; this study). Not only the sex of a zygote or embryo influences the subsequent sex or genetic condition of younger siblings, but several genetic systems also influence the genetic proportions (included sexual traits) among younger siblings (Valenzuela et al., 1982, 1984; Valenzuela and Walton, 1985; this study). Both, FBO authors and Biggar et al. (1999) are unaware that biotic or genetic causes of SR heterogeneity were demonstrated long ago (Shield et al., 1958; Valenzuela, 1985, 1987; Valenzuela and Walton, 1985; Rex-Kiss, 1991; next sections).

TOLERANCE-REJECTION ZYGOTE-EMBRYO-FETUS-MOTHER PROCESSES ACCOUNT FOR MOST OF SR HETEROGENEITY

There are at least three processes in which zygote-embryo-fetus-mother compatibility (tolerance)-incompatibility (rejection) have been well documented. (1) The fetomaternal incompatibility of the ABO, Rh, Kell, HLA and other genetic systems: immunological mechanisms lead mothers to reject embryos or fetuses with antigens not present in them. These rejections have produced a range of effects from a mild anemia or arrested development to severe diseases and death (Gessoni et al., 2002; Kumpel 2006; Mannesier, 2007; Baiochi et al., 2007); we call this system specific maternal fetus rejection (SM-F-R). (2) The necessary general system of maternal tolerance to embryos and fetuses that makes pregnancy (an allograft) possible involves the decidua, hormones, natural immunity, immunocytes, dendritic cells, cytokines, HLA and several other immune functions and systems and stops immune maternal rejection reaction (Ober,

1992; Szekeres, 2002; Le Bouteiller and Tabiasco, 2006; Davies, 2007; von Rango 2008). We call this the general mother-embryo tolerance system (GM-E-T), which develops primarily during embryo and fetal ontogeny, (3) a probable primary non-immune system that, at an early stage of development, leads zygotes or embryos with alleles different from maternal alleles to induce pregnancy and maternal tolerance better than zygotes or embryos who share both alleles with their mothers, (Valenzuela et al., 1982; Valenzuela and Harb, 1982; Valenzuela, 1985, 1987; Valenzuela and Walton, 1985; Lucarini et al., 1995; von Rango, 2008). We call this the SAN system; here it is called the specific maternal zygote embryo tolerance rejection (SM-ZE-TR) system. SM-ZE-TR was discovered in relation to Rh and ABO (Valenzuela et al., 1980, 1981, 1982, 1984; Valenzuela and Harb, 1982, 1993; Valenzuela, 1985, 1987, 1996; Valenzuela and Walton, 1985) and probably operates previous to the third week after fertilization, before the known immune reactions of the GM-E-T and SM-F-R systems can be installed. Zygotes or embryos whose genotypes are equal to the maternal one have more difficulty in being implanted or are lost immediately after implantation. The mechanism by which embryos different from their mothers induces more pregnancies and maternal tolerance is likely related to the need that the zygote or embryo to be recognized by the maternal immune system in order to be accepted (Szekeres-Bartho, 2002; von Rango, 2008); embryos different from their mothers are recognized better. This specific system fills in the knowledge gap about the factor that maintains polymorphisms in placental mammals. If mothers reject heterozygous zygotes, embryos or fetus with genes [expressed later than the second or third week after fertilization (ABO, Rh, Kell, HLA, genes for handedness or sexual orientation)] different from their genes, then heterozygotes decrease in the population leading to a loss of population polymorphisms, and to species sterility. The SM-ZE-TR system maintains the genetic variability in placental mammals that appeared near 90 millions years ago (Wible et al., 2007). It is a system that develops during zygote and embryo ontogeny and probably includes the natural immune system and has evolved along with placental mammals phylogeny. In this evolutionary context it is important to remark that in these same studies we found an association between the phenotypes of the Rh system and the plasma iron binding capacity (transferrin) level; phenotypes with CeD haplotype (the most hemolytic one in fetomaternal incompatibility) was associated with the highest iron binding capacity in Chile and Colombia (Valenzuela, Avendaño and Harb, 1991; Valenzuela, Bravo and Alarcon, 1995). Zygotes or embryos communicate to the mother (through some unknown molecular or cellular mechanism in the oviduct or the uterus at the first week of implantation) that his or her genome has a spectrum of genes equal to and different from those of the maternal genome (Valenzuela et al., 1980; 1981; 1982; 1984; Valenzuela and Harb, 1982; Valenzuela, 1985, 1987, 1996; Valenzuela and Walton, 1985; Lucarini et al., 1995; Szekeres-Bartho, 2002; von Rango, 2008). Zygote or embryo losses occur early because mothers do not register them as an abortion (Valenzuela et al., 1982, 1984; Valenzuela, 1985, 1987, 1996), and the analysis of waiting times after losses indicate that they occur before the third or fourth week post-fertilization. These genetic distortions were

