O brother, where art thou? The fraternal birth-order effect on male sexual orientation

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Sigmund Freud has a lot to answer for. As the 20th century began, he convinced medical professionals that abnormal family relationships caused children to develop a homosexual orientation, which could be "cured" by psychoanalysis. Not until the 1970s would psychiatric and psychological associations finally repudiate this idea that gay people have any illness that needs treating. Since then, a host of reports bolster the idea that prenatal events, rather than family relations, affect the likelihood that a person will grow up to be straight or gay. For example, for each additional brother that precedes him, a boy's chance of growing up to be gay increases by a third. If Freud had known that, he might have suggested that the presence of older brothers shifts family dynamics, subjecting the youngest son to a social milieu that leads to homosexuality. However, in this issue of PNAS, Anthony Bogaert (1) provides evidence that the social influence of an older brother is irrelevant to whether his younger brother will develop a homosexual orientation. It is the number of older biological brothers the mother carried, not the presence of older brothers while growing up, that makes some boys grow up to be gay. Older stepbrothers in the home have no effect, although older biological brothers raised apart still exert their influence. These data, by elimination, strengthen the notion that the common denominator between biological brothers, the mother, provides a prenatal environment that fosters homosexuality in her younger sons.

Since Simon LeVay's 1991 (2) report that a brain nucleus that is larger in men than women is also smaller in gay men than straight men, circumstantial evidence has accumulated suggesting that some people really are born to become gay. Most of these findings make family relationships of the sort Freud scrutinized seem irrelevant. For women, a bewildering array of body parts (ears, fingers, eyes, arms) all indicate that lesbians were, on average, exposed to more fetal testosterone (T) than straight women (3–6). The idea that the brains of lesbians might have been masculinized by exposure to fetal T fits easily with animal models, where researchers can make a mammalian brain as masculine or feminine as they like just by controlling how much T reaches the brain, especially early in life (7).

For men, those same putative markers of prenatal T do not paint as clear a picture: some suggest gay men had seen less prenatal T, some suggest they had seen more, and most suggest no difference between gay and straight men (5, 6, 8). But, if T did not provide an easy understanding of male sexual orientation, several other findings still implicated congenital origins for male homosexuality. Twin studies found that sexual orientation is heritable in both sexes (9), and a portion of the X chromosome was implicated in some cases of brothers who were both gay (10). Then, 10 years ago, Ray Blanchard and Anthony Bogaert (11) made a startling, counterintuitive finding: the more elder brothers a boy has, the more likely he is to grow up to be gay. There is no effect of older sisters and no effect of younger siblings of either sex. Curiously, neither older nor younger siblings seem to have any effect on the sexual orientation of females. So it is only older brothers affecting younger brothers. This fraternal birth-order (FBO) effect on male sexual orientation has been replicated in several data sets, including that gathered by Alfred Kinsey's team in the 1940s and 1950s, long before anyone had guessed there might be such an influence. How many men are gay because of older brothers? One estimate is that approximately one in seven homosexual men in North America are gay because of older brothers (12). That means that about a million Americans are either gay men today or boys who are going to grow up to be gay because their mother had sons before them. If their mothers had carried only sisters before, the demographics say, those males would be straight. It stretches the meaning of the word to suggest these boys and men "choose" to be gay. Who gets to choose how many brothers their mother had before them?

But the question of mechanism remains. How do older brothers affect sexual development in their younger brothers? Is it the social influence of the older brothers or something else? Several reports address this question indirectly. For example, retrospective examination of records revealed an FBO effect on birth weight: each subsequent baby a mother carries tends to weigh more, but boys whose mother carried brothers before them did not weigh as much as boys with older sisters (13). The FBO effect on birth weight was greater among boys who turned out to be homosexual than those who became straight, suggesting that those boys who are made gay by older brothers are also more susceptible to the FBO effect on birth weight. Scouring the literature, these authors found an old report that placenta weight, which also tends to get heavier with each subsequent child carried, weighs even more for boys if they have elder brothers rather than elder sisters (14). So, elder brothers make subsequent brothers lighter than they would have been and their placentas heavier. It is hard to see how older brothers could accomplish this socially, but neither do we know that these FBO effects on birth weight and placenta weight have anything to do with FBO effects on orientation.

Most recently, Blanchard *et al.* (15) collated several data sets and found another surprise: older brothers increase the probability of a boy becoming gay only if that boy is right-handed. Among left-handed men, there's no difference in the incidence of homosexuality no matter how many brothers they have. What's curious about this finding is that, by itself, left-handedness makes males and females slightly more likely to be gay (16). So left-handedness makes males slightly more likely to be gay but also negates the effects of older brothers on orientation. Note that, unless the presence of older brothers affects the development of handedness, this result makes it seem unlikely that older brothers are affecting sexual orientation through social influences. Why would boys with a brain organized in a right-handed fashion be affected by their older brothers' antics when boys with a left-handed brain organization are not?

Still, if we want to know whether the social influence of older brothers is

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See companion article on page 10771.

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what is making some younger brothers gay, that hypothesis must be tested directly. This is what Bogaert (1) has done, and the results are compelling. He replicates the oft-reported FBO effect, but finds no effect of older brothers who do not share the same mother, i.e., stepbrothers and brothers with the same father only. That failure to see an effect of stepbrothers might be blamed on a modest sample size, but, on the other hand, an even smaller sample size shows that biological brothers (sharing the same mother) who are raised apart still significantly increase a younger brother's likelihood of becoming gay.

If the presence of the older brothers during development is not responsible for the FBO effect on orientation, what is? One idea proposed by Gualtieri and Hicks (17) in 1985 for other traits found more commonly in males than in females is the "maternal immunization hypothesis" (Fig. 1). A mother carrying a first son has very little exposure to the proteins he is making because of the placental barrier. But upon delivery and the inevitable mixing of fetal and maternal blood, her immune system will now see proteins it has never seen before, including proteins encoded on her son's Y chromosome. If she mounts an immune response to these proteins, then any subsequent sons will be exposed, via active transport across the placenta, to maternal antibodies directed against the male-specific proteins. These maternal antibodies might then perturb development of the younger son, decreasing birth weight and affecting his brain to increase the probability that he will grow up to be gay (13). Whether this is what is really happening for sexual orientation remains to be seen, but it is a provocative hypothesis. Freud thought that a distant, emotionally cold father might prevent a boy from identifying with Dad and steer him to homosexuality. How much stranger it will be if, instead of the father's psychological rejection, it is the mother's immunological rejection that inadvertently but actively makes her son gay?

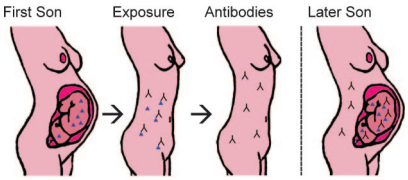

Fig. 1. Maternal immunization hypothesis. When a mother is carrying her first son, the placental barrier protects each from exposure to the other's proteins. But inevitable mixing of blood upon delivery will expose the mother for the first time to male-specific proteins (blue triangles), including those encoded on the Y chromosome. If her immune system produces antibodies to these proteins, then the placenta may actively transport those antibodies (indeed, all IgGs) to subsequent offspring *in utero*, potentially affecting development of later-born sons, but not later-born daughters.

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