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How Studies Of Human Sex Ratios At Birth May Lead To The Understanding Of Several Forms Of Pathology

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REVIEW ARTICLE

HOW STUDIES OF HUMAN SEX RATIOS AT BIRTH MAY LEAD TO THE UNDERSTANDING OF SEVERAL FORMS OF PATHOLOGY

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1. ABSTRACT

This paper deals with the problem of the causes of the variation of sex ratio (proportion male) at birth. This problem is common to a number of areas in biology and medicine e.g. obstetrics, neurology/psychiatry, parasitology, virology, oncology and teratology. It is established that there are significantly biased, but unexplained, sex ratios in each of these fields. Yet workers in them (with the possible exception of virology) have regarded the problem as a minor loose end, irrelevant to the field's major problems. However, as far as I know, no-one has previously noted that unexplained biased sex ratios occur, and thus pose (perhaps similar) problems, in all these fields. Here it is suggested that similar sorts of solution apply in each. Further research is proposed for testing each solution. If the argument here is substantially correct across this range of topics, it may lead to an improved understanding not only of sex ratio, but of some of the pathologies in these specialties.

2. INTRODUCTION

Sexual reproduction is a phenomenon that is central to biology; moreover there is substantial variation in the sex ratio at birth. Yet the causes of this variation are not established, and some influential commentators (e.g. Wilcox 2010) are sceptical about present prospects for progress in this area of human reproduction.

This note adduces data on several forms of variation of human sex ratio at birth, viz those associated with autism, hepatitis B, toxoplasmosis, testicular cancer, Manning's finger length ratio 2D:4D, and some obstetric pathologies and congenital malformations. My intention is to argue that each of these forms of sex ratio variation presents a problem to which I may have provided a general solution. However though I may propose, I am not qualified to test, potential mechanisms for this solution. Instead I suggest that specialists in each of these pathologies might be inspired by the variations of sex ratio in one or more of these other fields. (This is especially so for workers on *T. gondii* and hepatitis B because they seem to have similar problems - viz an apparently interactive relationship between host androgenicity and 'wellbeing' of parasite and virus). If these various specialists were to recognise that they have a common problem, that might give the impetus to study the solution suggested herein. And if this were established, others might work on the proposed mechanisms.

Some years ago I published a review of the literature on the human sex ratio at birth, and a hypothesis to account for its variation (James 1987 a,b). In the intervening years, there have been further studies in this area, and some progress with the hypothesis. Here I shall briefly describe both. Most studies on human sex ratios are, of necessity, observational. And most have described the variations associated with such variables as

maternal age, paternal age, parity, social class, race, time, season, cohort etc. Heritable variation of sex ratio has been reported too, but, though significant and well confirmed, its magnitude (and the magnitudes of the other forms of variation mentioned above) seem so small as to suggest that the variations are too 'far' from their causes to throw any useful light on the identity of those causes. However more recent research suggests that progress may come from work on the unusual sex ratios associated with a few specified pathological conditions. Some of these pathologies (e.g. hepatitis B, autism, testicular cancer, and some congenital malformations and obstetric conditions) seem sufficiently important to warrant testing whether these (sometimes apparently substantial) forms of sex ratio variation may have implications for the causes of the associated pathology. First I shall outline the hormonal hypothesis of sex ratio variation, and then I shall describe its potential application to several of these reportedly biased sex ratios at birth. I shall also offer methods of testing each application.