also found in relation to the HLA, and in ABO associated with ADA polymorphism (Ober et al., 1983; Astolfi et al., 1990, 1996; Lucarini et al., 1995; Beydoun and Saftlas, 2005). In all these studies SM-ZE-TR was strongly associated with a large heterogeneity of the SR of newborns, filling the conceptual gap on biotic factors involved in the major SR heterogeneity (Shield et al., 1958; Valenzuela et al., 1980, 1981, 1984, Valenzuela, 1985, 1987, 1996; Biggar et al., 1999). The system also fits the universal SR over 0.5 and its decay with birth order; male zygotes or embryos induce better pregnancies and maternal tolerance than female ones, because under equal genome conditions, males always have the Y chromosome genes (not in the PAR region) not shared by females. As other late expressed maleness genes are present in younger brothers (inducing rejection by the SM-E-R system), males may be rejected more frequently than females in successive pregnancies (caution, however, the paternal X chromosome of female embryos could carry more genes than those on the Y chromosome that are not shared by the mother). In agreement with this hypothesis, an increase in heterozygosity was found associated with Rh, ABO or HLA in male newborns (Valenzuela, 1985; Dorak et al., 2002). For SM-ZE-TR, the ABO, Rh, HLA or other genetic systems are only markers that may be causally associated with tolerance-rejection mechanisms, functionally associated with the true systems involved in SM-ZE-TR or in linkage disequilibrium with actual SM-ZE-TR genes. It seems that SM-ZE-TR prevents rejection mainly of genes expressed late in development affected by the SM-F-R system, and induces a better general maternal acceptance of embryos by the GM-E-T system. The zygote-embryo-maternal molecular "talk" in the oviduct is well documented (Hill, 2001; Barnea, 2001; Krussel et al., 2003; Lee and Yeung, 2006; Pui-Keung et al., 2008). If the SR is regulated by SM-ZE-TR, where ABO, Rh, HLA and the residual genome (the remaining genome excluding the mentioned systems) are involved, then any couple, sample or population has its own SR. SM-ZE-TR, solves the enigma of the SR heterogeneity and provides a new understanding of the FBO effect on sexual orientation. Genes for handedness or sexual orientation are probably part of SM-ZE-TR, thus providing a different explanation from that of FBO Authors.

THE NEW ALTERNATIVE (THE SAN OR SM-ZE-TR SYSTEM)

SM-ZE-TR was found for the 18 phenotypes of the RHCE and RHD (present nomenclature for the two Rh loci) loci typed with 5 antisera (Valenzuela, et al., 1981, 1982). The same occurred in the ABO system where A-B and B-A mother-infant pairs were more frequent than expected, in England (Boorman, 1950), Australia (Kirk et al., 1955), Germany (Krauss and Zimmerman, 1970), Chile (Valenzuela, 1985; Valenzuela and Walton, 1985) and India (Rajanikumari, and Srikumari, 1987; Kumari et al., 1992). Table 1 shows the 16 consecutive sib-sib pairs, where indexes (first sib) had the RH3 phenotype [mostly (96.6%) homozygous Rh(+) CeD/CeD, ancient nomenclature but actual chromosome order] and were no more than 3 years older than their sib. The CeD haplotype is the most frequent (0.5); thus both the father and the mother had at least one CeD haplotype. The expected number of RH3 sibs is 8, the observed one was 1 (thus, 16 mothers rejected at least 7 RH3 homozygous embryos after

