HYPOTHESIS

Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception

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Abstract

An attempt is made to summarize the evidence that the offspring sex ratios (proportions male at birth) of mammals (including man) are causally related to the hormone levels of both parents around the time of conception. Almost all of the cited studies were reported by non-endocrinologists. This being so, it would seem desirable to have comments of endocrinologists on this topic. The purpose of this article is to elicit such comment. Readers are requested to read the accompanying editorial (Clark & Davis 2008) to gain a better perspective of this hypothesis article.

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Introduction

The human sex ratio (proportion of males) at birth is strikingly stable, seldom varying significantly from values that lie roughly between 0·505 and 0·520 (James 1987). Thus, in almost all human populations, there is a slight excess of males at birth. The cause of this excess has not been established and will not be further discussed here. Over the last century, a huge quantity of epidemiological data has been accumulated on human sex ratios. It has become clear that there is a variation in sex ratio shown by a number of such demographic variables available in birth certificates and hospital registries (e.g. birth order, maternal age, social class, smoking, marital status of mother, race, wartime, etc). However, these variations are so small that they give little reasonable prospect of suggesting the causes of the variation and they will not be treated here. However, more recently it has been suggested that some selected adverse prior parental experiences (such as illness, occupational and chemical exposures) are associated with subsequent human sex ratios that are substantially and significantly different from expected population values. It is appropriate to seek explanations for these differences.

It had been conventionally believed that

(a) there are equal numbers of X and Y in mammalian sperms,
(b) X and Y stood equal chances of achieving conception,
(c) therefore equal numbers of male and female zygotes were formed, and that
(d) therefore any variation of sex ratio at birth is due to sex-selective spontaneous fetal wastage.

Evidence has been put forward against these conclusions. It may readily be conceded that some sex ratio variation is due to sex-selective foetal and embryonic wastage (as, e.g. with glucose (Gutierrez-Adan 2001) and psychological stress during pregnancy (Catalano *et al.* 2006)). However, some sex ratio variation is almost certainly present at the time of formation of the zygotes (James 2006*a*, Cameron & Linklater 2007) and so the question arises: what is the cause of this variation in sex ratio the time of formation of the zygotes?

It is possible that some environmental agents directly affect the ratio of men's X- and Y-bearing sperm: this has been suggested by Robbins *et al.* (2007) as a cause of the low offspring sex ratio reported in men exposed to boron (James 1999, Chang *et al.* 2006). However parental hormone concentrations around the time of conception may play a role by predisposing to the production of one sex or the other, for example, high levels of gonadotrophins to the production of daughters (James 1980). And in their review of non-human mammalian sex ratios, Clutton-Brock & Lason (1986) wrote: '…in view of… the apparent lack of genetic variance in the sex ratio, a hormonal mechanism mediated by environmental factors operating either at conception or during the individual's development appears to be the most likely explanation of sex ratio variation'. Later it was suggested that high paternal concentrations of testosterone are associated with the production of sons (James 1986). These

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suggestions were augmented with proposals that high levels of oestrogens were associated with sons and progesterones with daughters (James 1996, 2004*a*). The idea can be encapsulated in the proposal that offspring sex ratio correlates positively with R, where R is a function of the form

$$(T + E)/(G + P)$$

where T, E, G and P are the sex-standardized concentrations of testosterone, oestrogen, gonadotrophins and progesterone of both parents. The relationship between offspring sex ratio and parental hormone levels may be mediated by glycerylphosphorylcholine in the male and its diesterase in the female tract (James 1997). As far as I know, this latter hypothesis has not been tested.

Although this endocrinological speculation is in the public domain, it has, in a sense, gone on behind the backs of endocrinologists. Data on the relationships between mammalian offspring sex ratio and parental hormone levels have been published in a large variety of journals (within the fields of, e.g. evolutionary biology, environmental medicine and animal husbandry) by researchers with different interests and approaches, most of whom (like me) are not qualified in endocrinology. Yet even if the hypothesis was substantially correct, it would need developing by experts in the field of endocrinology. For instance, if hormone concentrations are involved, then hormone sensitivity/insensitivity, agonists/antagonists and hormone receptors are also probably involved.

If the hypothesis was substantially correct, it would have ramifications in a wide range of medical specialties (toxicology, teratology, radiation medicine, neurology, psychiatry, oncology, dermatology, rheumatology, occupational medicine, virology and parasitology as well as obstetrics and gynaecology; James 2001*a*). In particular, it may throw light on the present concern over endocrine disruptors (James 2006*b*). Lastly, if the hypothesis was correct, it may help solve a recurrent problem in endocrinology: namely the assessment of past hormone profiles of people now diagnosed with illness. Sex ratios may be potential surrogates for hormone profiles that existed many years in the past, namely at the time when children were conceived. The point is that if people with a given pathological diagnosis produce children with an unusual sex ratio before the diagnosis, then *ex hypothesi*, the corresponding hormone profile is a potential cause of the pathology. Furthermore, if the unusual sex ratio (or another one) were to apply only to children conceived after disease onset, one may suspect that the disease (or its treatment) has hormonal consequences.

