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AN ANTIBOY ANTIBODY? RE-EXAMINATION OF THE MATERNAL IMMUNE HYPOTHESIS

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Summary. The maternal immune hypothesis (MIH) argues same sex attraction (SSA) results from maternal immune attack on fetal male-specific brain structures and involves the previous biological influence of elder brothers. One of the surveys supporting this is shown to be based on an unsuitable sample and to contain some strong contrary evidence. The hypothesis relies on at least four speculative ideas and there is evidence against each. (1) Likely immune response prevalence is too low compared with calculated SSA prevalence resulting from the fraternal birth order effect. (2) Testis immune attack would be more likely than brain attack but is not known. (3) Fetal brain structures are practically indistinguishable at birth and subsequent brain anatomical gender differentiation only occurs after birth when no attack is occurring. (4) The hypothesis also predicts unfavourable biology for late birth-order males but in fact the reverse is generally true, and neurological effects are very minor. Studies show aborted fetuses caused by likely maternal immune attack are predominantly girls rather than boys, which also argues against the theory. Studies on identical twins show that common factors such as uterine environment are only a small influence on SSA and post-natal idiosyncratic reactions and non-shared environmental factors are much larger influences.

Introduction

The maternal immune hypothesis (MIH) in its most mature form was due primarily to Gualtieri & Hicks (1985), who argued that mothers may be immunized against male-specific antigens by male fetuses, and in subsequent pregnancies may immunologically attack them, particularly their neural structures. Subsequently Blanchard & Bogaert (1996a, 1996b, 2004) argued that male SSA was one consequence. Good support for this came from the Fraternal Birth Order (FBO) effect, in which each elder brother increased the odds of SSA by about 30% in a male fetus (Cantor *et al.*, 2002). This elder brother effect has been much studied. At least a score of papers confirm it and only a few found a very weak or zero effect. It has been linked with handedness in a rather complicated way (e.g. Blanchard & Lippa, 2006), adding further connections to biological factors. The idea of a biological explanation for this

finding has achieved such currency that some accounts assert that there is essentially no room left for social explanations: 'We may therefore conclude with some degree of certainty that the big brother effect on male sexual orientation has nothing to do with living with older brothers, learning or family dynamics . . . sexual orientation (both straight and gay) is a matter that is pretty much settled well before birth,' (Wilson & Rahman, 2005).

Since the elder brother effect increases SSA odds by about 30% for each elder brother, and people with SSA may have only sisters or be a first-born, it may be calculated that the theory explains as little as 17% of total SSA (Cantor *et al*., 2002). Nor does the hypothesis try to explain SSA in a first-born, which is a major difficulty because a behavioural difference between the two types has never been demonstrated, yet the origins according to the MIH are quite distinct, one involving neurological damage and the other not.

This paper primarily discusses the biology, but first raises some questions from recent papers which make even the FBO a little less certain than has been assumed.

Some general difficulties with the MIH/FBO effect

Bisexuality is both opposite sex attraction (OSA) and SSA. In the study of Bogaert *et al*. (1997), both SSA and bisexual respondents had the same birth order value. One would have expected a birth order value for bisexuals between those of OSA and SSA respondents. This inconsistency needs explanation. There is also a possible clash with the findings of McConaghy *et al*. (2006) on bisexuality, as outlined below.

Bem (1996), who tried to explain the older brother phenomenon in terms of social learning, predicted that effeminacy of young boys would predispose to SSA because of negative older brother reactions. This was a testable idea and taken up in Bogaert (2003) but needs re-evaluation and replication, because as now shown, its sample was inappropriate. But more importantly, it contains evidence that casts doubt on the MIH.

Bogaert used the sample assembled by the Kinsey Institute in 1970 (Bell *et al*., 1981), which has had a strange subsequent history. Bell *et al*. used it to examine the role of social factors in the emergence of SSA, and their work is also frequently cited as showing no social contribution. They suggested biological factors (not studied) were more probably the explanation. However, 30% of the variance in SSA was explained by their social factors, which in one part of their publication is said to be statistically significant and in another not significant. The probable resolution of the conflict is a different context of the word 'significant'. The results were statistically significant, but the effect was not very significant, in the sense of an overwhelming influence. Real social effects on SSA were found; but at each step in their path diagram most of the variance was not explained, meaning that social explanations were not zero, but not predominant. The predominant un-captured factors could have been biological or sheerly random, but Bell *et al*. did not pay much attention to the possibility of chance factors. It is argued below that these are more important than usually appreciated.

Bogaert explained that the '70s Kinsey sample was important because it looked in detail at sex-typed behaviour in childhood, as well as having information about family

structure, such as older siblings. However, he commented that this was an unusual sample. It is one of the few that show only a weak big brother effect on SSA and is therefore atypical in some way. Bogaert suggests that family sizes were small so the full range of bigger brothers was not present to test and the sample was somewhat unrepresentative.

Bogaert's work on this sample shows clearly that effeminacy in a male does not always lead to SSA (though the data allows for the possibility that it may for a few individuals). However, because the sample had atypically few elder brothers one can conclude little about the more general case connected with the fraternal birth order effect, and Bem's suggestion was not thoroughly tested. More significantly, for those with OSA, as femininity decreased, an elder brother effect intensified, meaning there was evidence for an elder brother factor in the development of OSA rather than SSA and the OSA effect in this sample was stronger than the SSA effect. This means that OSA was developing under the influence, biological or social, of elder brothers. A biological elder brother influence on OSA could demand complete reformulation of the MIH but was not commented on in the paper. If the OSA effect is social, this raises the possibility that SSA also might involve social influences. Therefore, in this paper, only one factor was tested against SSA, that only partially, and the OSA influence casts serious doubt on the basis of the MIH.

It is remarkable and ironic that the same 1970s Kinsey Institute sample has formed the basis of two independent studies which are generally taken as showing no social influence on SSA, whereas Kinsey himself thought social explanations were one factor in explaining the SSA–OSA differences he found (Kinsey *et al*., 1948).

Recently Bogaert (2006) reported that the fraternal birth order effect survived adoption, i.e. a boy who was adopted showed a fraternal birth order effect from his biological brothers, not his adoptive elder brothers, and that if elder brothers had the same father but different mothers the elder brother effect vanished. This seemed strong support for biological rather than social origins of the effect. However, the effect size was only 10%, meaning it was a weak effect and could benefit from replication.