3. THE HORMONAL HYPOTHESIS

I have suggested that mammalian (including human) sex ratios at birth are partially controlled by the hormone levels of both parents around the time of conception. *Ex hypothesi,* high levels of testosterone (in either parent) or of oestrogen (in the mother) are associated with the production of sons: and high levels of gonadotrophins (in either parent) with daughters. Evidence for the hypothesis has accrued (James 1996; 2004 a; 2008 a; 2011 a; In press). But it has not achieved the status of orthodoxy, perhaps *inter alia* because of ignorance about the mechanism(s) underlying the control of sex ratio by these hormones. Conventional wisdom has it that there are equal numbers of X- and Y-bearing sperms, and that they have equal probabilities of fertilizing the ovum, and that therefore variation in sex ratio at birth is controlled by sex-selective mortality in pregnancy. During the last decade, overwhelming evidence for such a phenomenon has been published by Catalano and his colleagues. They have shown that when pregnant women are stressed, they are more likely than controls to abort their pregnancies, and that the abortions are frequently of small, male, frail foetuses (e.g. Catalano & Bruckner 2006; Catalano et al 2009; Catalano et al 2012). However, I have suggested that such sex-selective foetal mortality is not the only mechanism controlling sex ratio at birth. I have adduced evidence that sex selection is already present at the time of conception (James 2006 a). *Ex hypothesi,* at that time, sex selection occurs under hormonal control as specified above. The exact mechanism by which the selection occurs is unknown: it may be by sex-specific mortality of sperm prior to fertilization, or sex-selection of sperm at the time of fertilization. It is interesting to see what light this hypothesis casts on the sex ratios associated with several forms of pathology as will now be shown.

4. AUTISM

Around 1% of children born in the developed world are later diagnosed with one of the conditions within the autism spectrum. Baron-Cohen (2002) hypothesized that one cause of autism is exposure to high levels of intrauterine testosterone (T). There is a marked excess of males among probands, and since male foetuses excrete more T than female foetuses, this author proposed further that the foetus is the source of the additional T (thus accounting for the biased sex ratio of probands) (e.g. Baron-Cohen et al., 2011). In contrast, I have suggested a different explanation for this sex ratio. Noting that women's T levels remain fairly stable through their reproductive lives (Apter & Vihko 1990), I suggested that if Baron-Cohen's hypothesis and mine were both correct, then autistic probands should contain a high proportion of males; and that they should also have an excess of brothers among their unaffected sibs (James 2008 b). In that paper I cited significant support for this suggestion of excess brothers. Two further significant confirmations of this suggestion have since been published (Mouridsen et al 2010; Mouridsen & Hauschild 2010), while another study showed no support for it (Parner et al 2012). Lastly, I strengthened the evidence that the mother is a source of the T by showing that all the major established risk factors for autism could – with some imagination - be reconciled with this suggestion (James 2012 a). (The point was that all these risk factors could be interpreted as markers or causes of stress : and that stressed women have high T levels). An interesting and relevant suggestion was recently made by Beaudet (2012) who proposed that environmental causes (like intrauterine T) are associated with only that minority of cases of autism who are high-functioning. Beaudet's suggestion is that the remaining majority of cases are mainly attributable to genetic factors. If Beaudet were

correct, Baron-Cohen's hypothesis and mine only apply to the high-functioning minority of cases.

There are a number of difficulties in this field of male-biased neurodevelopmental disorders. The first is the proliferation of overlapping categories of diagnoses (autism spectrum disorder ASD, attention-deficit-hyperactivity disorder ADHD, reading disorder RD, oppositional defiant disorder ODD, Tourette's Syndrome TS, Asperger's syndrome AS, pervasive developmental disorder – not otherwise specified PDD-NOS, etc). There are substantial degrees of co-morbidity across these diagnoses, and there is also considerable genetic overlap (Smalley et al 2005).

The question also arises of overlap of environmental causes. If Beaudet (2012) were correct, then Baron-Cohen's and my hypotheses would apply only or mainly to the high-performing categories within the list (e.g. ADHD, AS, and RD). And if that were so, if probands are 'lumped' (rather than 'split' into the high-performing few and the low-performing majority), then a failure (as e.g. of Parner et al 2012) to find an excess of brothers among the sibs of a pool of cases labelled 'autism' might be due to a true excess (in the minority of high performing probands) being swamped by an expected normal sex ratio of the sibs of the low-performing majority. The results of such categorizing ('splitting') in James (2008 b) and in Mouridsen's two cited papers give some support to Beaudet's suggestion.

Further Research (Testing)

Further data on this point must lie untapped in registries around the world. What are the sexes of unaffected sibs of probands with Asperger's Syndrome and other high-performing categories? If it were established that these sibs contain excesses of brothers,

that would support Baron-Cohen's hypothesis that one cause of these disorders is high intrauterine T, and mine that one source of that T is the mother. And since it is well established that one cause of high T in women is psychological and physiological stress, it would follow that, as Beaudet suggested, some categories of autism may, in principal, be avoidable. Moreover if this line of reasoning were correct, levels of autism would be further reduced by countering maternal obesity and diabetes, both of which are associated with high levels of T and thought to be partially responsible for the well-established secular rise in reported rates of autism.

