Available online at www.sciencedirect.com
SCIENCE DIRECT®
Environmental Research 100 (2006) 77–85
Environmental Research
www.elsevier.com/locate/envres

Offspring sex ratios at birth as markers of paternal endocrine disruption

William H. James

The Galton Laboratory, University College London, Wolfson House, 4 Stephenson Way, London NW 1 2 HE, UK

Received 4 November 2004; received in revised form 2 March 2005; accepted 8 March 2005
Available online 26 May 2005

Abstract

There is good evidence that paternal (and maternal) hormone levels at the time of conception are associated with offspring sex ratios (proportions male) at birth. The mechanisms underlying this association (pre- or postzygotic) are not of primary relevance here. When people are exposed to endocrine-disrupting agents, these agents may have different hormonal effects on men and women. So, if endocrine disruption is to be revealed by offspring sex ratios, it is necessary to categorize the sexes of subsequent offspring by the four possible parental mating classes, viz. exposed/unexposed mothers/fathers. In general, substantially altered sex ratios may reveal endocrine disruption, but the tiny (admittedly significant) secular meanderings of national live birth sex ratios across the 20th Century (and before) are not now readily interpretable.

Keywords: Endocrine disruption; Estrogen; Gonadotropins; Sex ratios at birth; Testosterone

1. Introduction

I will argue that under some limited specifiable circumstances, the human sex ratio—that is the proportion of boys at birth—can be a useful marker of endocrine disruption or endocrine modification to one or both parents around the time of conception. The claim is that an unusual sex ratio at birth is provisional evidence that something was unusual about the hormone levels of one or both parents at the time of conception. Ex hypothesi, high levels of estrogen and testosterone (in either parent) are associated with subsequent births of sons and high levels of gonadotropins and progesterone with daughters.

Later I shall indicate some of the limitations of offspring sex ratios as markers of parental endocrine disruption. However, it is worth remarking here that—if sex ratios were accepted as valid markers—they have two great advantages over other criteria of endocrine disruption such as sperm counts and hormone assays: sex ratios are noninvasive and are readily referable to the distant past. People can usually remember the sexes of their children—even those who were born a long time ago—and in most cases no embarrassment or pain is involved in eliciting this information.

2. Materials and methods

The papers cited below are almost all in journals held in the Library of the Royal Society of Medicine, London. The following deliberations were occasioned by almost daily visits to this library over the past 25 years.

3. Results and discussion

There are huge numbers of scientific papers on human sex ratio at birth, how it varies, and what causes this variation. Since there are very large numbers of human births with the sexes accurately recorded, the topic has

E-mail address: c.auger@elsevier.com.

0013-9351/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2005.03.001

attracted the attention of mathematical statisticians. They have used the data to illustrate increasingly complex methods of analysis, but the scientific yield of this labor across the second half of the 20th Century was minimal. There is statistically significant variation of sex ratio with such readily available variables as birth order, maternal age, paternal age, social class, and race—but it is tiny (James, 1987) and uninformative with regard to the causes of the variation. However, in contrast, studies of sex ratios of offspring of selected groups of parents have been informative. The sex ratios of offspring of men who have undergone selected chemical exposures, selected occupational exposures, or illnesses are illuminating. Table 1 illustrates this point. In a sense it is my whole point (namely that a range of adverse chemical, occupational, and medical exposures to men are associated—presumably causally—with declines in both offspring sex ratios and testosterone/gonadotropin ratios). This table summarizes the reported effects (or associations) of eight different sorts of chemical exposure to men, four different illnesses to men, and four different forms of occupational exposure. The table suggests two relationships: many forms of illness or adverse paternal exposure are associated with subsequently siring significant excesses of daughters and such exposed or ill men have significantly low testosterone/gonadotropin ratios.