A recent paper (Frisch & Hviid, 2006) raises a question about the general applicability of the FBO effect. It surveyed the fraternal birth order effect for the whole population of Denmark in an appropriate age range (n=2,000,000!), taking as a measure of SSA those in the official records who had formalized homosexual marriages. They could find no fraternal birth order effect. Although only a small percentage of those with SSA should be expected to contract such marriages, the lack of a positive finding is disturbing in a survey with such statistical power. One is reduced to arguing that those who contract such marriages are atypical in some way – they are certainly far less closeted than average – but it is hard to see how such a difference could be predominantly biological. This raises the possibility that many previous studies have been affected by sample bias, and this needs checking.

Another recent paper, by McConaghy *et al.* (2006), casts doubt on the MIH and possibly the FBO effect. The authors, rather than studying the 2–3% of subjects in the population whose SSA is predominant, studied the 20% of the population who have predominant OSA and slight SSA attraction. These subjects (compared with

exclusively heterosexual controls) showed both an elder brother and a weaker elder sister effect for men, and an older brother effect for women. The finding of an elder sister birth order effect for women did not reach statistical significance. Several replications were performed though with rather modest size samples. The authors argued that for the results they observed, an MIH was untenable, and social mechanisms were much more likely. Their paper, together with that of Blanchard & Lippa (2006), seem to be the first in which any birth order effect has been shown for women with SSA, though both will need replication by others. It might still be argued, however, that predominant rather than slight SSA is for some speculative reason more definitely biological in origin.

For the remainder of this paper we assume, contrary to the above few papers, that the fraternal birth order effect is real, and examine whether the MIH is a good explanation of it.

The common idea that all social effects on SSA should be dismissed, because of published experimental evidence demonstrating links to biological factors, is greatly exaggerated. However, we now suggest this argument is in fact an almost irrelevant sideshow and that twin studies demonstrate that most of the usually considered biological and social factors are not predominant influences.

Twin studies

Twin studies have an important bearing on the MIH because they measure the influence of biological/genetic factors. For SSA the result is unexpected.

The pairwise concordance of identical twins is one combined measure of pre- and postnatal factors that affects both twins. Identical adult twins, male or female, show pairwise SSA concordance of 11% (14% for female SSA; Bailey *et al*., 2000); identical adolescent twins show pairwise concordance of 7% and 5% for males and females respectively (Bearman & Brueckner, 2002). These results rely on a sample of hundreds of identical twins but based on the numbers involved, probably all the percentages are the same within statistical error. Two other papers give results consistent with these percentages, and earlier papers that conflicted are now universally agreed to have been the result of accidentally biased sampling. Simply, if one identical twin has SSA, the co-twin usually doesn't. These low degrees of concordance are some of the lowest found for any behavioural trait. Prenatal and social factors for twins that they both experience (i.e. common to both) produce an unexpectedly low concordance. This means *neither* biological *nor* social factors are predominant in the genesis of SSA. What makes these twins differ so much? It cannot be the common biological or social factors. In twin studies, factors that produce low concordances are traditionally called 'non-shared environmental experiences', which generally mean postnatal factors, since the prenatal environment mostly involves factors affecting both twins. Hormonal influences, and maternal immune attack, would therefore be minor factors in SSA development, at best.

Non-shared environmental factors include idiosyncratic reactions to the same environment and erratically different features of the same environment. One could imagine, for example that one twin might encounter internet SSA porn and the other might not. One could imagine that one twin is sexually abused and the other is not.

One could imagine one twin reacts against and disidentifies with certain masculine stereotypes, and the other does not. Regardless, there is an unusually high influence in the development of SSA from factors not common to each twin, and these factors are probably difficult to capture in surveys because they are very diverse.

Opposite sex attraction on the other hand has an identical twin pairwise concordance of 94%, one of the highest on record for any behavioural trait. Some reaction to a combination of the biological and social factors they both experience is responsible rather than erratic factors. Same sex attraction and OSA are thus very different.

Unless a special case can be made that SSA from an FBO effect is a class apart, and the above twin studies are misleading, the assumption should be that the origin of SSA is mostly postnatal, not prenatal as the MIH asserts, and that the factors that lead to OSA have little or no effect on individuals who develop SSA.

Gebhard (1965) remarks on anecdotal data from his research experience which show in the development of sexual orientation, the power of chance operating through variables in the immediate situation to an 'almost frightening degree'.

Immunological aspects of the MIH

Researchers have chiefly tried to explain the big brother effect in terms of biological influences. This section aims to show that, when considered in detail, there are considerable difficulties in explaining SSA by the MIH, *viz*. there are at least four layers of hypothesis, each with significant evidence against it. James (2004, 2005, 2006) has also pointed out weaknesses in the MIH, and his accounts should be consulted for facets different from those in this paper.

The MIH (Blanchard & Bogaert, 1996b) suggests an immune reaction in the mother rather similar to the development of Rhesus-D sensitivity in a Rh-negative mother with a Rh-positive baby. The first child is untouched, but the mother has an immune reaction, and subsequent Rh-positive children are severely attacked by the antibodies of the mother, and neurological damage is one of the consequences. This type of immune attack is known as an alloimmune reaction. The hypothesis for SSA development is that the mother reacts to the specifically male gene products of the first boy and creates antibodies. These, like the other maternal antibodies, penetrate the placenta and enter any subsequent fetus. If the fetus is male, the hypothesis argues for a male-specific neurological-structure attack. It also argues for some less specific attack that results in a lower birth weight (Blanchard *et al*., 2002). The resulting boy is supposed to be predisposed to SSA.

According to the theory, the antibodies in the mother increase with each subsequent pregnancy of a male, which explains the constant increase in SSA probability.

Hypothesis 1: Male-specific gene products are immunologically targeted

The first layer of hypothesis is that male-specific gene products are targeted. However, the status of specifically anti-male antibodies is very doubtful and the point of this section is to show that generalized reaction to the more common paternal

antigens is far more likely, and is known. It also argues that, generally, alloimmune reaction prevalence is too rare to cause the SSA under discussion.

Ironically, neither free testosterone, nor the sex-hormone-binding globulin, nor the androgen receptor site on cell membranes in the fetal brain is a possible antigen, because each is already present in the mother. It has been known for many years that testosterone itself is not antigenic. In spite of this, exposition of the MIH usually assumes (without specific assertion) lowered fetal testosterone levels, presumably created indirectly by unspecified means.