5. HEPATITIS B

Worldwide, this pathogen causes hundreds of thousands of deaths each year via hepatocellular cancer. The late Nobel Laureate Baruch Blumberg and his colleagues repeatedly reported that hepatitis B virus (HBV) carriers of both sexes had significantly higher offspring sex ratios (proportions male) than uninfected controls; and that HBV immune subjects had lower offspring sex ratios than uninfected controls. This work was reported from mainly low-prevalence areas viz Papua New Guinea, Greenland, Greece, France and the Philippines: and it was summarised by Chahnazarian et al (1988). Towards the end of his life, Blumberg (2006) confessed that he was mystified by this sex ratio variation.

Evidence that healthy male HBV carriers have higher T levels than healthy uninfected controls was published by Yu et al (1993) and Yuan et al (1995). So in conformity with my hypothesis, I proposed that HBV carriers have higher offspring sex ratios because they have higher T levels (James 2006 b). Moreover there are grounds for supposing that the virus is associated with highly androgenic environments because it replicates faster in them (James 2011 b; Tian et al 2012).

Thus, this reasoning may solve Blumberg's problem with his data on the variation of offspring sex ratio with hepatitis B status. However, further complexities have since arisen. Two recent sets of data (from high-prevalence areas) suggest that HBV carriers do not always have high offspring sex ratios. Oster et al (2010) studied 67000 births in Haimen City, China. They concluded that there was no significant effect of parental (maternal or paternal) hepatitis B carrier status on offspring sex ratio. Moreover, Lin et al (2012) studied three million births in Taiwan. These authors concluded that in these data,

HBV carrier status in women is associated with a very small (but significant) rise in offspring sex ratio (proportion male). This sex ratio difference was estimated to be about 0.005, and is thus far smaller than the effect previously reported by Blumberg and colleagues. What can be the cause of the difference between Blumberg's earlier data and those later reported in Taiwan and China? These bodies of data are so substantial that they cannot be simply dismissed on the ground that they are inconsistent. Instead we should try to find a means of reconciling them.

The epidemiology of hepatitis B is different in high-prevalence areas (parts of the Far East) and low-prevalence areas (N. America and Europe) (Aspinall et al 2011). In low-prevalence areas, HBV infection is mainly acquired in adulthood by reckless or careless behaviour (sexual or otherwise). For this reason, one may propose that in low-prevalence areas, infection is associated with the high T levels typical of reckless and careless behaviour (Zuckermann 1994). In contrast, in high-prevalence areas, HBV is mainly acquired perinatally or in early childhood. As noted above, there is evidence that HBV replicates faster in highly androgenic environments. There is also the suspicion that, once established, the virus depresses the male host's T levels : this is so because many forms of stress and pathology lower men's T levels (e.g. Semple 1986; Kemper 1990). Seroconversion is predicted by low viral load (and, by inference, low T level) (Arai et al 2012). Moreover, seroconversion in infected men occurs more rapidly to those with greater cumulative exposure to T (Wu et al 2010). Accordingly one may propose a dynamic reciprocal relationship between viral load and hormone concentration which controls the duration of time between infection and sero-clearance (James 2010 a). In

principal, as I suggested in that paper, the hypothesis could explain the difference between Blumberg's data and the more recent data from the Far East.

Further Research (Testing)

1. In that paper, I also suggested that one means of testing the present reasoning would be to administer anti-androgens to infected individuals. If the present argument were substantially correct, then HBV infection might be combated by anti-androgens because they would lower the replication rate.

2. Moreover, mathematical modelling might be used to test whether the proposed long-term interactions between viral loads and androgen levels would tend to achieve sero-clearance earlier in low-prevalence than high-prevalence areas (as implied by the finding of Wu et al 2010, cited above).