The purpose of this note is to persuade endocrinologists that mammalian sex ratios merit their attention. Here, as noted above, variables will be ignored which only have minor variation with sex ratio. Moreover (with some exceptions e.g. dioxin), topics will be ignored if they are the subject of conflicting reports.

It is hoped that the wealth of data reviewed here will provoke endocrinologists into commenting on, and experimentalists into testing, the hypothesis. This is so because – even if it were substantially correct – only after such comment and testing will the hypothesis stand any chance of becoming accepted.

The data to be reviewed will be considered under the following categories:

(A) observational studies of human beings and
(B) observational and experimental studies on non-human mammals.

Observational studies on human beings

Time of insemination within the menstrual cycle

It is suggested that offspring sex ratio (proportion of males) is associated with the time of insemination within the fruitful cycle. The length of the fertile window (that time within the cycle in which insemination may result in conception) is of the order of 5 days or more (Schiphorst *et al.* 1985, Keulers *et al.* 2007). Apparently, the regression of sex ratio on time of insemination (vis-à-vis time of ovulation) is U shaped. In other words, if the insemination occurs early or late in the fertile window, the resulting offspring is more likely to be male: if insemination occurs in the middle, it is more likely to be female. The author performed a meta-analysis on 10 independent data sets on this point and the resultant Mantel–Haenszel test statistic was significant at the 0·005 level (James 2000*a*). Similar phenomena have been reported in other species viz white-tailed deer (Verme & Ozoga 1981), Barbary macaque (Paul & Kuester 1987), golden hamster (Pratt *et al.* 1987), Norway rat (Hedricks & McClintock 1990), mouse (Jimenez *et al.* 2003) and pig (Brooks *et al.* 1991). It is suggested that hormonal changes across the cycle are responsible for the observed variation of offspring sex ratio. In the human being, the luteal hormone surge in the middle of the cycle is *ex hypothesi* responsible for the excess of females reportedly conceived at that time.

Finger length ratios

There is good evidence that R, the ratio of the lengths of the second ($2D$) and fourth ($4D$) fingers (where $R = 2D/4D$) correlates negatively with men's testosterone concentrations (Manning *et al.* 1998, Manning 2002). According to the author's hypothesis, it was predicted that men's R values should correlate negatively with their offspring sex ratios (James 2001*b*). The prediction was confirmed by Manning *et al.* (2002).

Direct treatment with hormones

Women

Hormonal induction of ovulation

The sex ratio of children following the induction of ovulation with gonadotrophins or clomiphene is low (James 1985*a*). This result is highly significant ($P < 10^{-6}$, tested against a contemporary expected live birth sex ratio of 0·514 in the USA). It is not totally due to any association between sex ratio and female sub-fertility: this may be inferred from the fact that

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the sex ratio of artificial insemination offspring is also significantly lower if ovulation is hormonally induced rather than natural (James 1985*b*). I suggest that the excess of females among the offspring following hormonally induced ovulation is due to gonadotrophins used in the induction of ovulation (or secreted as a consequence of treatment by other agents).

Women exposed to diethylstilbestrol (DES) in utero

Wise *et al.* (2007) reported a raised offspring sex ratio in women who themselves were exposed to DES *in utero*. Those exposed earliest in gestation and having the highest doses had the highest odds of a male birth. There can be no reasonable doubt that postnatally these 'DES-Daughters' have higher levels of testosterone than controls (Giusti *et al.* 1995). It is suggested that this testosterone is responsible for the high sex ratio.

Men

Sas & Szollosi (1980) administered gonadotrophins to one group of sub-fertile men and methyltestosterone to another. Both groups of men subsequently sired highly significant excess of sons ($P<0{\cdot}00005$ and $P<0{\cdot}005$ respectively) which could lead to the implication that the excess to the testosterone group was directly due to the hormone. Sub-fertile men treated with mesterolone, a synthetic androgen of lower potency than methyltestosterone, have also been reported to sire a significant excess of sons (James 1990).

The gonadotrophin sample of Sas & Szollosi (1980) was treated with 1500 I.U. intramuscularly twice a week. When gonadotrophin is administered to men in this quantity, it clears rather rapidly from the system, peaking at 6 h and being no longer detectable at 48 h (Padron *et al.* 1980). However, the administration of such doses of gonadotrophin to men results in sustained high levels of both testosterone and oestradiol (Matsumoto *et al.* 1983). So it seems reasonable to suggest that the high sex ratio of offspring of Sas & Szollosi's gonadotrophin-treated patients was due to the fathers' high levels of testosterone and oestradiol and relatively low levels of gonadotrophin. At any rate it seems that the sex ratios of offspring of Sas & Szollosi's patients were not caused by a tendency of (untreated) sub-fertile men to sire boys. This is because untreated sub-fertile men tend to produce girls (perhaps because of their low testosterone levels; James 1990). I suggest that the failure of Jacobsen *et al.* (2000*a*) to find this depended – as they suggest – on a heterogeneity across sub-fertile men in regard to offspring sex ratios. Such heterogeneity would be expected to arise as a consequence of pooling untreated men (who produce an excess of daughters) with men who had been treated with androgens (who produce an excess of sons).