Fetal cells are shed in various ways and are easily detectable in the mother (Singal *et al*., 1984). Immunization of the mother against fetal paternal antigens definitely occurs; 15–30% of mothers develop antibodies against various paternal antigens before a second pregnancy (Dankers *et al*., 2003). This is similar to the 10–20% for the Rhesus-D problem. In spite of this, according to the theory, any attack on male fetuses is relatively imperceptible compared with the devastating Rhesus-D attack. This could be because this general mammalian problem of male-fetus toleration probably has a generic solution whose details are presently unclear.

Three of these alloimmune conditions are relatively well known. The first is Neonatal AlloImmune Thrombocytopenia (NAIT; Turner *et al*., 2005), which has a clinically significant prevalence of 0·04%, and perhaps as high as 0·12% if the clinically insignificant variety is included. It is an attack on the blood platelets. The second is the Rhesus-D problem (e.g. Chavez *et al*., 1991), with a prevalence of 0·10%, which is an attack on the red blood cells. The third is Neutropenia (Han *et al*., 2006), which is an attack on the neutrophils, and has a prevalence for neonates of 0·04% but the error may be ± 50% (personal communication, Hutt Valley Health, NZ). The antigens are paternal rather than specifically male. These are all blood components rather than from other tissue types, and the immune reaction may arise because exposure of the mother to fetal blood during the trauma of birth is more likely than exposure to tissue components. Although an immune reaction is not proportional to the absolute amounts of antigens, it is certainly a factor, other things being equal. There are 15 g Hb per 100 ml in male blood and 120 mg of platelets, macro amounts, which should be compared with the amounts of some specifically male targets, such as the family of H-Y antigens (Blanchard & Klassen, 1997), which are only present to act as antigens in micro amounts. This lack of antigenicity is exacerbated because most of the proteins are internal to cells.

Let us say the neonatal prevalence for effects of an anti-male antibody is 0·1%, equal to the non-clinically significant prevalence of NAIT, the most common alloimmune condition. But this is a long way short of the 0·4% prevalence estimated for those with SSA who have elder brothers (conservative estimated total male SSA prevalence 2%, and taking FBO SSA to be 20% of that). The three best known conditions have neonatal prevalences much less than the calculated SSA prevalence and this makes a proposed explanation of an alloimmune condition to explain SSA quite unlikely.

To argue further that MIH causes SSA one would have to say that the actual prevalence of alloimmune attack is 0·4% but that most of the male fetuses do not survive, giving a final prevalence of 0·1%. There is some literature that might support this. According to Lee & Silver (2000) as many as 1% of couples suffer Recurrent

Spontaneous Abortion, defined as three consecutive early miscarriages. About half of these, 0·5%, involve fetuses with normal karyotypes that are thought to be caused by alloimmune reactions to a significant degree. This is close to the figure of 0·4% SSA males with older brothers.

However, from the sex ratios reported (see later), the majority of these spontaneously aborted fetuses are female, so the 0·5% figure has to be a conservative maximum and any male-specific attack would have to be very small.

Alloimmune antibodies, like other antibodies, are presumably secreted in milk in physiologically significant amounts (Gasparoni *et al*., 1992). Haemolytic disease (the Rhesus-D reaction) can be triggered by the antibodies in milk (Beer & Billingham, 1975). One similarly might suspect milk containing male-protein antibodies would be not well tolerated by later birth-order male babies, particularly those who develop SSA. The fascinating possibility that SSA could be partly transmitted or triggered by antibodies in mother's milk seems, alas, an illusion. Breast-feeding should stop unusually early if the milk is not tolerated by the baby. The literature (even cross-culturally) shows the opposite – either that birth order is unrelated to duration of breast-feeding or positively correlated (e.g. Martin *et al*., 2002); however, for further research it might be worth checking whether those who develop SSA and had elder brothers were breast-fed more frequently and/or for less time, than a suitable control group. Again, a very small effect might be hidden at the level of error in the above surveys.

A prevalence figure for unidentified allergic colitis (which should be an indicator of antibodies in milk) among 0- to 4-year-olds in the county of North Stockholm is 0·0001% (Hildebrande *et al*., 2003), much smaller than the FBO-related SSA prevalence of 0·4%. The upper error limit might make the Swedish result as high as 0·0008%, which is still very low. This might seem to rule out a role for milk, but the figure is based on very few cases. The authors say their figure is the lowest on record, but do not cite references for comparison. Order-of-magnitude calculations from medical statistics of immune-related allergic colitis in babies fed breast milk from three cities with far larger numbers of cases, taking account of the likely catchment populations, gives prevalences of 0·05% (Cincinatti: Xanthakos *et al*., 2005), 0·075% (Taipei: Chang *et al*., 2002) and 0·05% (Vienna: Pumberger *et al*., 2001). These are higher than the Swedish figures, approximately in line with the alloimmune prevalences (ca. 0·1%), but remain too low to explain the 0·4% SSA figure above. Both boys and girls are reported with this condition, and it is certainly not male-specific. Also, reactions to cow's milk will be included to an unknown degree and thus the prevalences will be too high. In summary, human milk is unlikely to contain anti-male antigens.

An overall conclusion of this section is that antigenic reaction to paternal blood components in the fetus is numerically unlikely to correspond to FBO/SSA prevalence; male-specific tissue reaction would be even less numerically likely and is hence hypothetical at best.

Hypothesis 2: The male brain is attacked

This seems to fail for the following reasons: (1) partly because there is no testis attack (expected as a parallel consequence); (2) partly on the basis of the brain–blood

barrier; (3) partly because the likely neurological symptoms are not shown by those with SSA; and (4) because at the fetal stage, differences between male and female brains are only statistical (overlapping distributions) rather than dichotomous, and most anatomic differentiation takes place long after birth, when immune attack has ceased.

The total human gene count is currently 22,000 (International Human Genome Sequencing Consortium, 2004), of which male-specific proteins (counting only those on the Y-chromosome) comprise 78 genes (27 different proteins or about 0·3%; Ginalksi *et al*., 2004). These tend to be expressed particularly in the testis, which should be the prime immune target. It contains far more male-specific immune targets than the brain, and both are alike in difficulty of immune attack, having a blood–organ barrier. The only argument advanced against this in the literature (Blanchard & Klassen, 1997) is the weak reason that the testis stem cells that would be attacked are not immediately important to the developing fetus.