I have argued elsewhere that the one is the cause of the other: namely, this endocrine profile causes the men to sire excesses of daughters (James, 1996, 2004). However, it is no essential part of the present note to argue this. I simply wish to emphasize the association; viz. there are a large number of reported adverse circumstances under which men both (a) have low testosterone/gonadotropin ratios and (b) sire significant excesses of daughters. The usefulness of these observations to workers investigating endocrine disruption depends on their generality. I have adduced evidence that parental hormone levels and offspring sex ratios are associated in mammals in general—not simply in humans (James, 1996, 2004). This evidence will not be entirely reproduced here, but the hypothesis should be specified more precisely. It is that high parental periconceptional levels of testosterone and estrogen are ex hypothesi associated with an increased probability of subsequently producing sons and high parental levels of gonadotropins and progesterone with daughters. Ex hypothesi these hormones affect the probability with which an X- or Y-bearing sperm fertilizes the ovum. Thus the hypothesis invokes something other than sex-related fetal mortality to explain variations in live birth sex ratios. Sex-related fetal mortality is admittedly the explanation of some variation in mammalian sex ratios at birth, but I contend that it is not the sole explanation. However, strictly speaking, the explanation is irrelevant here: it is merely the association (between parental hormone levels and offspring sex ratios) that is relevant.

I have offered a mechanism for this association (James, 1997a). The proposed explanation depends on the curious facts that glycerylphosphorylcholine (GPC) exists in the male reproductive tract and that its diesterase exists in the female reproductive tract; why they are there is unknown. Moreover, GPC and its diesterase are reportedly controlled by hormones in a manner consistent with the notion that hormones ultimately control offspring sex ratios. I mention this merely to tease experimentalists who might be motivated to test the hypothesis.

Feminists may feel uneasy with the suggestion that having daughters is a criterion by which to judge that men were ill or were exposed to deleterious environmental agents at the time of conception. This unease may be assuaged by three points. (1) Whatever the other determinants of biological sex, chance would seem to be major. So arguments based on individual sibships are unlikely to be valid. (2) Some classes of pathology apparently cause women to produce excesses of sons. This is reportedly so, for example, of women who conceive when they have multiple sclerosis (James, 1994) or polycystic ovarian syndrome (Kitzinger and Willmott, 2002) or when they are hepatitis B carriers (Chahnazarian et al., 1988) or X-chromosomal recessive retinoschisis carriers (Fellman et al., 2002). (3) Some classes of ill men also produce excesses of sons, e.g., those who are destined to suffer prostatic cancer (James, 1990) and those who are hepatitis B carriers (Chahnazarian et al., 1988).

However, it seems that, in general, most sorts of adverse chemical exposures to men are associated with subsequently siring statistically significant excesses of daughters (though the generalization is far from perfect; see the reports cited below in Table 3). In contrast, there are few data on the sex ratios of offspring of women (mated to unexposed men) following suspect chemical or occupational exposure, though there are strong suggestions that under some adverse circumstances their offspring sex ratios are biased in one direction or the other; e.g., they apparently produce excesses of sons following exposure to heavy metals (Fertmann et al., 1997) and perhaps dioxin (Mocarelli et al., 2000). However, under other circumstances they reportedly produce significant excesses of daughters, e.g., with exposure to polychlorinated biphenyls (PCBs) (Taylor et al., 1989) and nonionizing radiation (Larsen et al., 1991; Irgens et al., 1997).

I realize that a proposal to use an untested, unexplained criterion such as sex ratio is like a red rag to some bullish endocrinologists. However, I am not sure that they can afford to be bullish. Endocrine disruption is a term that was coined some years ago; yet not a lot of hard evidence has been since gleaned about

Table 1
References substantiating the claims that selected male illnesses and paternal occupational and chemical exposures are associated with both low offspring sex ratios and low testosterone/gonadotropin ratios