Pathological conditions

Cancers

Pre-menopausal breast cancer is reportedly associated with a significantly high offspring sex ratio (James 2006*c*). This may be provisionally ascribed, *ex hypothesi*, to the high levels of oestrogenic activity that are thought to be causally associated with the disease. Several other cancers are reportedly associated with significantly low offspring sex ratios (non-Hodgkin's lymphoma, testicular cancer and post-menopausal breast cancer). Table 1 gives references to these reports and to papers confirming that the hormone profiles of patients conform with this hypothesis.

Infectious conditions

Toxoplasma gondii infection

This parasite is common in human beings with between 20 and 60% of the populations of most countries being infected (Flegr *et al.* 2005). Kankova *et al.* (2007*a*) reported that (in contrast to uninfected controls) infected women are more likely to produce sons ($P=0{\cdot}001$), and that the offspring sex ratio (proportion of males) increases with the concentration of anti-*Toxoplasma* antibodies in *Toxoplasma*-positive mothers ($P=0{\cdot}001$). This group of workers also reported similar findings on experimentally infected female mice (Kankova *et al.* 2007*b*). Comments on this experiment will be made in a later section (*T. gondii*).

These human data may be explained as follows. A number of reports have given grounds for supposing that the testosterone (T) concentrations of infected people are high.

Flegr *et al.* (2005) reported that infected men and women (as contrasted with uninfected controls) have lower values of

Table 1 References substantiating that the given cancers are associated with (a) low offspring sex ratios and (b) hormone profiles *ex hypothesi* responsible for those sex ratios

	Low sex ratio	Hormone profile
Cancer		
Non-Hodgkin's lymphoma	Olsson & Brandt (1982)	Olsson (1984)
Testicular cancer	Moller (1998) Jacobsen *et al.* (2000*b*) Gundy *et al.* (2004)	Petersen *et al.* (1999)
Post-menopausal breast Cancer	James (2006*c*)	Collins *et al.* (2005) Beral *et al.* (2003)

The author gratefully acknowledges Dr M Zwitter (Ljubljana, Slovenia) for information on confirmatory data on the offspring sex ratio of patients with non-Hodgkin's lymphoma (NHL; 96 boys and 106 girls born to female patients before diagnosis).

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Manning's *R* (where $R=2D/4D$, 2*D* is the length of the second digit and 4*D* the length of the fourth digit). As noted above (in section Finger length ratios), R reportedly correlates negatively with circulating *T* levels (Manning *et al.* 1998, Manning 2002). Flegr *et al.* (2005) also reported that *R* correlated negatively with levels of anti-*Toxoplasma* antibodies in *Toxoplasma*-free subjects. Lastly, Hodlova *et al.* (2007) reported that female students judged that men with latent toxoplasmosis appeared more dominant ($P=0{\cdot}009$) and masculine ($P=0{\cdot}052$) than uninfected controls.

Hodlova *et al.* (2007) inferred that infected men have higher *T* levels than uninfected controls. Flegr *et al.* (2005) concluded that their 'results suggest that some of the observed differences between infected and non-infected subjects may have existed before infection'. The author suggests that both conclusions are correct and that there is lower natural resistance to toxoplasmosis infection in subjects with high testosterone levels.

The point may be further tested as follows:

(a) The T levels of infected men and women should be directly assayed.
(b) Experimentally infected animals should be given anti-androgenic treatment: it would be interesting to know whether this ameliorates the effects of infection.
(c) The offspring sex ratio of infected men should be examined.
(d) The dynamics between *Toxoplasma* and testosterone are not established.

Evidence has been presented to show that subjects with high T levels are more vulnerable to infection, but since women react to stress by increased secretion of adrenal androgens (Christiansen 2004), one may suspect that the infection may also initially cause a rise in adrenal androgens in women. This needs investigation in longitudinal studies. If I am correct, then the T levels of infected women (and of experimentally infected female mice) are initially high (partially as a response to the stress of infection). Furthermore, these high T levels gradually diminish (perhaps as the subject becomes habituated to the stress).

Hepatitis B virus (HBV)

During their work on HBV, Blumberg and his colleagues repeatedly found that HBV carriers (of both sexes) produce statistically significant excesses of sons. This work was summarized by Chahnazarian *et al.* (1988) and the result confirmed by Oster (2005). These authors were unable to explain their findings, and indeed, the result has remained a major unsolved problem in hepatitis B research (Blumberg 2006).

However, Yuan *et al.* (1995) found that in healthy men, the geometric mean T was 21% higher in $HBsAg^{+}$ individuals than in $HBsAG^{-}$ individuals ($P=0{\cdot}0006$, two-way analysis). So it is suggested that hepatitis B carriers have an excess of sons because they have high T levels. This may explain some of the other curious forms of variation of hepatitis B by sex (Blumberg 2006) and may indicate endocrine control of rates of viral transmission and/or replication. This line of reasoning is supported by the (otherwise unexplained) highly significant excess of brothers among the siblings of hepatitis B carriers (Mazzur & Watson 1974). Testosterone concentrations have strong genetic determinants (Harris *et al.* 1998).