having one RH3 infant, with whom they share the CeD haplotype), and the total distribution of Rh phenotypes of the second sib a more extreme distribution occurred with a probability of 9.8×10^{-8} . There were only 2 males among 16 indexes (SR=.125, in favor of females, $P=.00146$), and 7 males among sibs (SR=. 4375, in favor of females; $P=.3567$). RH3 indexes come mostly from RH3xRH3 couples; however, only one RH3-RH3 sib-sib pair came from an RH3xRH3 couple, where the mother resulted to be RH6. Thus, no RH3xRH3 couples gave rise to 16 RH3 indexes (expected number is 4; $P=.0183$). These independent probabilities yield a joint probability for the genetic and sex ratio distortion equal to 9.3×10^{-13} . The ABO system shows a similar or more distorted segregation in males and females (2 male indexes were A and only one sib among seven was O, the most frequent phenotype in the population); however, this may be due to another type of distortion by which males have a higher proportion of A and females a higher proportion of O (Valenzuela et al., 1980), we call this consociated chromosome segregation (it is beyond the scope of this analysis). A sib with a genotype different from the index was accepted better (it is possible that SM-ZE-TR have maternal memory). Our prediction was that large samples of newborns typed according to Rh and ABO phenotypes would present a highly significant heterogeneity of the SR. The test of this prediction is presented in Table 2, which shows four 2x2 matrices of mother-newborn pairs from Santiago and Leipzig, that should have the same number of newborns (in each of the four elements of the matrix) according to Mendelian and Hardy-Weinberg laws for the Rh system [Rh(-)-Rh(+)] should equate Rh(+)-Rh(-) mother-newborn pairs]. The ABO phenotypes are classified as non-O (N-O = AB, A and B) and O and the Rh phenotypes as Rh(+) and Rh(-). We chose a sample from Santiago (Chile, Valenzuela and Walton, 1985) and Leipzig (former East Germany, Krauss and Zimmermann, 1970; Valenzuela, 1996) to show that this is a ubiquitous phenomenon. The first element, in Santiago, is 156 {[Rh(-),N-O]-[Rh(+)-N-O]} mother-male-newborn couples; it should be equal to the number of {[Rh(+),N-O]-[Rh(-)-N-O]} mother-male-newborn couples, this resulted to be exactly 156; but the other three elements (of the 2x2 matrix) issued when changing the newborn sex and maternal ABO are quite different (82 vs. 65, $\chi^2_1 = 3.5$, $P = .061$; 188 vs.126, $\chi^2_1=20.5$, $P = 6.1 \times 10^{-6}$; 60 vs. 58, $\chi^2_1=0.07$, $P=.791$). The matrix to the right side with O newborns is still more deviated; the four comparisons of their elements are: 99 vs. 50, $\chi^2_1=24.3$, $P < 10^{-6}$; 300 vs. 215, $\chi^2_1=24.1$, $P=1.01 \times 10^{-6}$; 88 vs. 44, $\chi^2_1=22$, $P = 2.4 \times 10^{-6}$; 267 vs. 213, $\chi^2_1=10.9$, $P = .00096$; respectively. The lowest SR was .4535 and the highest was .5775, within the same matrix (χ^2_1 for the difference =5.7, $P = .017$). However, the SR heterogeneity among the 8 columns was not significant $\chi^2_7=10.1$, $P = .1847$; this indicates that the fusion of classes is not valid and misleading, because significant differences in SR of the opposite sign counterbalance one another; the total average SR does not represent any biotic reality. The sample from Leipzig and several other large samples from Chile, Hungary, Australia, Great Britain, India (Valenzuela, 1985; Valenzuela and Walton, 1985; Rex-Kiss, 1991; Kumari et al., 1992) confirmed this result. The total samples from Santiago and Leipzig are found in literature (Valenzuela and Walton 1985; Valenzuela, 1996). In that total sample, the