6. INFECTION BY *TOXOPLASMA GONDII*

This parasite is common in human beings, between 20% and 60% of populations of most developed countries being infected (Flegr et al 2005). It has a complex life-cycle. It can only reproduce in a feline, its definitive host : and only when its intermediate hosts (e.g. rodents) are predated by felines, is it able to continue its life-cycle. From the point of view of *T. gondii,* other hosts (e.g. human beings) are evolutionary dead-ends (because, in general, they are not eaten by felines). The major sources of foodborne transmission to humans are undercooked meat especially pork, lamb and wild game meat, and soil contaminated with cat faeces on raw fruit and vegetables (Jones & Dubey 2012). It has been demonstrated that infected rodents (in contrast with healthy uninfected controls) are less afraid of cat odour. This change in rodent behaviour is apparently caused by direct action of *T. gondii* on the host's brain, rather than (or as well as) on the host's hormones. There is good evidence too that human toxoplasmosis infection is associated with increases in the risks of schizophrenia, autism, Down's Syndrome and involvement in car crashes. Its roles in these phenomena are the subjects of ongoing research (Prandota 2011).

Significantly high sex ratios (proportions male) have been reported in the offspring of recently infected female mice, and significantly low sex ratios in the offspring of female mice with long-standing infection (Kankova et al. 2007 a). Significantly high sex ratios have been reported among the offspring of infected women (Kankova et al. 2007 b), the sex ratio being positively correlated with the antibody concentration (a surrogate for duration of time since seroconversion). This group of authors interpreted these sex ratios in terms of a 'decreased stringency of embryo quality control in partly

immunosuppressed *T. gondii* mothers' (Kankova et al 2012), a suggestion previously made by e.g. Flegr & Striz (2011). However, it is not clear how such a mechanism would explain the extent of the decline in offspring sex ratio with duration of maternal infection. Moreover, the evidence that mammalian sex ratios are credibly associated with immunosuppression has been contested. So, in accordance with my hypothesis, I suggested that these *Toxoplasma gondii* sex ratios are due to hormonal involvement (James 2010 a). The nature of that involvement is not established, so it is worth summarising the history of research on this point.

a. Testosterone

Initially, grounds were given to suggest that infected people (of both sexes) have high testosterone (T) levels viz

1. Flegr et al (2005 a) reported that infected men and women (in contrast with uninfected controls) have lower values of Manning's ratio R = 2D:4D (where 2D and 4D are the lengths of the index and ring fingers). Flegr et al (2005 a) also reported that R correlated negatively with the level of anti-*Toxoplasma* antibodies in *T. gondii*-free subjects. As noted later in Section 8, Manning (1998) reported that low values of R are associated with high circulating testosterone (T) values in men, so one may suspect that infection is associated with high T levels. Flegr et al (2005 a) also reported that infected men were significantly taller than uninfected controls and concluded that these 'results suggest that some of the observed differences between infected and non-infected subjects may have existed before infection, and could be caused by the lower natural resistance to *T. gondii* infection in subjects with high prenatal testosterone (T) levels'. If to this sentence were

added ‘and/or high postnatal testosterone levels’, I would agree with this judgment. However, as will be seen, this group of authors may have altered their view on it.

2. Hodkova et al (2007) reported that women perceive infected men to be more dominant than controls. They interpreted this as evidence that infected men had higher T levels.

3. Flegr et al (2008) directly reported that men infected with *T. gondii* have higher T levels than uninfected controls.

The question arises : if hormone levels differ as between infected and uninfected subjects, why do they do so? Are subjects with high T levels more vulnerable to infection, or does the organism alter the T level, or both? Lim et al (2013) reported that *T. gondii* infection enhances expression of genes involved in facilitating synthesis of T in male rats. In contrast, Kankova et al (2011) found a decrease in the T levels of male mice following experimental infection with *T. gondii*, and wrote : [apparently at odds with the statement of Flegr et al (2005a) cited above] “The present results indicate that *Toxoplasma* infection changes the concentration of serum T in mice and human (sic) rather than changed concentration of T influences the probability of *Toxoplasma* infection”. However, these two propositions are not contradictory: establishing one does not falsify the other. I suggest that both are true. The grounds for supposing that men with high T are more vulnerable to infection are those cited above. Those grounds are not invalidated by the finding that the parasite affects the (male rodent) host’s T level. And indeed if it were shown that the parasite depresses the steroid hormones of female hosts too, that would be consistent with the decline in sex ratio with duration of infection in female mice and women (Kankova et al. 2007 a,b). However, as will be judged from the foregoing, much research needs to be done before the details become clear.