Any attack on the testis should result in impairment of fertility in human males with SSA and one would be likely to detect increases in some conditions that usually group together – poor semen quality, hypospadias, cryptorchidism, testicular cancer: collectively testicular dysgenesis. Birth weight is lower for these conditions. However, none of the factors is known to be associated with SSA and indeed individuals with hypospadias, in spite of levels of testosterone that are low right through pregnancy to the postnatal period, have slightly increased levels of psychological masculinity (Sandberg *et al*., 1995). However, paradoxically, the levels of testosterone associated with the MIH, although theoretically producing SSA, do not produce hypospadias. This requires further explanation.

Testicular torsion is moderately well known in male neonates, and produces inflammation (orchitis), but other types of neonatal orchitis that might be considered symptoms of immune attack are uncommon in males. If immune attacks on the testes are so rare, why should there be any on the brain? The simplest interpretation is that no such attack takes place.

A suggestion that some SSA is due to deficient fetal testosterone and some to excess testosterone, a theory to explain reasonably well confirmed sex-ratio differences found in older siblings of right-handers and non-exclusively right-handers (Blanchard *et al*., 2006, Blanchard & Lippa, 2006), adds yet another layer of speculation, and requires much more direct evidence of mechanisms.

In the brain, antigenic targets could be the products of male-specific *SRY* and *ZFY* genes, which are expressed in the fetal brain as they are in the adult brain (Mayer *et al*., 1998), also the products of the two Y-chromosome genes *PCDH11Y* and *NGLN4Y*, which in the brain govern male-specific cell-to-cell communication and cell adhesion (Ginalksi *et al*., 2004), but the products are present in very small amounts.

The blood–brain barrier is forming in the fetus at 4 weeks (Zusman *et al*., 2005), well before the testosterone surge, and is therefore present during any immune attack. The MIH proposes that antibodies to products from the above genes, previously formed in the mother, are transported back into the fetus and enter the brain. However, they could not normally enter the brain because of the blood–brain barrier, except under strongly pathological conditions. These are not supposed to be present in the MIH situation, so some other speculative explanation is required.

The MIH theorizes that there is an excess of male fetus neurological damage (as compared with amounts in female fetuses) in various autoimmune diseases of the mother, though only a minority of children are affected. One survey (Crawford *et al.*, 1992) found that maternal immunoreactivity (presumed in the theory under discussion to include cases where there is reaction to male proteins) was significantly associated with learning difficulties in boys (reading and attention span), but there was no fraternal birth order effect, and only 7·4% of the variance was explained by MIH attack. It was a weak effect, if real. Ross *et al.* (2003) similarly found difficulties with reading and writing (rather than arithmetic) in accompanying maternal immunoreactivity against males.

But in contrast to the MIH, the most definitive study to date with a very large sample of 17,283 mother-and-son pairs, tested whether enhanced autoimmunity in the mother was associated in the fetus with cerebral palsy, mental retardation, seizures, articulation disorder, reading or arithmetic disability, verbal or performance aptitude deficits and ADHD with negative results. After controlling for perinatal variables, enhanced autoimmunity did not correlate with any of the above neurological problems (Flannery & Liderman, 1994). This large survey contradicted the earlier surveys with poorer control, which were the basis of the original Gualtieri–Hicks idea.

So the most definitive study does not support the MIH. It is possible in principle that some male-specific neurological damage might be hidden within the Flannery and Liderman data, but if so, for the moment it must remain speculative.

Further contradicting the MIH, boys with Gender Identity Disorder (GID, presumably proto-SSA) have no deficit in verbal skills (Zucker & Bradley, 1995). Also, the known better verbal fluency in males with SSA (Sanders & Wright, 1997), and the fact that they are not known for learning difficulties, argues against the supposed anti-male immune attack. Zucker and Bradley do note a spatial skills deficit in their GID sample, which might be interpreted as a weak anti-male effect.

In the past the MIH has implied, without being very specific, damage to macro-level neurology. It will now be shown that this is virtually untenable, because of lack of macro-level differences in male and female fetal brains, even shortly after birth, meaning selective attack on a macro scale is not possible, and the hypothesis will have to be restricted to cellular-level attack, but even this will be shown to have difficulties.

The very idea that there is human gender-linked fetal neural organization has been difficult to demonstrate and is doubtful. Adult neural organization is clearly gender-linked and might form a clear basis for selective attack, but the MIH can only be involved with the fetus, and as will be shown now there are only very slight and statistical gender differences just after birth. (The period soon after birth is chosen to avoid as much as possible any confounding factor from later social influences.)

MRI scans have reported only statistical differences in brain structure of neonates, with considerable overlap between the sexes. These instrumental methods are still arguably not capable of differentiating fine enough detail so it is next necessary to consider behavioural traits, which may reflect fundamental differences. Importantly, claimed infant gender behavioural differences also seem statistical in nature rather than dichotomous, and many alleged differences are arguably differences in the properties of skin, ears, adrenals or other organs. There is a definite difference in sleep/wakefulness maturation which lags in boys, and seems specifically a brain

difference (Cornwell, 1993). There is a statistical increase in the attention to faces paid by infant girls compared with boys (Connellan *et al.*, 2000). A sex difference in sensitivity to prenatal injury of the brain is a trend, but often does not reach statistical significance (Lauterbach *et al.*, 2001; Nunez & McCarthy, 2003).

These minor differences, if real, may reflect minor sex differences in brain function or structure, but all differences demonstrated so far between the sexes in infancy are statistical, with great overlap. Because nothing indicates clear dichotomous differences, the hypothesis now must suggest attack on very subtle differences, probably at the cellular level, which develop into the different structures of gendered adulthood after birth, after the immune attack has ceased.

Same sex attraction indeed correlates with more 'feminine' brain structures in adults in several studies. But since the vast majority of brain development in terms of size and function is postnatal and not happening during alleged immune attack, such structures are most likely the result of postnatal experience, not prenatal factors. Several studies show macro changes in the brain due to experience, known as 'plasticity'. This known effect must be weighed against the undocumented MIH assertion that SSA develops regardless of these changes. More evidence is needed.