heterogeneity of SR was significant in Santiago ($\chi^2_{15}=27.1$, $P = .0278$), but not in Leipzig ($\chi^2_{15}=19.2$, $P = .206$). In Santiago Rh(+)-Rh(-) and Rh(-)-Rh(+) mother-newborn pairs (that are expected to be equal numbers) were 1240 and 927, respectively ($\chi^2_1=79.0$, $P < 10^{-20}$). In Leipzig, this test was $\chi^2_1=6.6$, $P = .0105$. Results for Rh mother-infant pairs were not homogeneous for males and females or ABO phenotypes, as in Santiago with male newborns from N-O - N-O pairs (156 vs. 156) and with an inversion in Leipzig 109 vs. 123 pairs. Both samples confirmed the universal SR in favor of males (0.5160 in 25501 newborns and 0.5163 in 4507 newborns, respectively), but with a significant heterogeneity around this parameter, according to Rh and ABO systems. Technical or clerical errors, bias of ascertainment or of medical policies are definitively ruled out (Nath et al., 1992; Valenzuela and Harb 1993; Valenzuela, 1996). Searching for regular patterns of SR in all the populations is hopeless and misleading; three loci with two alleles each produce more than 134,000,000 of ill (male or right-handed), healthy (female or non-right-handed) linear or non-linear genetic interactive models (Hartl and Maruyama, 1968; Valenzuela, 1997). Moreover, here the statistical rule that a large sample should give a higher significance is not applicable and misleading. We showed, on the contrary, that the smaller the sample of different genotypes (of systems causing SR heterogeneity), the higher the probability of finding a significant difference or heterogeneity (this appears even in contradiction to current operational statistical rules, but in agreement with the epistemology of statistics).

Table 1

Rh, ABO and sex of RH3 indices and their sibs born no more than 3 years after (from Valenzuela et al., 1982, 1984)

INDEX			SIB		
Rh	ABO	Sex	Rh	ABO	Sex
RH3	A	M	RH3	A	M
RH3	A	F	RH6	A	M
RH3	O	F	RH5	O	M
RH3	O	F	RH6	A	M
RH3	A	F	RH6	A	M
RH3	B	F	RH6	B	M
RH3	O	F	RH6	A	M
RH3	A	M	RH6	O	F
RH3	AB	F	RH6	A	F
RH3	A	F	RH5	O	F
RH3	O	F	RH6	O	F
RH3	B	F	RH6	AB	F
RH3	O	F	RH5	A	F
RH3	O	F	RH18	O	F
RH3	O	F	RH6	O	F
RH3	A	F	RH6	O	F

RH3 is the most frequent Rh(+) phenotype (25.89%). The probability (P) for and RH3 index to have a RH3, RH5, RH6 and RH18 sib is 0.6035, 0.1901, 0.1932 and 0.0132, respectively. The tetranomial P of this or more extreme distributions is 9.8×10^{-8} . P of 2 males and 14 female indices (SR = .5146) is 0.00146; and among siblings (7M, 9F) is 0.3567. The joint probability is in the text.

Table 2**Sex Ratio (SR) in Rh and ABO mother-newborn couples**

Newborns ABO	N-O		O				
	Mothers ABO	N-O	O	Total	N-O	O	Total
SANTIAGO							
Rh (-) Mothers - Rh (+) Newborns							
Male	156	82	238	99	300	399	
Female	188	60	248	88	267	355	
Total	344	142	486	187	567	754	
SR	0.4535	0.5775	0.4897	0.5294	0.5291	0.5292	
Rh (+) Mothers - Rh (-) Newborns							
Male	156	65	221	50	215	265	
Female	126	58	184	44	213	257	
Total	282	123	405	94	428	522	
SR	0.5532	0.5285	0.5457	0.5319	0.5023	0.5077	
LEIPZIG							
Rh (-) Mothers - Rh (+) Newborns							
Male	109	42	151	51	59	110	
Female	127	29	156	34	45	79	
Total	236	71	307	85	104	189	
SR	0.4619	0.5915	0.4919	0.6000	0.5673	0.5820	
Rh (+) Mothers - Rh (-) Newborns							
Male	123	27	150	31	43	74	
Female	99	27	126	35	54	89	
Total	222	54	276	66	97	163	
SR	0.5541	0.5000	0.5435	0.4697	0.4433	0.4540	

INCONSISTENCY OF THE FBO HYPOTHESIS ON THE ORIGIN OF GAYS SHOWN WITH THE SAME DATA

Table 3 presents two studies, the first study from Blanchard and Lippa (2006) and the second study from Blanchard and Lippa (2007) of the SR of older siblings according to the sexual orientation and handedness of index cases. The general SR used to test a particular SR was $[106 \text{ (males)}] / [206 \text{ (males + females)}] = 0.5146$ (formal SR = 1.06 or 106). The second study shows results from the general population from a British Broadcasting Corporation (BBC) and BBC One television documentary "Secrets of the Sexes" Internet research survey (hereafter *BBC report*). This study is not completely comparable to the first study because it includes bisexuals together with homosexuals and there is evidence that the rule of stopping child bearing once siblings of both sexes are present, operates in this sample (Blanchard and Lippa, 2007).