	Low human offspring sex ratio	Low testosterone/gonadotropin ratio
Chemical exposures		
Dioxin and dioxin-like substances	Mocarelli et al. (2000); del Rio Gomez et al. (2002)	Egeland et al. (1994)
Dibromochloropropane	Potashnik and Yanai-Inbar (1987)	Whorton et al. (1979)
Fungicides	Garry et al. (2002, 2003)	Garry et al. (2003)
Methylmercury	Sakamoto et al. (2001)	Homma Takeda et al. (2001) (rats)
Vinclozolin	Zober et al. (1995) (N.S.)	Zober et al. (1995)
Borates	James (1998a, 1999)	Fail et al. (1998) (experimental animals)
Alcohol	Dickinson and Parker (1994)	James (1992)
Cigarette smoke	Fukuda et al. (2002)	Zmuda et al. (1997)
Illnesses		
HLA B 15 positivity	Astolfi et al. (2001)	Ollier et al. (1989)
Non-Hodgkin's lymphoma	Olsson and Brandt (1982)	Olsson (1984)
Testicular cancer	Moller (1998); Gundy et al. (2004); Jacobsen et al. (2000)	Petersen et al. (1999)
Multiple sclerosis	James (1994)	James (1994)
Occupational exposures		
Professional driving	Dickinson and Parker (1994)	James (1992)
Professional diving	Lyster (1982); Rockert (1977)	Rockert and Haglid (1983)
Nonionizing radiation	James (1997b); Snyder (1961)	Grajewski et al. (2000); Ortiz et al. (2000)
Pilot of high-performance aircraft or astronaut	Goerres and Gerbert (1976) Little et al. (1987); Irgens and Irgens (1999)	Strollo et al. (1998) Strollo (1999)

Methylmercury: I know of no data on the effects of methylmercury on the endocrine functions of men beyond the observation of Dufresne and Cyr (1999) that it "causes reproductive dysfunction in men". These authors and others (Burton and Meikle, 1980; Homma Takeda et al., 2001) offer evidence that methylmercury causes low testosterone levels in the male rat and mouse.

I have hypothesized that the low testosterone/gonadotropin ratio associated with paternal exposure to some of these chemicals causes the low offspring sex ratios (James, 1996); however, the present argument is in no way dependent on the truth of this hypothesis. In particular, the low human offspring sex ratio associated with methylmercury is apparently due to maternal, not paternal exposure (Sakamoto et al., 2001). Moreover these authors suggested persuasively that sex-related postimplantation loss was responsible. This argument is given some support by a report that when pregnant mice are dosed on methylmercury, there is a dose-related (though admittedly nonsignificant) lowering of live birth sex ratio. In this experiment there was also a highly significant rise in postimplantation loss rate (Colomina et al., 1995).

Dioxin and dioxin-like chemicals: I should declare an interest here: on the basis of my hypothesis and the finding of a low testosterone/gonadotropin ratio in exposed men (Egeland et al., 1994), I predicted that exposed men would sire an excess of daughters (James, 1995b). At first, the results of Mocarelli et al. (2000) seemed to confirm the prediction, but since then other data have become available. See Table 2. There are some discrepancies across the results, and these may be the consequence of different degrees of contamination with congeners (James, 2002a). Some congeners have estrogenic properties, and some have antiestrogenic or androgenic properties (Karmaus et al., 2002) (which ex hypothesi would affect offspring sex ratios (James, 1996, 2004)). Mocarelli et al. (2000) were explicit that dioxin (TCDD) (but not a range of associated chemicals) was released by the Seveso explosion. So though there is uncertainty concerning the exact effects of TCDD, the data of Mocarelli et al. (2000), Ryan et al. (2002), and perhaps those of del Rio Gomez et al. (2002) may be regarded as provisional but powerful evidence of a relationship between paternal chemical exposure and subsequent low offspring sex ratio.

It is worth noting that some exposures have been the subject of more than one paper. In particular, the conclusion of Rogan et al. (1999) (that the Yucheng cooking oil incident had no significant effect on offspring sex ratio) seems to have been superseded by that of del Rio Gomez et al. (2002) (that paternal exposure to the contaminated cooking oil was associated with a low subsequent offspring sex ratio). Table 2 summarizes the reported effects on sex ratio of dioxin and dioxin-like compounds. The table indicates an area where further knowledge is urgently needed. It is worth remarking that though dioxins and PCBs may have structural similarities, their (presumably endocrine-mediated) effects may be quite different. For instance, Vreugdenhil et al. (2002) reported that girls who were exposed to high levels of PCBs in utero showed masculinized play behavior, whereas girls prenatally exposed to dioxins showed more feminized play behavior, as contrasted with controls.