There are also grounds for supposing that infected female mice and women both have high levels of estrogen (E) as well as T. These will now be adduced.

b. Estrogen (E)

Evidence has been cited for the following phenomena: 1. Infected female mice develop more severe brain inflammation than infected males. 2. Gonadectomy increased resistance whereas E administration exacerbated the condition. 3. Pregnant female mice are more susceptible to infection with *T. gondii* than nonpregnant controls. 4. Infected pregnant mice show higher mortality than infected nonpregnant controls (Roberts et al 2001). These observations suggest that levels of E correlate positively with *T. gondii* infection in female mice.

It will now be argued that E plays a role in *T. gondii* infection in women as well as in female mice. Flegr (2007) reviewed the behavioural features of men and women infected with *T. gondii.* This author noted that consistent and significant differences were found between *T. gondii*-infected and uninfected subjects in 9 of 11 studies, and that these differences were not the same for men and women. In brief, these differences were as follows. Infected men showed lower superego strength (were more likely to disregard rules) and were more expedient, suspicious and jealous than uninfected controls. In contrast, infected women had higher superego strength, and were more warm-hearted, affectionate, outgoing and conscientious than controls. A reading of Ellis (1986) suggests that higher T in infected men may explain the differences between the psychometric findings in infected and uninfected men. In contrast, I have suggested that the differences between infected and uninfected women are not due to higher T, but to higher E, in infected women (James 2010 a). This suggestion could account for the psychological

differences noted above. Moreover, Ni et al (2002) reported that high maternal E levels are associated with long gestations in (presumably uninfected) women. So high E in infected women would also account for the reportedly longer durations of gestation of infected than uninfected women (Flegr et al 2005b; Kankova & Flegr 2007). I suggest that these hypothesized high levels of E in infected women are markers for the risk-taking behaviour in the kitchen (and elsewhere) earlier cited to be required for acquisition in the first place (Zuckermann 1994). Lastly, E is thought to play a key role in stress (Ryan et al 2011), being correlated e.g. negatively with anxiety (Schwartz et al 2012). If the E levels of infected women are depressed as a consequence of parasitic stress (as are the T levels of infected male mice) this may prove the basis for the significant decline in offspring sex ratio with duration of maternal infection.

Summary

It is suggested above that

1. *T. gondii* infection is associated with high levels of T in male mammals and with high levels of E in female mammals.

2. One of the causes of hosts' high steroid hormone levels (T in males and E in females) is that they are markers in each sex of the risk-taking, careless, unhygienic behaviour associated with infection in the first place.

3. Another cause may be that *T. gondii* infection enhances expression of genes involved in the synthesis of T in male mammals of some species.

4. The high offspring sex ratios of infected females are caused by high levels of maternal E and

5. The decline in this sex ratio with duration of maternal infection may be due to a decline in E caused by stress occasioned by the parasite (as a decline in T is reported to be caused by the stress imposed by *T. gondii* in male mice).

Further Research (Testing)

The above hypothesizing needs testing. Examples of such testing would include

a. Directly assaying E levels of infected vs uninfected women (to test whether the levels of the infected exceed those of uninfected controls at the time of infection)

b. Making longitudinal studies of the steroid levels of infected subjects (to test whether they do decline with duration of infection as proposed above).