If the above argument was correct, then hepatitis B infection might be treated with anti-androgens. It is noteworthy that an analogous suggestion has recently been made in respect of HIV/AIDS. It has been shown that oestrogen protects against vaginal transmission of simian immunodeficiency virus (SIV) in ovariectomized Rhesus monkeys (Smith *et al.* 2000) and that progesterone implants enhance SIV vaginal transmission and early viral load in Rhesus monkeys (Marx *et al.* 1996). On the basis of this (and other) evidence, it was proposed that oestrogen and progesterone may alter women's susceptibility to HIV infection and that oestrogen treatment might accordingly ameliorate or protect against this condition in women (Short 2006).

Cytomegalovirus (CMV)

Women who are seropositive for CMV reportedly bear a significant excess of daughters (Piazze *et al.* 1999, Shields *et al.* 2002). Oestrogen has a generally suppressive effect on CMV replication (Speir *et al.* 2000). Therefore, oestrogen concentrations may be assumed to be low in CMV-positive women: hence *ex hypothesi* the low offspring sex ratio of CMV-positive women.

Pathological obstetric conditions

Unusual offspring sex ratios are associated with a number of obstetric conditions. Highly significant male excesses have been reported in placenta praevia, the fatty liver of pregnancy and (some forms of) toxaemia (James 1995*a*); dermatoses of pregnancy (James 2000*b*); highly significant female excesses in placenta accreta and extrauterine pregnancy (James 1995*a*) and hyperemesis gravidarum (HG; James 2001*c*). Foetal sex is not thought to cause any of these conditions, and it is suggested that the abnormal sex ratios are caused by unusual maternal hormone profiles around the time of conception, and that these same abnormal hormone profiles persist and later are partially responsible for the pathology (James 1995*a*). The suggestion was speculative at the time but has gained strength in the interim. Notes are given here on some of these pathologies and their associated sex ratios.

Placenta praevia and extrauterine pregnancy

The author adduced further evidence that placenta praevia is associated with male births (James 2001*d*). The hypothesized mechanism underlying the biased sex ratios associated with these two forms of pathology is as follows. The ovum is normally fertilized at the upper end of the fallopian tube. It is helped on its journey to the uterus by smooth muscle contractions of the tube, and it has been shown that these

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contractions are positively associated with oestrogen concentrations (Jansen 1984) and negatively associated with progesterone concentrations (e.g. Paltieli *et al.* 2000). So if the oestrogen/progesterone ratio is below optimum (and thus *ex hypothesi* associated with female conceptions) these contractions may be presumed to be insufficient to discharge the ovum into the uterus before it 'hatches' from the zona. Under these conditions, one may expect nidation in the tube itself and an ectopic pregnancy.

In contrast, in cases of placenta praevia, one may suspect an undue degree of hormonally induced tubal motility. In such cases, the fertilized ovum would be discharged into the uterus some days before it was due to 'hatch' and nidate. Under these circumstances, one would expect an excess of nidations in the vicinity of the cervix as a consequence of either random movement within the uterus or any slow escape of fluid from the uterus through the cervix.

In short, it is suggested that placenta praevia is due to high oestrogen/progesterone ratios (*ex hypothesi* associated with male conceptions) and that (some) ectopic pregnancies are caused by low ratios. Explanations are available for both these phenomena and for the unusual sex ratios associated with each. It is not claimed that anomalous degrees of tubal and myometrial motility or ciliary action are the only cause of either condition. The hypothesis could be tested by examining the extent to which hormone concentrations control such motility.

Hyperemesis gravidarum

Looking at data from 11 samples it is concluded that the sex ratio associated with HG is significantly below population live birth sex ratios (James 2001*c*). It has been reported that cases have high gonadotrophin levels (Hsu & Witter 1993, Askling *et al.* 1999). Moreover, Depue *et al.* (1987) cited epidemiological data and direct endocrinological data to support the hypothesis that this condition may be caused by 'an extremely rapid rise in oestradiol in early pregnancy'. So there are grounds for suspecting that women destined to suffer HG have a low oestrogen/gonadotrophin ratio around the time of conception. The point stands in need of confirmation.

Pathological conditions known or thought to arise *in utero*

It is well established that most forms of congenital malformation affect one sex more than the other (Arena & Smith 1978, Lubinsky 1997). For instance, polydactyly is more common in boys and anencephaly in girls. The explanations for most of these sex ratio biases are not established, so it is suggested that some sex-predisposing maternal hormone profiles may also (partially) cause specific congenital anomalies. The point may be tested by examining the sex ratio of unaffected siblings of probands with a particular sex-related malformation. If the sex ratio of these siblings is biased in the same direction as that of the probands, then the hypothesis is supported in respect of that malformation. And if the sex ratio is not so biased, the hypothesis is impugned. Such a line of reasoning would explain the unusual (and otherwise unexplained) sibling sex ratios of probands with polydactyly (James 1998*a*,*b*), transposition of the great arteries (James 1999), oral clefts (James 2000*c*) and pyloric stenosis (James 2004*b*). It may also explain the highly significant male excess in the siblings of probands diagnosed with some male-biased neurodevelopmental disorders (e.g. autism spectrum and attention deficit hyperactivity disorder; James 2008).