Dibromochloropropane (*DBCP*): Critics have noted that the data on DBCP are many years old. This is because the substance has been banned from use in most countries, and (to my knowledge) no further data on the effects of human exposure have since emerged. Potashnik and Yanai-Inbar (1987) reported that they had conducted more than one study and that the later work confirmed their original result.

Vinclozolin and borates: I include these data here not because I think that they are persuasive of my point but because I think that they are suggestive. Even in the absence of curiosity, the precautionary principle would seem to mandate more research into their endocrine effects. I urge any readers with access to relevant data (on offspring sex ratios and/or hormone levels of exposed men) to publish them.

Alcohol: I include these data merely because they are consistent with my hypothesis. I acknowledge that—without further data—the association between alcohol and sex ratio (if there is one) is so small that it cannot be the basis for any persuasive argument on the actual cause of it. The same comments apply to the data on professional driving.

Cigarette smoke: Here the effect, though small, is more persuasive. Both maternal and paternal smoking are reportedly associated with a diminution of offspring sex ratio, and the effect seems dose related (Fukuda et al., 2002). I have suggested that assessment of the endocrine effects of smoking is complicated by an apparent confounding by gonadal hormones between voluntary risky behavior and many pathologies which are associated with (or caused by) high or low levels of these hormones (James, 2001a, 2002b). In the present case, I suggest that, *at the time of initiation*, smoking is a

Table 1 *footnote continued*

marker for high levels of gonadal hormones (e.g., Martin et al., 2002) and that smoking has the direct pharmacological effect of lowering those hormone levels. The antiestrogenic effect of smoking on women is well established. The effect of smoking on men's testosterone levels is the subject of a very confused literature on cross-sectional studies. I suggest that this is because of the confounding suggested above; in contrast, longitudinal studies are more persuasive (Zmuda et al., 1997). I suggest that these latter authors are correct in inferring that smoking lowers men's testosterone levels (and ex hypothesi the sex ratios). In short, smoking seems to be a weak endocrine disruptor in both men and women. This conclusion is supported both by direct endocrine data and by data on offspring sex ratios.

Illnesses: Not all forms of paternal illness are associated with siring daughters. However, most nonendocrine diseases in men are associated with low testosterone/gonadotropin ratios (Semple, 1986) and ex hypothesi with the production of daughters. But this does not hold for all diseases—even nonendocrine diseases. It is true that men destined to suffer prostatic cancer (an endocrine cancer) reportedly sire an excess of sons (James, 1990) ex hypothesi as a consequence of the high androgen levels that are causally associated with the disease (Bosland, 1988). However, men (and women) who are carriers of hepatitis B (which is not thought to be caused by hormone concentrations) also produce an excess of sons (Chahnazarian et al., 1988), ex hypothesi as a consequence of high levels of testosterone associated with hepatitis B carrier status (Jilma et al., 1998). Finally, (quite apart from conditions associated with child bearing) there are at least two pathological conditions in women which are associated with their producing excess daughters, viz. cytomegalovirus (CMV) seropositivity (Piazze et al., 1999; Shields et al., 2002) and celiac disease (James, 2001b). The association with CMV is ex hypothesi because estrogen has a generally suppressive effect on viral replication (Speir et al., 2000). The association with celiac disease is apparently mediated by dietary treatment, the sex ratio being significantly higher in offspring of mothers with gluten-free diets (Ludvigsson and Ludvigsson, 2001).