c. It would be interesting to know the offspring sex ratios of infected males

7. TESTICULAR CANCER

Testicular cancer (TC) is the most common form of cancer affecting young men and incidence rates are reportedly increasing rapidly (Maule et al 2012). There is good evidence that men destined to be diagnosed with TC suffer impaired fertility. They reportedly are significantly more likely than controls to have been given a diagnosis of infertility or low sperm count (Baker et al 2005; Doria-Rose et al 2005; Hotalling & Walsh 2009; Raman et al 2005); to be subfertile (Fossa & Kravdal 2000; Hemminki & Jiang 2001; Richiardi et al 2004) or to have testosterone deficiency (Puhse et al 2011). This suggests that the cancer may be caused by low androgens, and this suspicion is strengthened by the repeated finding that baldness and acne (which are indicative of high androgens in men) protect against TC (e.g. Trabert et al 2011). Moreover, there can be no reasonable doubt that men destined to be diagnosed with TC sire a statistically significant excess of daughters (Moller 1998; Jacobsen et al. 2000; Gundy et al 2004). Some of the established risk factors for TC (e.g. heat and pesticides) are also known causes of low testosterone/gonadotrophin (T/G) ratios in men. So I proposed that (in conformity with my hypothesis) low postnatal T/G ratios of probands cause both their low offspring sex ratio and some cases of the cancer (James 2010 b), a suggestion that I interpret as being consistent with Trabert et al (2011) and McGlynn & Trabert (2012) who argue that one cause of the disease is some form of postnatal exposure. A curious impediment to this line of reasoning is that one established risk factor for TC is early puberty (Maule et al 2012): yet early puberty is a typical precursor of high fertility – not the impaired fertility that obviously characterises TC. It seems that the cause of the cancer may interfere with

the dynamic interactive relationship between T and G (UK Testicular Cancer Study Group 1994). This might cause the T/G ratio to diminish as suggested here.

Further Research (Testing)

1. If, as suggested here, one cause of TC is low T levels, at least some of the risk factors for low T (e.g. heat and pesticides) should also be risk factors for TC. It would be useful if systematic meta-analytic searches were initiated to test this suggestion.

2. A promising area for further research is TC in firefighters. This is so because there is good evidence that men in this occupation are at increased risk of TC, possibly because of exposure to heat (Guidotti 2007; Le Masters et al 2006; Bates 2007). Moreover there is direct (Roy et al 2003) and indirect (Voracek et al 2010) evidence for low testosterone levels in firefighters. Given this evidence, it would be interesting to know whether (as I would predict) male firefighters have a low offspring sex ratio.

8. THE INTERPRETATION OF MANNING'S FINGER LENGTH RATIO 2D:4D

Manning et al (1998) introduced the ratio R = 2D/4D where 2D and 4D are the lengths respectively of the index and ring fingers. These authors reported that in men, R correlated negatively with T and positively with gonadotrophin (G) levels. So, in accordance with my hypothesis, I predicted that parents' R values should correlate negatively with their offspring sex ratios (proportions male) (James 2001). This prediction was confirmed in regard to men (Manning et al 2002) and women (Ventura et al 2013). Consistent with the prediction was evidence that within sibships, low (masculinized) R values in younger sibs are associated with high sex ratios in their older sibs (Saino et al 2006).

It is generally reported that R is sexually dimorphic, being lower, on the average, in men than women. And it is generally agreed that R is at least partially determined by prenatal exposure to T and oestrogen. Correlational studies lead to this conclusion (e.g. Honekopp et al 2007): and so do experimental studies (Zheng & Cohn 2011; Manning 2011). Moreover, individuals' R values generally remain fairly stable through their lives (McIntyre et al 2005; Manning et al 2004; Trivers et al 2006). So it has frequently been inferred that correlations between R and postnatal behaviour or morphology may involve a fetal 'programming' or 'organizing' process. However (though the point sometimes tends to be discounted) there is now increasing evidence that finger length ratios correlate, if perhaps weakly, (as originally reported by Manning et al 1998), with current adult (as well as prenatal) hormone levels. For instance, there have been reports of negative relationships between men's reproductive potential and their R values [Augur & Eustache (2011); Coco et al (2011)*; Garcia-Cruz et al (2012)*; Manning & Fink (2008); Manning

et al (2003); Muller et al 2011)*]. The italicised studies above explicitly reported significant negative correlations between men's R values and T levels.