If we assimilate the ABO phenotypes to those of sexual orientation, Rh phenotypes to those of handedness and SR of newborns to the SR among older siblings, we are astonished by the similarities of results of Table 2 and Table 3. First, the average SR is over 0.5 among siblings, and therefore in the general population. Second, both tables show significant heterogeneity of SR among phenotypes within each sample. Third, mothers may be classified as those who preferentially have pro-male or anti-female factors, those who have anti-male or pro-female factors, and those with a balance between both kinds of factors. Fourth, there is significant heterogeneity of SR among phenotypes between samples.

Other important specific results of Table 3 are: I) non-right handed lesbians were born to mothers of siblings with the highest SR in both samples (maternal pro-male and anti-female factors); II) there is a tendency of non-right handed individuals to be born in families with low SR (maternal pro-female or anti-male factors), with a remarkable exception of lesbians in both studies; III) high SR or SR distortions are not limited to gays as FBO authors have remarked. IV) In the first study, right-handed individuals have significantly higher SR, with the exception of heterosexual females. Table 4 presents data on younger and older siblings of indexes classified according to sex and sexual orientation in two studies, one from Britain (Bogaert, 2005) and another from Denmark [Blanchard (2007) summarizes data from Frisch and Hviid, 2006]. The Danish study should be considered with care; it includes married individuals and "married" is another phenotype. They consider subjects over 18 years of age. Thus married subjects between 19 and 27 years of age may have more definite sexual traits and may correspond to other sexual phenotypes; on the other hand, the proportion of married males or females in the population may be very different at these ages.

Unfortunately samples of gays and lesbians from Britain are small, but they show a clear tendency towards a high SR in older siblings that decays in younger siblings, in agreement with the universal tendency. Heterosexuals had similar SR in both sets of siblings. In more than 1,300,000 Danes, the universal tendency of SR and of its decay was clearly found, in all categories. It is remarkable that the SR of the whole sample is 0.5329, a high SR (in singleton Danish newborns SR = 0.513, Jacobsen et al., 1999; in Danish siblings SR is 0.512 for the first birth, Biggar et al., 1999). These data definitively refute the expected SR predicted by FBO authors: (1) older siblings of gays should have the highest SR among the phenotypes (the only affected group), but instead they had the lowest SR; (2) younger siblings of gays should present the lowest SR among classes, because of anti-male factors in their mothers, but instead Danish gay younger siblings had the highest SR; (3) the older-younger siblings SR decay of gays is the only non-significant decay ($P=0.276$). Blanchard (2007) argued that the SR of gay siblings was still higher than 0.5146 (or 106). It is evident that this argument shows that using SR = 0.5146 is not valid when the SR for the reference population is known. The Danish authors responded to Blanchard's (2007) interpretation of results (Frisch and Hviid, 2007). We tested the hypothesis of FBO with the SR of the other phenotypic classes and found significant older-younger siblings decay of SR among Danes, in heterosexual men ($P < 10^{-20}$), heterosexual women ($P < 10^{-30}$) and homosexual women ($P = .0024$).

DISCUSSION AND THE NEW HYPOTHESIS BASED ON FETAL-MATERNAL TOLERANCE-REJECTION MECHANISM

In articles on handedness, homosexuality and SR (Blanchard and Lippa, 2006; Blanchard, 2006, 2007, 2008), FBO authors have attempted to show that handedness and sexual orientation of gays predict a high sex ratio (SR) in older siblings (this is rather a post-diction). In the present analysis, the inverse and more logic perspective is taken (Cantor et al., 2002). Maternal conditions determining the SR in older siblings should influence the sex orientation and handedness