It is worth noting that in general I would hypothesize nonendocrine diseases to have opposite effects on the offspring sex ratios of male and female patients. This is so because stress causes a decrease in testicular androgens in men and an increase in adrenal androgens in women (Kemper, 1990). Since these are, respectively, the main sources of androgens in men and women, ex hypothesi one would expect ill men (suffering from nonendocrine disease) to sire excesses of daughters and ill women to produce sons.

Table 3 summarizes all the information (known to me) on the associations between parental pathologies and offspring sex ratios. There is some confirmation of the above suggestion (that, in general, ill men sire daughters and ill women produce sons), but there are many exceptions to this generalization. The important point is that many forms of illness in parents (of both sexes) are associated with significantly biased offspring sex ratios. Ex hypothesi, this is a consequence of unusual hormone profiles which either cause, are caused by, or facilitate, the pathologies. The point of presenting this table here is to support suspicion that a biased sex ratio may generally be indicative of pathology and frequently of endocrine disruption.

Occupational exposures: Three of the suspect occupational exposures listed above (diving, alteration in gravity, and nonionizing radiation) fall (at least partially) within the purview of defence establishments. I have had difficulties in obtaining information on potentially deleterious effects of such exposures on men in the armed forces. Seeking further data on the offspring sex ratios of naval divers, I had a long but eventually fruitless correspondence with doctors in the Royal Navy. Naval doctors of increasingly exalted rank told me that the data on the sex ratios of the offspring of their men were not available.

Meanwhile the extensive literature on the harmful effects of recreational (McQueen et al., 1994) and professional (Leplow et al., 2001) 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 changes. Perhaps it would be useful to direct requests (concerning offspring sex ratios) to doctors who are retained by trades unions (who may be assumed to represent the interests of employees rather than employers). I urge any reader with access to such data (on the offspring sex ratios and/or hormone levels of men occupationally exposed to changes in gravity, atmospheric pressure, or nonionizing radiation) to please publish or forward them to me.

the existence—let alone the effects—of endocrine disruption in humans. However, lest it be thought that I am being over enthusiastic about sex ratios, I shall now describe some limitations of them as markers of endocrine disruption.

3.1. Necessity to specify the affected parent

The data in Table 1 all relate to men. Much less is known about the reproductive effects of occupational and chemical exposures to women. But there are very good grounds for supposing (1) that the hormone levels of both fathers and mothers are involved in the sexes of their children (James, 1996, 2004) and (2) that the endocrine responses of men and women to deleterious chemical agents may be quite different—even opposite. The logical upshot is that, in testing for endocrine disruption, it is necessary in principle to examine the offspring sex ratios of all four of the categories of matings of exposed and unexposed fathers and mothers. In the absence of such data, an overall unchanged sex ratio is uninformative because the effect on fathers may be opposite and equal to the effect on mothers. As an illustration, let us suppose, for a moment, that we all are subject to weak exposures of exogenous estrogen. As I understand it, such exposure would be expected to be accompanied by higher levels of estrogen in women and lower levels of testosterone in men. According to my hypothesis, exposed men will then have an enhanced tendency to produce daughters and exposed women an enhanced tendency to produce sons—the two effects potentially counteracting if both parents are so exposed.

Hence, sex ratios 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. So, for instance, studies have been made of offspring sex ratios in the vicinity of waste incinerators, chemical dumps, and leakages of natural gas. Results have been equivocal: significantly high sex