The HLA-B15 gene

This gene is reportedly more common in men with rheumatoid arthritis than in healthy controls (Cutolo & Accardo 1991). Ollier *et al.* (1989) found that men who carried the HLA-B15 gene had significantly lower testosterone levels than other men. So Astolfi *et al.* (2001) tested a prediction based on the present hypothesis, namely that men carrying HLA-B15 should sire a high proportion of daughters. The prediction was confirmed and these authors wrote: 'These results suggest an effect of HLA-B15 on the secondary sex ratio mediated by a low testosterone level'.

Pathological chemical exposures and the possibility of detecting endocrine disruptors

It has been known for many years that national sex ratios at birth change slowly but significantly up and down across time (Gini 1955). Some of these movements may have been due to changing methods of reporting. Moreover, increases of sex ratio have sometimes been ascribed to reductions in rates of spontaneous abortion and regarded as evidence of an increasingly healthy population. But though these movements of national sex ratios at birth have been shown to be statistically significant, their causes have not been established. Those in the 19th century and early 20th century occurred before a huge variety of pesticides and other chemical compounds were introduced. These movements may also have been due to industrial pollution (mediated *ex hypothesi* by endocrine disruption) or they may have been the consequence of genetic stabilizing mechanisms (Bodmer & Edwards 1960). These qualifications are mentioned here for the following reason.

During the 1960s, 1970s and 1980s, sex ratios at birth declined in many (though not all) developed countries. It was known that paternal exposures to some specified chemicals (e.g. dibromochloropropane (DBCP) and other pesticides) caused (or at least were associated with) the production of a significant excess of daughters (e.g. Potashnik & Yanai-Inbar 1987), so some people interpreted these falling sex ratios as evidence of deleterious environmental chemical agents. The argument is inconclusive because we do not know – and are unlikely to know until Gini's (1955) data have been explained – how the sex ratios might have moved in the absence of environmental pollution.

Nevertheless there are circumstances under which sex ratios may be used to detect endocrine disruptors: these will now be described.

There are grounds for supposing that the hormone levels of both fathers and mothers are involved in the sexes of their children (James 1996, 2004). Moreover, the endocrine

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responses of men and women to some noxious stimuli are thought to be not just different, but opposite. For instance, Christiansen (2004) cited evidence that the endocrine responses of men and women to stress are opposite: men experience a lowering of testicular androgens and women an increase in adrenal androgens. And one might suspect opposite endocrine responses of men and women to the current ubiquitous exposure to weak environmental oestrogens. These may be suspected of raising women's oestrogen levels and lowering men's testosterone levels. If these were correct, then *ex hypothesi* if both parents were exposed, the effects on sex ratio may be counterbalanced and go undetected. So when using sex ratios to test for endocrine disruption, it is necessary in principle to examine the offspring sex ratios of all four categories of matings of exposed and unexposed mothers and fathers. In the absence of such provision, an overall unchanged sex ratio may mask opposing effects in mothers and fathers. So sex ratio may not be a useful criterion of endocrine disruption where, for instance, chemical spillages into water sources or the atmosphere have occurred and where, therefore, both parents are likely to have been exposed. This has been illustrated in reportedly opposite trends in offspring sex ratio in response to maternal and paternal exposure to dioxin, DDT, polychlorinated biphenyls and lead. There follow brief surveys of the effects of selected chemical exposures where the exposure status of both parents was known.

Dioxin (TCDD) and dioxin-like chemicals

TCDD is one of a group of highly potent environmental pollutants. It induces a broad spectrum of biological responses including the disruption of normal hormone signalling pathways (Mandal 2005). It is a ubiquitous contaminant, originating from many sources (e.g. emissions from incineration sources, effluents and solid waste from pulp and paper processing, metal reclamation, petroleum refining, wood preservation and the production of specified chlorinated chemicals; Orban *et al.* 1994). For these reasons, it may be seen as a prototypical endocrine disruptor and has become the focus for much research. On the basis of the present hypothesis and the finding of a low testosterone/gonadotrophin ratio in men exposed to dioxin (Egeland *et al.* 1994), it was predicted that these men would sire an excess of daughters (James 1995*b*). Mocarelli *et al.* (1996, 2000) reported on births following the Seveso explosion (which released large quantities of dioxin into the atmosphere). These data seemed to confirm the prediction, but since then, other workers have reported both raised and lowered offspring sex ratios (see James 2006*b*, Table 2). In that note, the author gave grounds for suggesting that this heterogeneity may have been the consequence of contamination of dioxin with congeners with androgenic, oestrogenic or anti-oestrogenic properties. Mocarelli *et al.* (2000) were explicit that pure dioxin (but not a range of associated chemicals) was released at Seveso. Figa-Talamanca *et al.* (2003) examined the sex ratios at birth in the municipalities surrounding Seveso in the years following the explosion: these authors found a reduction only in the following 8 years (1977–84) and they found that the reduction occurred only in the two municipalities with the highest levels of contamination. Moreover, recent experimental pre-mating administration of dioxin to male mice (Ishihara *et al.* 2007) and guinea pigs (Hwang *et al.* 2004) was reportedly followed by significantly lowered offspring sex ratios. So provisionally one may conclude, following Mocarelli, that male exposure to dioxin causes subsequent births of excess daughters.