of younger siblings. The authors' post-diction is based on the theory that mothers who bore male embryos develop anti-male antibodies that de-masculinize younger embryos or fetuses, increasing their probability of being gay as the number of older brother increases. This probability of homosexuality did not increase in non-right-handed men, hypothetically because of the four possible conditions already mentioned. This theory and its predictions have inner contradictions. I) Cells of the embryo or fetus circulate in the maternal blood during pregnancy (Johnson, Stroh, Khosrotehrani, and Bianchi, 2007; von Rango, 2008), thus after the first pregnancy with a male embryo, mothers should produce anti-male factors and should have siblings with low SR (this is the true expectancy of the hypothesis) and not high SR as the FBO authors have assumed. After two or more brothers, the probability of being a male or a heterosexual male should decrease to nearly zero (Green, 2000). II) A high SR should not be found in lesbian siblings because female fetuses do not immunize their mother as male fetuses do, but instead, lesbians have the highest sibling SR. III) Heterosexual individuals should not present SR heterogeneities, but they did show the largest heterogeneity and SR distortions in their siblings (Blanchard, 2006; Valenzuela, 2008; this study). IV) SR distortions associated with handedness should only be found in gays, but there were major SR distortions associated with handedness in both hetero and homosexuals. V) The

production of gays by this mechanism should be nearly 100%, not 15%. VI) Only gays should present a great decay of SR between older and younger siblings; the data show the reverse situation. These contradictions render the FBO authors' hypotheses and predictions untenable.

FBO authors have assumed that this effect is similar to that of Rh fetomaternal incompatibility, but Rh incompatibility often produces mild to severe fetomaternal impairment. Even the milder ABO incompatibility sometimes leads to neurological impairment (hemolysis and jaundice). The proposed anti-H-Y antigen should act in the same way, and in fact, it is used to sex, arrest development and kill male embryos (Shelton and Goldberg, 1984; White et al., 1987; Ramalho et al., 2004). In our hypothesis, H-Y, which is present from the eight-cell embryo (Blanchard, 2004; Blanchard and Klassen, 1997), and SRY (the main gene for gonad differentiation into testis), present twelve hours after fertilization (Ao, Erickson, Winston and Handyside, 1994) are good candidates to induce maternal tolerance rather than rejection. They are probably responsible for the universal SR in favor of males. To propose that general maternal anti-male antibodies are the cause of homosexuality is incompatible with the universal SR over 0.5, and among older or younger siblings of gays, particularly when they are right-handed. FBO authors have given non-convincing explanations (Blanchard, 2004, 2008) for these refutations of predictions based on some properties of the immune system. This belt of

Table 3

Sex Ratio of older brothers according to sexual orientation and handedness

		1° STUDY (Blanchard and Lippa, 2006) OLDER SIBLING			2° STUDY (Blanchard and Lippa, 2007) OLDER SIBLING				
MALE	FEMALE	TOTAL	SR	P	MALE	FEMALE	TOTAL	SR	P
RIGHT-HANDED HETEROSEXUAL MEN									
326	263	589	0.553	.03	31071	30828	61899	0.502	<10 ⁻⁸
NON-RIGHT-HANDED HETEROSEXUAL MEN									
40	46	86	0.465	.21	4509	4540	9049	0.498	.001
RIGHT-HANDED HOMOSEXUAL MEN (Gays)									
381	305	686	0.555	.02	3734	3577	7311	0.511	.549
NON-RIGHT-HANDED HOMOSEXUAL MEN (Gays)									
86	104	190	0.453	.05	653	658	1311	0.498	.235
RIGHT-HANDED HETEROSEXUAL WOMEN									
329	327	656	0.502	.26	27613	24866	52479	0.526	<10 ⁻⁶
NON-RIGHT-HANDED HETEROSEXUAL WOMEN									
59	74	133	0.444	.06	3256	3061	6317	0.515	.882
RIGHT-HANDED HOMOSEXUAL WOMEN (Lesbians)									
406	359	765	0.531	.20	2648	2254	4902	0.540	.0004
NON-RIGHT-HANDED HOMOSEXUAL WOMEN (Lesbians)									
93	50	143	0.650	.0007	362	307	669	0.541	.169
TOTAL									
1720	1528	3248	0.5296		73848	70089	143937	0.5131	
χ^2 TEST FOR SR HETEROGENEITY									
$\chi^2_7 = 23.53, P=.00138$					$\chi^2_7 = 92.38, P<10^{-15}$				