An attack on 'maleness' should particularly affect development of male genitalia in any fetus which is later SSA-prone. The opposite has been found. From the data gathered by Kinsey, penile lengths were statistically 0·8 cm longer for males with SSA than males with OSA (Bogaert & Hershberger, 1999). These data and their interpretation have not been universally accepted (Krisel, 2000), but even a null finding would be evidence against the theory.

Similarly, male puberty should be delayed if there were fetal genital attack, but the very large *Add Health* longitudinal adolescent study (Savin-Williams & Ream, 2006) showed no difference in age of puberty between those with SSA and those with OSA, contrary to earlier surveys with smaller samples which gave small effects consistent with the MIH.

Hypothesis 3: General immune attack reduces the birth weight

The MIH requires a third layer of hypothesis to explain how the attack affects birth weight. The birth weight deficit for males with SSA who have older brothers is about 170 g or 5%, which is moderate. However the evidence for elder brothers causing a general relative weight deficit in later-born males as compared to females (which ought to occur if a maternal immune effect is involved) is doubtful at best. Later-born brothers ought to suffer immune attack if there are elder brothers, later-born sisters with elder brothers should not, but the evidence is that both are affected equally (Magnus *et al.*, 1985). The effect is very small – about 0·6% for both sexes or a mean lighter weight of $20 \pm 4{\cdot}5$ g compared with a typical birth weight of 3500 g. The Magnus *et al.* study had a sample of 181,000, and was based on the Norwegian Birth Register, and hence is little subject to selection bias. Three other studies had much smaller samples such that even their errors were larger than the 20 g effect above. Their results were varying and two found evidence for possible immune attack. There are three difficulties with the studies. One is that the studies with smaller samples may not have had enough sensitivity; another, that the Magnus *et al.* study

did not follow best practice and included fetuses less than 2500 g in their sample. Another general criticism is that looking for differences of one per cent or less demands stringent control for systematic errors, and none of the studies did that. This is essentially the perennial experimental difficulty of looking for differences between two large numbers. The best conclusion is that the case has not been made for a consistent elder brother effect on weight of later males alone.

The Magnus *et al.* study also compared biologically intact families with those in which the mother had remarried and given birth to further children. If paternal antigens are involved in an immune response, on remarriage the next birth weight should return to the initial state (i.e. comparable to that of the first child, because a different set of immune responses are developing and should only affect the second child after remarriage), but it did not. This is more evidence that the birth weight has nothing to do with an immune response. The authors concluded that for their sample a sensitization hypothesis could not be sustained, at least as it is supposed to be connected with low birth weight.

Obstetricians, on hearing of a low birth weight, first assume the most common cause – prematurity. The second most common cause is placental insufficiency. However, both these reasons militate against the idea of an immune attack. A premature baby is also significantly immune deficient (e.g. Costa-Carvalho *et al.*, 1996) because the mother's usual antibodies transfer later in the pregnancy. Therefore anti-male antibodies are unlikely to transfer either. Placental insufficiency frequently and similarly causes inadequate transfer of maternal antibodies and therefore this would apply to anti-male antibodies. Both the common causes of low birth weight are therefore likely to minimize immune attack by anti-male antibodies. However, Vernier (1975) showed that the placenta weight was greater with increased birth order, *a fortiori* if there were elder brothers. This makes placental insufficiency very unlikely to be the cause of the low birth weight. However, in line with the MIH, it should allow increased levels of any antibody transfer from the mother.

A third cause of low birth weight is strong and general autoimmune attack on a fetus in such conditions as lupus erythematosus, accompanied by many obvious symptoms at birth. It seems unlikely that the subtle and mild immune attack posited for those with SSA would lead to significant weight deficit.

A fourth cause of low birth weight, noted above, is associated with the hypospadias cluster of conditions, but this should not apply in the present case, because hypospadias is not known to be elevated in SSA.

It seems none of the above four reasons is likely to produce the low birth weight observed. Although there appears to be a real low-birth-weight effect associated with SSA, it does not seem associated with an MIH, and thus its cause is a further layer of speculation.

Hypothesis 4: The intensifying immune attack does not affect most subsequent male fetuses

Immunization of the mother to male fetuses should be very common – possibly a majority of cases and certainly much higher than the 2–3% level expected for SSA (Laumann *et al.*, 1994). Why then is SSA prevalence so low?

By analogy with the Rhesus-D syndrome, virtually all subsequent male babies should be attacked with increasing virulence, because the antibodies are male-specific. However, after the birth of a boy who develops GID (hence probably SSA), few subsequent males in the birth order will have GID (Green, 2000); at least 95% of them will develop OSA. Generally, later birth-order OSA males should suffer many physical problems if increasingly immunologically attacked by the mother. However, the opposite is true. Later birth-order males are increasingly heavy (Juntunen *et al*., 1997; possibly a biological 'elder sister' effect), have less Type I diabetes (Cardwell *et al*., 2005), less male breast cancer (Sorenson *et al*., 2005), less testicular cancer (Richiardi *et al*., 2004), better reading skills and fewer attention problems (Crawford *et al*., 1992). Cryptorchidism is not correlated (Preiksa *et al*., 2005), fluctuating asymmetry increases with birth order, but there is no fraternal birth order effect (Benderlioglu & Nelson, 2004; the earlier, much smaller study of Lalumiere *et al*. (1999) showed a significant effect). Later birth-order males are consistently slightly heavier than females (Velonakis *et al*., 1997) – not a sign of generalized immune attack. Many of the male-associated conditions in the above list would plausibly be candidates for attack by anti-male antibodies, but although there are some exceptions, late birth-order is generally a factor for better health, not worse.

There are slightly fewer males born with increasing birth order (James, 1975), but statistical analysis shows this is probably due to paternal age, secondarily maternal age (Jacobsen *et al*., 1999), rather than increased death rates of male fetuses. Although it is generally thought that male fetuses are more vulnerable and predominate in miscarriages, closer analysis shows the opposite is found in that proportion of miscarriages from recurrent spontaneous abortion which could be ascribed to alloimmune conditions (taken as those with normal karyotype). Surveys for the sex ratios (male:female) give 0·76 (Eiben *et al*., 1987), 0·71 (Eiben *et al*., 1990), 1·03 (Be *et al*., 1997), 0·77 (Smith *et al*., 1998), 0·77 (Evdokimova *et al*., 2000), 0·83 (Morikawa *et al*., 2004), 0·35 (Haler & Fauzdar, 2006) and 0·09 (Kano *et al*., 2004). From this we conclude that female fetuses are selectively aborted in probable alloimmune conditions, not male. This is contrary to the MIH, which if it exists at all and is responsible for selective male fetus wastage, must only exert a very small effect.