The organochlorine pesticide DDT

Cocco *et al.* (2005) reported on DDT applicators involved in an anti-malarial campaign in Sardinia in 1946–50. The offspring sex ratio of these men decreased significantly by their tertile of cumulative DDT exposure. Moreover, exposure to DDT reportedly lowers testosterone levels in men (Martin *et al.* 2002) and male rats (Rhouma *et al.* 2001). Thus, these human data are accommodated by the presented hypothesis.

Evidence on the effects of prior maternal chemical exposures on offspring sex ratio is not abundant. So the recent paper of Khanjani & Sim (2006) is important. Khanjani (private communication to me dated July 2006) reported that their most heavily contaminated women produced 32 boys and 13 girls ($\chi^2 = 7{\cdot}0$, $P < 0{\cdot}01$, tested against an expected live birth sex ratio of 0·513 in Australia). Apparently, DDT does not raise women's oestrogen levels (Perry *et al.* 2006), but organochlorine pesticides have been shown to act as oestrogen receptor agonists (Hodges *et al.* 2000). So it seems reasonable to propose that this sort of mechanism is responsible for the excess boys produced by exposed women. At any rate, the data on DDT seem to present evidence that a pollutant may have opposite effects on exposed men and women, judging by their offspring sex ratios.

The nematocide dibromo chloropropane (DBCP)

Potashnik & Yanai-Inbar (1987) reported that men exposed to DBCP thereafter sired statistically significant excesses of daughters. These workers had conducted more than one study, and reported that the later work confirmed their original result. It had originally been reported that DBCP lowers men's sperm counts (Whorton *et al.* 1977), and for this reason, to the author's knowledge it was then banned in many countries, no further data have been published on its effect on offspring sex ratios. It has also been reported that exposure to DBCP causes increases in men's luteinizing hormone (LH) and follicle-stimulating hormone levels, while leaving their testosterone levels unchanged (Whorton *et al.* 1979). The author suggests that this hormone profile is responsible for the female excess among the offspring of these men.

Fungicides

In some ways, the studies of Garry *et al.* (2002*a*,*b*, 2003) are unique. Not only did these workers replicate their earlier finding that male fungicide applicators sired a significant excess of daughters, but also the men whose hormones were assayed

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were the same subjects whose offspring sex ratios were reported. These authors concluded that fungicide exposure determines the sex of offspring. The author suggests that this is correct, the effect being mediated by the variation of testosterone levels later reported by this team (Garry *et al.* 2003).

Adverse occupational exposures

The author has cited evidence that four different classes of male occupational exposure are associated both with significantly low offspring sex ratios and significantly low paternal testosterone levels. These are: a) pilot of high-performance aircraft and astronaut, b) non-ionizing radiation, c) professional driver and d) professional diver (James 2006*b*). Of these four categories, only the last two will be elaborated on here.

Professional driver

Noting the evidence that professional drivers have poor sperm quality, and the evidence that lead lowers male testosterone levels, the author speculated that – if his hypothesis were correct – then professional drivers should sire an excess of daughters (James 1992). This prediction was confirmed first by Dickinson & Parker (1994), who found a significant excess of daughters born to professional drivers, and second by Simonsen *et al.* (2006), who reported a significant dose-related decline in sex ratio with paternal blood lead level.

Professional diver

The only two sets of data (known to the author) on offspring sex ratios of professional divers are both strikingly low. Rockert (1977) reported 20 sons and 40 daughters born to deep sea divers in the Swedish Royal Navy, and Lyster (1982) reported 45 sons and 85 daughters born to Australian abalone divers. These two sex ratios are significantly lower than comparable national live birth sex ratios ($P=0{\cdot}005$ and $P<0{\cdot}0002$ respectively).

Though the author has no information on the medical status of the Swedish divers, Lyster himself reported on the flabby, unhealthy appearance of the Australian divers, and his comment was later amplified by expert authority: Edmonds & Hayward (1987) wrote: 'The Australian abalone divers were interesting because of their extremely provocative diving procedures, the high prevalence of occupational diseases of diving, and the alleged presence of a punch-drunk syndrome …' Meanwhile the extensive literature on the harmful effects of recreational (McQueen *et al.* 1994) and professional (Leplow *et al.* 2001, Ross *et al.* 2007) diving – even in the absence of accidents and decompression illness – is worth noting. These harmful effects may at least be suspected of being caused by or associated with endocrine change. Rockert *et al.* (1978) reported that the testosterone levels of rats exposed to a hyperbaric environment of air were significantly reduced; and Rockert & Haglid (1983) reported that divers' testosterone levels decrease after diving.

Psychological and sociological variables

Personality: dominance and the Trivers–Willard hypothesis

During the past three decades, theoretical biologists have explored the notion of adaptive variation of sex ratio at birth. This would occur, when, by skewing the sex ratio of their offspring, parents increased their expected number of grandchildren. Theorists have devised several models embodying such adaptive variation. The most influential of these was described by Trivers & Willard (1973; henceforth TW). Basically their idea was that under specifiable circumstances, there would be reproductive advantage if females were to skew their offspring sex ratio in one direction or the other. The circumstances were as follows:

(a) males have a higher variance of reproductive success than females,
(b) offspring inherit their mothers' 'condition' and
(c) 'condition' is positively associated with reproductive success.