I now explain why I think sex ratios may cast light on the interpretation of Manning's R. During the last decade, it has become apparent that [in spite of its appreciable standard error of measurement (Voracek et al 2007)], R (in men and women) correlates negatively, significantly and sometimes substantially, with many forms of athletic and sporting success in men and women. This has been reported in respect of rugby (Bennett et al 2010); athletics (Giffin et al 2012); surfing (Kilduff et al 2011); rowing (Longman et al 2011); skiing (Manning 2002); sprinting (Manning & Hill 2009); endurance running (Manning et al 2007); wrestling (Tamiya et al 2012) and fencing (Voracek et al 2010). Most such reports contain speculation that the relationship is mediated by fetal 'programming' or 'organizing' processes. I wish to question these speculations. The point is that this speculation seems at the expense of the more obvious explanation viz of 'activational' processes. In view of the widespread willingness of professional athletes to engage in steroid hormone abuse (Connor & Mazanov 2009), the potential role of 'activational' processes seems obvious. So advocates of fetal programming as an explanation of the established powerful associations between finger length ratios and sporting prowess should offer data that would exclude activational processes. In this context, further research is needed to test whether (contrary to a rather general assumption) finger length ratios are appreciably affected by postnatal hormone variation.

My point is strengthened by the (admitted) assumption that the reported relationship between parental R and offspring sex ratio has an activational (and not an organizational)

explanation. As far as I know, no-one has suggested programming or organizing processes to explain this relationship.

9. SEX-BIASED CONGENITAL MALFORMATIONS

Many forms of congenital malformation show sex ratio biases in one direction or the other. The argument used above in regard to autism has wider applications. If the maternal hormone profiles that cause sex ratio variation were also to cause (at least partially) specified sex-biased congenital malformations, than one would expect that malformed probands themselves would show sex ratio biases, and also that their unaffected sibs would show sex biases in the same direction. Applying this argument to published family data, I have found sib sex ratios to justify proposing that maternal intrauterine hormones are partially responsible for polydactyly (James 1998), transposition of the great arteries (James 1999), oral clefts (James 2000) and pyloric stenosis (James 2004 b). An attractive feature of such reasoning is that explains not only the sex bias of the probands themselves but the (otherwise unexplained) biases of the sex ratios of their sibs.

Further Research (Testing)

Here again, relevant data must exist in registries worldwide. Do these further data confirm that there are excesses of brothers among the unaffected sibs of probands with polydactyly, transposition of the great arteries, cleft lip, and pyloric stenosis? And an excess of sisters among the sibs of probands with cleft palate only? If so, that would add to the evidence that the causes of these malformations include maternal hormone profiles .

10. OBSTETRIC PATHOLOGIES

I have invoked the same argument in relation to obstetric pathologies. It is well established that there are excesses of sons born to women with placenta previa, abruptio placenta, fatty liver of pregnancy and pre-eclampsia : and excesses of daughters born to women with ectopic pregnancy, placenta accreta and hyperemesis gravidarum. In all these cases, it is not thought that the sex of the foetus causes the pathology. So I suggested that the hormone levels which initially were associated with the offspring sex persisted through the pregnancy and were then also responsible for the disorder (James 1995). Recent evidence strongly supports this interpretation in respect of hyperemesis gravidarum (Seow et al 2013). These authors administered hCG to ovariectomized rats : this inhibited gastric emptying. I suggest, in conformity with my hypothesis, that a high maternal hCG level was also responsible for the excess of female offspring associated with this pathology.

Further Research (Testing)

This line of reasoning could be tested by examining the sex ratios of the sibs of probands. If they are biased in the same direction as those of the probands themselves, that would confirm that maternal hormones are a cause of each of these disorders.

11. ANOTHER RESEARCH APPROACH : BAYESIAN NETWORKS

I cited evidence for the hypothesis that the sex ratio of offspring is associated with time of insemination within the fruitful cycle (James 1971). The evidence suggested that p (the probability of a male birth) varies with time of insemination within the cycle, the regression perhaps being U-shaped. In other words, *ex hypothesi,* conceptions following inseminations in the middle of the fertile interval are more likely to be of girls ; and conceptions following insemination at either end of the fertile interval are more likely to be of boys. The evidence for this proposition was strengthened in a brief meta-analysis (James 2000 b). But though the Mantel-Haenszel test statistic in the latter paper was significant at the 0.005 level, the idea has never achieved wide acceptance. However, this notion that timing of insemination influences offspring sex would support (and derive support from) my hormonal hypothesis. This is so because the notion is consistent with the luteal hormone surge in the middle of the cycle.

Data reliably relating offspring sex to the time of insemination within the fruitful cycle are understandably rare and only published very occasionally. But the matter may be pursued indirectly by simultaneously considering a set of propositions that are related to it. If a proposition under discussion is related (mathematically, logically or factually) to one or more propositions with assignable likelihoods, then using Bayesian network theory, one may provide grounds for reassessing the likelihood of the given proposition.