On the other hand, Turner (1995) found an excess of female relatives of male homosexuals, possibly implying male fetal wastage. Although the evidence is quite indirect, if it is so, this does not seem connected with immune reaction.

It is still possible in principle that the small subset of boys with future SSA are selectively affected, but there are few studies specifically on their progenitors, the very effeminate boys. It is perhaps worth noting that Zuger (1974) found an excess of 'imperfect descent of the testes' and speech impairment in his sample of effeminate boys, but Zucker & Bradley (1995) did not notice this in their more recent clinical experience.

So the unexplained difficulty with the MIH is: why are so few male fetuses affected when maternal immunization is so high. And why does SSA appear so erratically in both earlier and later born males rather than consistently? It might be worth looking at whether males with effeminacy later in the birth order are born increasingly physically impaired, though adequate sample sizes will be a problem.

There are at least four layers of hypothesis in the MIH as outlined in the last four sections. Since there are reasons from the literature why each layer is improbable, a further series of speculative reasons must be advanced and this takes the theory beyond the 'speculative' in the words of Bogaert (2003), into the highly speculative realm. Occam's razor suggests simpler ideas would be preferable.

Conclusion

An antiboy antibody? Unlikely. Gooren (2006), in his review on psychosexual development, bluntly concludes 'The biological basis advanced for the fraternal birth order hypothesis lacks any experimental support'. The present paper argues further that there is a significant weight of evidence against the MIH, whatever the explanation of the FBO effect may be. The MIH was an intellectually clean and satisfying explanation for the FBO effect, and its original authors are to be commended. However, present evidence is for alloimmune reactions being probably too rare to account for the SSA prevalence observed, no support for macro-structural-level attack, unlikely attack on brain if not on testes, no MIH-related lower birth weight, healthier late-birth-order males. At the least, any modification of the MIH would demand serious consideration of the apparent disproportionate deaths of female fetuses during immune attack. One might sincerely hope that any revised theory will be simpler than the present one – which in any case attempts to account for only 17% of SSA.

The very division of SSA into FBO origin and other more major origins seems to raise difficulties. Twin study conclusions are challenging because they simultaneously dispose of most biological and social reasons for SSA; erratic and individualistic causes should predominate.

Because of the erratic nature of SSA in later-birth-order boys, even an acceptance of the MIH would seem to demand an acceptance of a principle that something akin to chance predominates.

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References

Bailey, J. M., Dunne, M. P. & Martin, N. G. (2000) Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *Journal of Personality and Social Psychology* **78**, 524–536.

Be, G., Velasquez, P. & Youlton, R. (1997) Spontaneous abortion: cytogenetic study of 609 cases. *Revista Medica de Chile* **125**, 317–322.

Bearman, P. S. & Brueckner, H. (2002) Opposite-sex twins and adolescent same-sex attraction. *American Journal of Sociology* **107**, 1179–1205.

Beer, A. E. & Billingham, R. E. (1975) Immunologic benefits and hazards of milk in maternal-perinatal relationship. *Archives of Internal Medicine* **83**, 865–871.

Bell, A. P., Weinberg, M. S. & Hammersmith, S. K. (1981) *Sexual Preference: Its Development in Men and Women.* Indiana University Press, Bloomington, Indiana.

Bem, D. J. (1996) Exotic becomes erotic: a developmental theory of sexual orientation. *Psychological Review* **103**, 320–335.

Benderlioglu, Z. & Nelson, R. J. (2004) Season of birth and fluctuating asymmetry. *American Journal of Human Biology* **16**, 298–310.

Blanchard, R. & Bogaert, A. F. (1996a) Biodemographic comparison of homosexual and heterosexual men in the Kinsey Interview data. *Archives of Sexual Behavior* **25**, 551–579.

Blanchard, R. & Bogaert, A. F. (1996b) Homosexuality in men and number of older brothers. *American Journal of Psychiatry* **153**, 27–31.

Blanchard, R. & Bogaert, A. F. (2004) Proportion of homosexual men who owe their sexual orientation to fraternal birth order: An estimate based on two national probability samples. *American Journal of Human Biology* **16**, 151–157.

Blanchard, R., Cantor, J. M., Bogaert, A. F., Breedlove, S. M. & Ellis, L. (2006) Interaction of fraternal birth order and handedness in the development of male homosexuality. *Hormones and Behavior* **49**, 405–414.

Blanchard, R. & Klassen, P. (1997) H-Y antigen and homosexuality in men. *Journal of Theoretical Biology* **185**, 373–378.

Blanchard, R. & Lippa, R. A. (2006) The sex ratio in older siblings in non-right-handed homosexual men. *Archives of Sexual Behavior* doi:10.1007·210508-006–9107–6.

Blanchard, R., Zucker, K. J., Cavacas, A., Allin, S., Bradley, S. J. & Schachter, D. C. (2002) Fraternal birth order and birth weight in probably prehomosexual feminine boys. *Hormones and Behavior* **41**, 321–327.

Bogaert, A. F. (2003) Interaction of older brothers and sex-typing in the prediction of sexual orientation in men. *Archives of Sexual Behavior* **32**, 129–134.

Bogaert, A. F. (2006) Biological versus nonbiological older brothers and men's sexual orientation. *Proceedings of the National Academy of Sciences* **103**, 10771–10774.

Bogaert, A. F., Bezeau, S., Kuban, M. & Blanchard, R. (1997) Pedophilia, sexual orientation and birth order. *Journal of Abnormal Psychology* **106**, 331–335.

Bogaert, A. F. & Hershberger, S. (1999) The relation between sexual orientation and penile size. *Archives of Sexual Behavior* **28**, 213–221.

Cantor, J. M., Blanchard, R., Paterson, A. D. & Bogaert, A. F. (2002) How many gay men owe their sexual orientation to fraternal birth order? *Archives of Sexual Behavior* **31**, 63–71.

Cardwell, C. R., Carson, D. J. & Patterson, C. C. (2005) Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. *Diabetic Medicine* **22**, 200–206.