heuristic protective auxiliary hypotheses, added to save the theory, increases its weakness instead. For example, they have assumed (Blanchard, 2008) that as non-right-handedness is associated with some immune dysfunctions; the mothers of non-right-handed fetus should have an impairment of their immune system and decrease their anti-male reaction. The weakness of this hypothesis is at least twofold. I) The dysfunction should be general, not specific, so that mothers of non right-handed individuals should accept right or non-right handed and hetero or homosexual male embryos better than female ones, compared to right-handed mothers who have children with higher SR. The data contradict this prediction; non-right-handed siblings of gays showed a lower SR than siblings of right-handed gays (Blanchard, 2006; Valenzuela, 2008; Table 3). II) Mothers share half of their genome with their son (2/3 for the X chromosome), and heritability of non-right-handedness can with difficulty be over 0.5, thus the probability that a mother of a non-right-handed man is non-right-handed is less than 0.25; the expected immune impairment of the mother cannot appear in more than 25%; 75% of mothers of non-right handed persons should behave as mothers with normal immunity.

It is difficult to understand how FBO authors could be so blind to the most important conclusion of their results: the high SR of older siblings of lesbians, particularly when they are non-right handed. This is the only regular and systematic

result found in all studies with large samples. FBO authors are focused so strongly on gays that they have not seen the regularity of SR in siblings of lesbians, or the significant heterogeneity of SR within and among samples in all the other phenotypic classes. Searching for the prenatal mechanism of production of gays, they discovered but did not see a Cathedral of Serendipity among the other phenotypes.

Our proposition is founded in our discovery that, among *ceteris paribus* (all other things being equal) genome conditions, a zygote or embryo with a gene not recognized by the mother has a general advantage over those zygotes or embryos that share this gene with the mother, to induce a pregnancy and maternal tolerance. By default, the system rejects, not implanting or conserving, the implanted embryos sharing both alleles with their mothers (Valenzuela et al., 1982, 1984; Valenzuela, 1985, 1987; Valenzuela and Walton, 1985). Finding regularities depends on the population gene frequencies and on the non-linear interactions among the genetic systems involved. In the immune theory of FBO authors, the result depends mostly on the mothers; in our theory it depends mostly on the zygote or embryo interacting with the mother to induce her tolerance. Since several complex and highly polymorphic systems were found to participate in a non-linear equilibrium between tolerance and rejection, the system offers a very interesting spectrum of possibilities with multiple but sharp predictions

Table 4

SR among older and younger siblings of heterosexual and homosexual men and women

OLDER SIBLINGS			YOUNGER SIBLINGS		
Brothers	Sisters	Total SR	Brothers Sisters Total SR		
BRITISH SAMPLE (Bogaert, 2005)					
HETEROSEXUAL MEN					
1870	1758	3628	.5154	1905	.5261
HOMOSEXUAL MEN					
72	50	122	.5902	43	.5244
HETEROSEXUAL WOMEN					
2527	2402	4929	.5127	2412	.5141
HOMOSEXUAL WOMEN					
15	12	27	.5556	23	.5476
TOTAL					
4484	4222	8706	.5150	4383	.5195
DANISH SAMPLE (Blanchard, 2007)					
MARRIED HETEROSEXUAL MEN					
147704	117529	265233	.5569	200425	.5188
MARRIED HOMOSEXUAL MEN					
699	574	1273	.5491	745	.5280
MARRIED HETEROSEXUAL WOMEN					
171571	138838	310409	.5527	201065	.5146
MARRIED HOMOSEXUAL WOMEN					
611	433	1044	.5852	572	.5195
TOTAL					
320585	257374	577959	.5547	402807	.5167

that could be submitted to testing; moreover, this system is complementary to hormonal or the other proposed molecular interactive mechanisms. Here, only one of these multiple alternatives is proposed, but conserving the difference between early expressed genes on general maleness, such as SRY and H-Y, which could induce tolerance (SM-ZE-TR), and late expressed genes, such as those for brain maleness, which could induce rejection (SM-F-R) or developmental impairment. The proposition is based on homogeneous sexual phenotypes; if there are two or more types of gays or lesbians, other very interesting models could be proposed. In our proposition, we work with a stochastic theory; averages, variances and heterogeneities are present in every result. Zygotes are considered as one-cell embryos.