I suggested (James 2008 c, 2009 a,b) that such a set of propositions would include :

Proposition 1. There is a U-shaped regression of offspring sex ratio (proportion male at birth) on time of insemination within the fruitful human menstrual cycle,

Proposition 2. There is a U-shaped regression of sex ratio on duration of gestation,

Proposition 3. Sex ratio varies positively with coital rate at the time of conception,

Proposition 4. Sex ratio declines with duration of time taken to achieve conception in a period of risk (viz in the absence of birth limitation),

Proposition 5. The sex ratio at birth was high in all the major combatant countries during and just after World Wars 1 and 2, and

Proposition 6. The variances of the distributions of the combinations of the sexes within mammalian litters are sub-binomial.

Comments on the Propositions

a. The Empirical Evidence

The extent of direct accepted empirical evidence for these propositions varies very substantially. It is overwhelming in respect of Propositions 2, 5 and 6. It is weak (in spite of the 0.005 level of the cited Mantel-Haenszel statistic) in respect of Proposition 1, and weak in regard to Proposition 3 (though evidence is strong in regard to other mammals). Proposition 4 is controversial, but I have suggested that the human evidence in its favour is very much stronger than that which has been deployed against it (James 2012 b).

b. The Logical Relationships

1. If Proposition 1 were true in regard to polytocous species, Proposition 6 would necessarily follow as a consequence of the sub-binomial variance of Poisson binomials (e.g. Weatherburn 1949 or Feller 1964). It is worth pointing out that this topic requires some dedication on the part of the student : examples of sub-binomial variance are extremely rare in Nature (Gini 1951), so its mathematical description is an arcane topic. However, I know no other explanation of Proposition 6.

2. Proposition 2 is undoubtedly true, but no explanation for it has been established. However, using a simple mathematical model with plausible assumptions, I have shown that Proposition 2 is compatible with Proposition 1. The suggestion is that the U-shaped regression of p on cycle day of insemination is responsible for the similar (but much damped) regression 9 months later, of sex ratio on duration of gestation (James 1994).

3. The expected time of conception within the cycle may be shown to be (weakly) mathematically dependent on coital rate (e.g. Roberts 1978). So if Proposition 1 were true, Proposition 3 would be bound to be true. Strong direct evidence that parental coital rate is associated with offspring sex ratio has been cited in other mammalian species (horse, rabbit, rat, mouse, seal) (James 1996; 2004 a,c). So a relationship between coital rate and offspring sex ratio may be presumed to exist in the human being (even though it may be weak, difficult to detect and of no clinical significance).

4. The reported sex ratios relating to the two World Wars are extraordinary. During and just after both wars, sex ratios reportedly rose in almost all combatant countries, but not in the non-combatant countries. The rises were significant and substantial, and were unparalleled in previous and subsequent conflicts (James 2009 a). In that paper, I attributed the rises to high coital rates in couples of whom the man was a member of the armed services. The idea has never achieved widespread acceptance, though it was originally propounded independently by the distinguished epidemiologist McKeown (1956-57). To identify the causes of the rises in sex ratio associated with these two wars, it is necessary to specify how they differed from all other conflicts. The salient point, I suggest, is that prior to deployment in World Wars 1 and 2, men were granted a brief home leave. Crucially to the present argument, the duration of that leave typically did not

exceed one menstrual cycle. So the partners of servicemen conceived in that cycle – or not at all. In other words, there was a selection during those wars for fecundability. It is known that one powerful component of fecundability is coital rate (Potter & Millman 1986). Hence partners of servicemen who conceived during a wartime leave may be assumed to have done so following a mean coital rate that was rather higher than that of control women. So I suggest that the high sex ratios were a consequence of the high coital rates. I know no alternative explanation. The task of explaining these wartime rises in sex ratio seems pressing in view of the recent success in establishing the (countervailing) Catalano Phenomenon.

The intention is to test whether the likelihoods of all three uncertain propositions above may be simultaneously changed by the methods of Bayesian network theory. So I hope those with expertise in this technique may try using it on the above propositions.

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