Chang, J. W., Wu, T. C., Wang, K. S., Huang, I. F., Huang, B. & Yu, I. T. (2002) Colon mucosal pathology in infants under three months of age with diarrhea disorders. *Journal of Pediatric Gastroenterology and Nutrition* **35**, 387–390.

Chavez, G. F., Mulinare, J. & Edmonds, L. D. (1991) Epidemiology of Rh hemolytic disease of the newborn in the United States. *Journal of the American Medical Association* **265**, 3270–3274.

Connellan, J., Baron-Cohen, S., Wheelwright, S., Batki, A. & Ahluwalia, J. (2000) Sex differences in human neonatal social perception. *Infant Behavior and Development* **23**, 113–118.

Cornwell, A. C. (1993) Sex differences in the maturation of sleep/wake patterns in high risk for SIDS infants. *Neuropediatrics* **24**, 8–14.

Costa-Carvalho, B. T., Vieria, H. M., Dimantas, R. B., Aslanian, C., Naspitz, C. K., Sole, D. & Carneiro-Sampaio, M. M. (1996) Transfer of IgG subclasses across placenta in term and preterm newborns. *Brazilian Journal of Medical and Biological Research* **29**, 201–204.

Crawford, S. G., Kaplan, B. J. & Kinsbourne, M. (1992) The effects of parental immunoreactivity on pregnancy, birth and cognitive development: maternal immune attack on the fetus? *Cortex* **28**, 483–491.

Dankers, M. K., Roelen, D., Korfage, N., de Lange, P., Witvliet, M., Sandkuiil, I., Doxiadis, I. I. & Claas, F. H. (2003) Differential immunogenicity of paternal HLA Class I antigens in pregnant women. *Human Immunology* **64**, 600–606.

Eiben, B., Bahr-Porsch, S., Borgman, S., Gatz, G., Gellert, G. & Goebel, R. (1990) Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. *American Journal of Human Genetics* **47**, 656–663.

Eiben, B., Borgman, S., Schubbe, I. & Hansman, I. (1987) A cytogenic study direction from chorionic villi of 140 spontaneous aborters. *Human Genetics* **77**, 137–141.

Evdokimova, V. N., Nikitina, T. V., Lebedev, I. N., Sulchanova, N. N. & Nazarenko, S. A. (2000) Sex ratio in early embryonal mortality in man. *Ontogenez* **31**, 251–257.

Flannery, K. A. & Liderman, J. (1994) A test of the immunoreactive theory for the origin of neurodevelopmental disorders in the offspring of women with immune disorder. *Cortex* **30**, 635–645.

Frisch, M. & Hviid, A. (2006) Childhood family correlates of heterosexual and homosexual marriages: a national cohort study of two million Danes. *Archives of Sexual Behavior* **35**, 533–547.

Gasparoni, A., Avanzini, A., Ravagni Probizer, F., Chirico, G., Rondini, G. & Severi, F. (1992) IgG subclasses compared in maternal and cord serum and breast milk. *Archives of Disease in Childhood* **67**(1), Special No., 41–43.

Gebhard, P. H. (1965) Situational factors affecting human sexual behavior. In Beach, F. A. (ed.) *Sex and Behavior*. John Wiley and Sons, New York, pp. 483–495.

Ginalksi, K., Rychlewski, L., Baker, D. & Grishin, N. V. (2004) Protein structure prediction for the male specific region of the human Y chromosome. *Proceedings of the National Academy of Sciences* **101**, 2305–2310.

Gooren, L. (2006) The biology of human psychosexual differentiation. *Hormones and Behavior* **50**, 589–601.

Green, R. (2000) Birth order and ratio of brothers to sisters in transsexuals. *Psychological Medicine* **30**, 789–795.

Gualtieri, T. & Hicks, R. E. (1985) An immunoreactive theory of selective male affliction. *Behavioral and Brain Sciences* **8**, 427–441.

Haler, A. & Fauzdar, A. (2006) Skewed sex ratio and low aneuploidy in recurrent early missed abortion. *Indian Journal of Medical Research* **124**, 9–10**.**

Han, T. H., Chey, M. J. & Han, K. S. (2006) Granulocyte antibodies in Korean neonates with neutropenia. *Journal of the Korean Medical Society* **21**, 627–632.

Hildebrand, H., Finkel, Y., Grahnquist, L., Lindholm, J., Ekbom, A. & Aksling, J. (2003) Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990–2001. *Gut* **52** 1432–1434.

International Human Genome Sequencing Consortium (2004) Finishing the euchromatic sequence of the human genome. *Nature* **431**, 931–945.

Jacobsen, R., Moller, H. & Mouritsen, A. (1999) Natural variation in the human sex ratio. *Human Reproduction* **14**, 3120–3125.

James, W. H. (1975) Sex ratio and the sex composition of the existing sibs. *Annals of Human Genetics* **38**, 371–378.

James, W. H. (2004) The cause(s) of the fraternal birth order effect in male homosexuality. *Journal of Biosocial Science* **36**, 51–59, 61–62.

James, W. H. (2005) Biological and psychological determinants of male and female human sexual orientation. *Journal of Biosocial Science* **37**, 555–567.

James, W. H. (2006) Two hypotheses on the causes of male homosexuality and paedophilia. *Journal of Biosocial Science* **38**, 745–761.

Juntunen, K. S., Laara, E. M. & Kauppila, A. J. (1997) Grand grand multiparity and birth weight. *Obstetrics and Gynecology* **90**, 495–499.

Kano, T., Mori, T., Furudono, M., Kanda, T., Maeda, Y., Tsubokura, S., Ushiroyama, T. & Ueki, M. (2004) Sex differences of abortuses and neonates in women with allo-immune recurrent abortions. *Reproductive Biomedicine Online* **9**, 306–311.

Kinsey, A. C., Pomeroy, W. B. & Martin, C. E. (1948) *Sexual Behavior in the Human Male*. W. B. Saunders, Philadephia.

Krisel, W. (2000) Regarding ''The relation between sexual orientation and penile size'' by A. F. Bogaert and S. Hershberger. *Archives of Sexual Behavior* **29**, 303–305.

Lalumiere, M. L., Harris, G. T. & Rice, M. E. (1999) Birth order and fluctuating asymmetry: a first look. *Proceedings of the Royal Society (London) Series B* **266**, 2351–2354.