We propose that genes for male homosexuality are weak in determining brain maleness and tolerance (thus, rejection) for these male brain genes. When they are present, mothers produce anti-male (weak induction of tolerance) factors that, associated with their weak brain maleness, lead to the production of homosexual orientation in males. Embryos with these genes behave in some way as female embryos. Mothers that produce siblings with a high SR (pro-male and anti-female factors) would have a tendency to produce gays because their embryos are treated as females that cannot induce a good tolerance reaction for some male neural factors (but good tolerance for general maleness). The probability of producing a gay in such mothers increases with birth order, because of the universal decay of the SR, amplified by the specific genes for weak maleness and tolerance. This happens preferentially in right-handed males; non-right-handedness genes induce tolerance for these latter and for genes of brain maleness; thus embryos with these genes and with genes for brain maleness, especially those for a weak maleness should be protected from maternal anti-male factors and will not increase their probability to be a gay with birth order (male camouflage of their brains). Mothers of siblings with a low SR (anti-male or pro-female factors) should have a higher probability to produce gays (female phenotype); in this case, genes for non-right handedness induce tolerance for general maleness (neutralizes anti-male factors), but not the specific (weak) brain maleness factor that favors homosexual orientation. In mothers of siblings with high SR (anti-female or pro-male factors) genes for lesbianism induce tolerance for being a female embryo (male camouflage) and this increases when the embryo has genes for non-right-handedness (in right-handed mothers that do not have genes for non-right-handedness). In our hypothesis, lesbianism and male homosexuality (gayism) are syndromes that begin at fertilization (the same occurs for heterosexual individuals). The residual genome (the genome that is not one of the genes under study) plays a crucial role in maternal-fetal processes where ABO, Rh, HLA, maleness, femaleness, homo or heterosexuality and handedness (or its linked or associated genes) are involved.

A different alternative comes from the possibility that sexual orientation may not be definitively determined at the prenatal period. We proposed that sexual orientation (sexual diamorphophilia in our nomenclature) has a prenatal predisposition, but a final post-natal constitution (Valenzuela 1993, 2006). The fact that only 15% of gays are related to the FBO, that lesbians show more deviations than

gays in SR of their sibling, that heterogeneity of SR is found in all the classes of sex, sexual orientation and handedness, and several other general contradictions with the FBO hypothesis, indicate that sexual orientation is very probably not fully determined prenatally. Moreover, the studies of sex assignment of genetic intersex conditions indicate that an important part of adult gender identity is acquired postnatally (Cohen-Kettenis, 2005). The phenomenology of sexual orientation shows that we fall in love, have erotic fantasies, and are attracted to concrete human figures that are not in our genomes or in our prenatal life. Thus, we proposed considering sexual orientation as a set of configurations of appetite, that we call sexual diamorphophilia (androphilia, gynephilia, pedo-, zoo-, necrophilia, etc). Since these figures are not in genomes, brain, hormones or prenatal environment, they are probable acquired by imprinting in early postnatal life (Valenzuela, 1993). In agreement with this, we found evidence that neuro-anatomical sexual dimorphism of some nuclei of the human brain stem increases after birth (Cordero et al., 2000; 2001).

ABO, Rh and HLA systems imply clear-cut phenotypes and genotypes. This does not occur with handedness or sexual orientation. Are handedness and sexual orientation real phenotypes? They can hardly be considered "good" phenotypes. How many phenotypic classes are there in the right-handed category? Non-right-handedness includes several phenotypes. Sexual orientation is even more heterogeneous. It is evident that any category includes several different phenotypes and the consequent genetic heterogeneity. What is (sexual) orientation? A cognitive construct? An affective association? An appetite? Are bisexuals homosexual? Orientation has been ascertained not always in concordant instances: fantasies, coital-behavior, and non-coital-behavior, attraction, falling in love, oneiric representations, associated personality traits, and others (Remafedi et al., 1992; Traen et al., 2002; Narring et al., 2003; Zucker, 2005; Sandfort, 2005; Lippa, 2005). Is a person with homosexual fantasies, but heterosexual coital-behavior, homosexual, normal or psychotic? Ontogenetic studies are urgent. At what age is hetero-homosexuality established? Are all pre-homosexuals and pre-heterosexuals going to be homosexuals and heterosexuals, respectively (Blanchard, 2004)? The most probable situation is that FBO does not condition (determine) homosexuality (sexual homo-orientation), but predisposes towards homosexuality in a particular postnatal environment that completes the phenotype.

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