Under these circumstances, females would have more grandchildren if mothers in good 'condition' were to have more sons and if mothers in poor 'condition' were to have more daughters. The above three circumstances are fulfilled in many species, including man. For the purpose of testing TW, dominance rank has frequently been used as a surrogate for 'condition'. It is noteworthy that dominant women reportedly produce a statistically significant excess of sons (Grant 1994) and have high testosterone levels (Grant & France 2001). However, though the TW paper has been cited more than 1000 times, tests of the hypothesis in some taxa (e.g. primates) have been successful in about only 50% of (roughly 100) attempts (James 2006*d*). For this reason (among others), the author suggested, in that note, that parental hormones are not only responsible for adaptive variation of sex ratio, but also for constraints (processes which conflict with the adaptive processes) on that variation. In particular, it seems that high levels of testosterone in women may be associated with some forms of suboptimal health and (contrary to TW) the production of sons.

Domiciliary arrangements

The author noted the evidence that in human polygynous societies, where co-wives live together (in harems) they tend to produce an excess of sons: in contrast, where each co-wife resides in her own dwelling (and each is visited by the husband in turn), they tend to produce an excess of daughters (James 1995*c*). Perret (1990) reported a similar result after mating female mouse lemurs that were either previously isolated or grouped with other females. Perret (1986) had noted that, in that species, hormone levels throughout the ovarian cycle are strongly modified by the presence of other females. This association is mediated by urinary olfactory cues (Perret 1996). Perret & Colaz (1997) strongly suggested that the sex ratio bias exists at conception. One may conclude that maternal

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endocrine variation is associated (presumably causally) with offspring sex ratio in this species.

Observational and experimental studies on non-human mammals

The sexes of the mother's own adjacent litter-mates in gerbils and mice

It was evident that the intrauterine position of rodents was associated with their subsequent adult hormone levels, females adjacent to two males (2M females) being more androgenized than females adjacent to two females (0M females). The author proposed an experiment to test whether (as predicted) the sex ratio of offspring of 0M females differs from that of 2M females (James 1989). The prediction was confirmed by Clark *et al.* (1993) who found that the sex ratio of offspring of 0M female gerbils is significantly lower than that of 2M females. The authors make the point that 2M females from litters that contain a majority of females produced a significantly greater percentage of sons than 0M females from litters that contained a majority of males. This suggests that intrauterine position (and thus hormone levels) is responsible rather than maternal or foetal genotype.

Clark & Galef (1994) also report a significantly higher sex ratio of offspring of caesarean-delivered pregnant 2M dams than that of offspring of caesarean-delivered 0M dams (thus eliminating the possibility that sex-related maternal cannibalism was responsible for their original result). Lastly Vandenbergh & Huggett (1994) reported highly significant evidence for such a phenomenon in the mouse. Taken together, these data provide some of the most powerful support for the author's hypothesis.

Age of maturation in gerbils

In Mongolian gerbils, the age at vaginal opening is bimodally distributed with means of about 16 and 35 days. It has been shown (Clark *et al.* 1986, Clark & Galef 1988) that litters of late-maturing females have a highly significantly higher offspring sex ratio than those of early maturing females. The probability that a female matures early is strongly related to her own position *in utero*: the probability is much lower if she was situated adjacent to one or more male foetuses. And (as noted above) this in turn correlates with her adult testosterone level. Accordingly, the author proposes that the variation of offspring sex ratio with age at maturation in gerbils is mediated by testosterone levels.

Diet in mice

Rosenfeld *et al.* (2003) reported that female mice reared on a high-fat diet had a substantially and significantly higher offspring sex ratio than those fed a low-fat diet. The effect was reportedly dependent on the amount of fat consumed (Alexenko *et al.* 2007). The same group of authors reported that in female mice, the high-fat diet was associated with higher levels of oestradiol (Whyte *et al.* 2007). These authors further reported that female mice fed diets enriched with ω-6 polyunsaturated fatty acid produced a highly significant excess of female offspring (Fountain *et al.* 2007). It is established that ω-6 polyunsaturated fatty acid has anti-oestrogenic properties (Menendez *et al.* 2004).

The author suggests that the high and low offspring sex ratios reported in these two experiments are due respectively to the high and low levels of oestrogenic activity in the dams.

Duration of oestrus in heifers

Ideta *et al.* (2007) reported that heifers bearing males had a significantly longer duration of oestrus, on the average, than those bearing females. These authors write: 'further, studies are needed to evaluate to what degree maternal hormone levels are related to oestrus duration and sex ratio'. Mondal *et al.* (2006) reported that oestrus behaviour correlates positively with oestrogen levels in cows. The author suggests that the variation of offspring sex ratio with duration of oestrus is secondary to correlations of both with oestrogen levels.

Oestrogen fertilization medium and mouse embryos

Zhang *et al.* (2006) found that mouse embryos incubated in high levels of oestradiol 17-β (E_2) had a significantly high sex ratio as compared with controls. This research was prompted by and gives direct support to the author's hypothesis.