Laumann, E. O., Gagnon, J. H., Michael, R. T. & Michaels, S. (1994) *The Social Organization of Sexuality*. University of Chicago Press, Chicago.

Lauterbach, M. D., Raz, S. & Sander, C. J. (2001) Neonatal hypoxic risk in preterm birth infants: The influence of sex and severity of respiratory distress on cognitive recovery. *Neuropsychology* **15**, 411–420.

Lee, R. M. & Silver, R. M. (2000) Recurrent pregnancy loss: summary and clinical recommendations. *Seminars in Reproductive Medicine* **18**, 433–440.

Magnus, P., Berg, K. & Bjerkedel, T. (1985) The association of parity and birth weight: testing the sensitization hypothesis. *Early Human Development* **12**, 49–54.

Martin, R. M., Smith, G. D., Mangtani, P., Frankel, S. & Gunnell, D. (2002) Association between breast feeding and growth: the Boyd–Orr cohort study. *Archives of Diseases of Childhood – Fetal and Neonatal Edition* **87**, F193–201.

Mayer, A., Lahr, G., Swaab, D. F., Pilgrim, C. & Reisert, I. (1998) The Y-chromosomal genes *SRY* and *ZFY* are transcribed in the adult human brain. *Neurogenetics* **1**, 281–288.

McConaghy, N., Hadzi-Pavlovic, D., Stevens, C., Manicavasagar, V., Buhrich, N. & Vollmer-Conner, U. (2006) Fraternal birth order and ratio of heterosexual/homosexual feelings in women and men. *Journal of Homosexuality* **51**, 161–174.

Morikawa, M., Yamada, H., Kato, E. H., Shimada, S., Yamada, T. & Minakami, H. (2004) Embryo loss pattern is predominant in miscarriages with normal chromosome karyotype among women with repeated miscarriage. *Human Reproduction* **19**, 2644–2647.

Nunez, J. L. & McCarthy, M. M. (2003) Sex differences and hormonal effects in a model of preterm infant brain injury. *Annals of the New York Academy of Sciences* **1008**, 281–284.

Preiksa, R. T., Zilaitiene, B., Matulevicius, V., Skakkebaek, N. E., Petersen, J. H., Jorgensen, N. & Toppari, J. (2005) Higher than expected prevalence of congenital crytorchidism in Lithuania: a study of 1204 boys at birth and 1 year follow-up. *Human Reproduction* **20**, 1928–1932.

Pumberger, W., Pomberger, G. & Geissler, W. (2001) Proctocolitis in breast fed infants: a contribution to differential diagnosis of haematochezia in early childhood. *Postgraduate Medical Journal* **77**, 252–254.

Richiardi, L., Akre, O., Lambe, M., Granath, F., Montgomery, S. M. & Ekbom, A. (2004) Birth order, sibship size, and risk for germ-cell testicular cancer. *Epidemiology* **15**, 323–329.

Ross, G., Sammaritano, L., Nass, R. & Lockshin, M. (2003) Effects of mothers' autoimmune disease during pregnancy on learning disabilities and hand preference in their children. *Archives of Pediatric and Adolescent Medicine* **157**, 397–402.

Sandberg, D. E., Meyer-Bahlburg, H. F. L., Yager, T. J., Hensle, T. W., Levitt, S. B., Kogan, S. J. & Reda, E. F. (1995) Gender development in boys born with hypospadias. *Psychoneuroendocrinology* **20**, 693–709.

Sanders, G. & Wright, M. (1997) Sexual orientation differences in cerebral asymmetry and in the performance of sexually dimorphic cognitive and motor tasks. *Archives of Sexual Behavior* **26**, 463–480.

Savin-Williams, R. C & Ream, G. L. (2006) Pubertal onset and sexual orientation in an adolescent national probability sample. *Archives of Sexual Behavior* **35**, 279–286.

Singal, D. P., Butler, L., Liao, S. K. & Joseph, S. (1984) The fetus as an allograft: evidence for anti-idiotypic antibodies induced by pregnancy. *American Journal of Reproductive Immunology* **6**, 145–151.

Smith, M. J., Creary, M. R., Clarke, A. & Upadhyaya, M. (1998) Sex ratio and absence of uniparental disomy in spontaneous abortions with a normal karyotype. *Clinical Genetics* **53**, 258–261.

Sorensen, H. T., Olsen, M. L., Mellemkjaer, L., Lagiou, P., Olsen, J. H. & Olsen, J. (2005) The intrauterine origin of male breast cancer; a birth order study in Denmark. *European Journal of Cancer Prevention* **14**, 185–186.

Turner, W. J. (1995) Homosexuality, type 1: an Xq29 phenomenon. *Archives of Sexual Behavior* **24**, 109–134.

Turner, M. C., Bessos, H., Fagge, T., Harkness, M., Rentoul, R., Seymour, J. *et al.* (2005) Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to ani-HPA-1a. *Transfusion* **45**, 1945–1956.

Velonakis, E. G., Maghiorakos, P., Tzonou, A., Barrat, J., Proteau, J. & Lapdopoulos, I. (1997) The relation of birth weight and gestational age to biological, occupational and socio-economic factors. *Clinical and Experimental Obstetrics and Gynecology* **24**, 232–236.

Vernier, M. C. (1975) Sex differential of survival during perinatal period: an immunologic phenomenon? *Pediatric Research* **9**, 176–180.

Wilson, G. & Rahman, Q. (2005) *Born Gay. The Psychobiology of Sex Orientation*. Peter Owen, London.

Xanthakos, S. A., Schwimmer, J. B., Aldana, H. M., Rothenberg, M. E., Witte, D. P. & Cohen, M. B. (2005) Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: a prospective cohort study. *Journal of Pediatric Gastroenterology and Nutrition* **41**, 16–22.

Zucker, K. J. & Bradley, S. J. (1995) *Gender Identity Disorder and Psychosexual Problems in the Children and Adolescents.* Guilford Press, New York.

Zuger, B. (1974) Effeminate behavior in boys. Parental age and other factors. *Archives of General Psychiatry* **30**, 173–177.

Zusman, I., Gurevich, P. & Ben-Hur, H. (2005) Two secretory immune systems (mucosal and barrier) in human intrauterine development, normal and pathological (Review). *International Journal of Molecular Medicine* **16**, 127–133.