Excising sex glands of hamsters

After the coagulatory glands and/or seminal vesicles were excised bilaterally from male golden hamsters, they sired highly significant excesses of male offspring (Chow *et al.* 1996). These authors report that the phenomenon is not associated with reduced litter size (and hence is not caused by sex-selective abortion). In male rats, prostatectomy results in stimulation of testicular androgens (Chaudhuri *et al.* 1991). It seems reasonable to suppose that such a phenomenon may operate across species: so the author suggests that the male excess among the offspring of the experimental golden hamsters was due to their high T levels.

Heat stress in mice and sperm quality and fertility

Perez-Crespo *et al.* (2007) reported that male mice were exposed to heat stress and then mated 6 h later with unexposed females. These authors noted that heat stress has deleterious effects on sperm quality, and they found that the resulting offspring sex ratio was significantly low. They cited a study reporting analogous findings viz that in red deer, sperm quality of males also correlated positively and significantly with offspring sex ratio (Gomendio *et al.* 2006). The author has offered an explanation of the latter data (James 2007). The author suggests that this explanation may apply also to the data of Perez-Crespo *et al.* (2007). The correlation between sperm quality and offspring sex ratio is secondary to correlations of both with paternal testosterone/gonadotrophin ratio.

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Gomendio *et al.* (2006) also reported a significant positive correlation between the total fertility of red deer and their offspring sex ratio. A similar association has been described in human families. A century ago, the largest European families contained slightly but significantly higher proportion of boys (Schutzenberger 1950, Edwards 1958). This occurred in spite of negative associations between a) sex ratio and b) birth order and paternal age (James 1987). The association between human fertility and sex ratio may also be mediated by paternal T.

6-MBOA in voles

Berger *et al.* (1987) experimented with 6-MBOA, a plant derivative which initiates reproduction in field populations of the meadow vole. Experimental animals of both sexes received implants of 6-MBOA and were subsequently mated. Treated animals of both sexes produced significantly more female offspring than untreated controls. Schadler *et al.* (1988) showed that 6-MBOA provokes excretion of LH in pine voles. In conformity with the author's hypothesis, gonadotrophin selects for female offspring in the meadow vole. Apparently, the selection was pre-zygotic: the authors deny that resorption occurred to any extent.

Parasitic infection in mice

Heligmosomoides polygyrus

Ehman & Scott (2002) found that litters sired by male mice parasitized by this organism had significantly low sex ratios. Parasitic infection of male mammals (including mice) lowers their T levels (Hillgarth & Wingfield 1997, Barnard *et al.* 1998). So Ehman & Scott (2002) suggested that 'parasite-induced hormonal changes may alter the sex ratio of offspring', in confirmation of the author's hypothesis.

Toxoplasma gondii

As noted above (in section *T. gondii* infection), Kankova *et al.* (2007*b*) reported that experimentally infected female mice produce significantly high offspring sex ratios – just as had been reported by the same group of workers in respect of human beings (Kankova *et al.* 2007*a*).

Kankova *et al.* (2007*b*) claimed that the observational data on the offspring sex ratio of infected women gives no clue on whether the infection is the cause of the increase in sex ratio, or whether some other factor (e.g. high T) may be responsible both for the higher risk of infection and for the higher sex ratio. These workers also claim that their experimental mouse study 'clearly shows that the increased sex ratio is the effect of latent toxoplasmosis'. It is suggested that the argument is not as clear as their wording would imply. The infection may have caused their female mice to secrete high levels of adrenal androgens as a response to the stress of infection and thus *ex hypothesi* to produce an excess of male pups. Since, males (in contrast with females) characteristically react to stress by a lowering of (testicular) androgens (Christiansen 2004), one might provisionally expect a different sex ratio result in male subjects. It would be interesting to see such data on men and male mice.

Splenial area of rats

In the rat, the splenium of the corpus callosum is sexually dimorphic, being larger in males. Testosterone injections in females increase the size of their splenium. In accordance with the author's hypothesis, Nunez & Juraska (1998) found that the offspring sex ratio of females correlates with their splenial area.

Follicular fluid testosterone levels and subsequent sex of bovine embryos

Grant & Irwin (2005) reported that they took ova from bovine follicles and fertilized them *in vitro*. Each sample of follicular fluid was assayed for testosterone. These authors found that the testosterone levels significantly correlated with the sex of the resulting zygotes. These findings were confirmed in a subsequent study (Grant *et al.* cited in Grant 2007). The testosterone concentrations could be causally responsible for the sexes of the offspring.

Summary

In some quarters, there is public suspicion of, and antagonism towards, science. Scientists frequently deplore this suspicion and antagonism. Less frequently they deplore their own resistance to scientific evidence – though it is not unknown (Barber 1961). The present hypothesis was adumbrated nearly three decades ago. But deliberate attempts to test it have only recently been initiated. Readers should also read the accompanying editorial (Clark & Davis 2008) to gain a better perspective of this hypothesis article. As a retired armchair epidemiologist and not qualified to test it experimentally, the author hopes that the foregoing account will stimulate others to test the hypothesis.

Declaration of Interest

The author declares that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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