ratios (Fertmann et al., 1997; Lloyd et al., 1985; Saadat et al., 2002), low sex ratios (Lyster, 1981; Williams et al., 1992), and unchanged sex ratios (Bhopal et al., 1999; Kozlov, 1999; Vassilev et al., 2001; Williams et al., 1995) have all been reported. In short, in the absence of direct evidence of exposure to parents of a specified sex (mated to unexposed coparents), little about endocrine disruption can be inferred from sex ratios. In illustration of this point, Mocarelli et al. (2000) and Ryan et al. (2002) reported that, by controlling for sex of exposed parent, paternal (as contrasted with maternal) exposure to dioxin is associated with subsequently siring significant excesses of daughters. It should be acknowledged here that there have been a number of other studies on the effects of dioxin and dioxin-like chemicals on human offspring sex ratios and that these results have been contradictory. (The relevant data are given in Table 2). So how can the argument be sustained that sex ratios are a useful criterion of endocrine disruption? There are three points to be made. (1) The contradictory reported effects of dioxin and PCBs on sex ratio may be caused by contaminants and congeners which have variously been described as androgenic, antiandrogenic, estrogenic and antiestrogenic. If that were correct, then ex hypothesi one would expect the present chaos with regard to their effects on offspring sex ratio. (2) My overall argument is that a biased offspring sex ratio provisionally may be taken to imply endocrine disruption, not that a normal offspring sex ratio implies the absence of endocrine disruption. (3) In any case, the contradictory results on reported sex ratios associated with dioxins and PCBs cannot be ascribed to chance. The heterogeneity of reported sex ratios across samples is far too great to admit such an explanation. So we should first consider the possibility of publication (or other) bias. If that seems not the sole explanation, we may provisionally infer that altered sex ratios are, under some circumstances, caused by—or at least associated with—the chemical exposures (mediated ex hypothesi by endocrine disruption). Critics of such a view should explain how bias could have produced the present confusion.

3.2. *Interpretation of secular movements in national sex ratios at birth*

It has been known for many years that national sex ratios at birth meander slowly but significantly up and down across time (Gini, 1955). Some of these movements may have been due to changing methods of reporting, and increases in 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 are not established. Those in the 19th Century and early 20th Century occurred before the huge variety of pesticides and other suspect chemical compounds were introduced. They may possibly have been due to industrial pollution (mediated ex hypothesi by endocrine disruption) or these movements may have been the consequence of genetic stabilizing mechanisms (Bodmer and 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 significant excesses of daughters (e.g., Potashnik and 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

Table 2
Reported effects on offspring sex ratio of dioxin and dioxin-like agents

Site	Chemical agent	Effects of parental exposure on sex ratio			Authors
		Paternal	Maternal	Both	
Austria	TCDD	NS lowered	NA	NA	Moshammer and Neuberger (2000)
Seveso	TCDD alone	Lowered	?Raised	Lowered	Mocarelli et al. (2000)
Russia	Various dioxins	Lowered	Nil	Lowered	Ryan et al. (2002)
US factories	TCDD (+contaminants?)	Raised	NA	NA	Schnorr et al. (2001)
Yusho	PCBs and PCDFs but not TCDD			Raised	Yoshimura et al. (2001)
Yucheng	PCBs, PCDFs, and PCDDs	Lowered	?	NA	del Rio Gomez et al. (2002)
Michigan	PCBs and DDE	Raised	NS	—	Karmaus et al. (2002)
Vietnam (veterans)	TCDD (+ 2,4,5-T)	NS raised	NA	NA	Michalek et al. (1998)
?	PCBs	—	Lowered	—	Taylor et al. (1989)
Israel	DBCP	Lowered	NA	—	Potashnik and Yanai-Inbar (1987)

NA, not available or not applicable; NS, not significant; DBCP, dibromochloropropane; DDE, dichlorodiphenyl dichloroethene; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls.

Table 3
Statistically significantly biased (up or down) human offspring sex ratios associated with various pathologies

Pathological conditions	Male patients	Female patients
Celiac disease	Not known	Down (James, 2001b)
Cytomegalovirus seropositivity	Not known	Down (Shields et al., 2002)
Dermatoses of pregnancy	Not applicable	Up (James, 2000d)
Extrauterine pregnancy	Not applicable	Down (James, 1995a)
Fatty liver of pregnancy	Not applicable	Up (James, 1995a)
Hepatitis B carrier	Up (Chahnazarian et al., 1988)	Up (Chahnazarian et al., 1988)
HLA B 15 positivity	Down (Astolfi et al., 2001)	Not known
Hyperemesis gravidarum	Not applicable	Down (James, 2001c)
Measles	Not known	Up (Langaney and Pison, 1979)
Multiple sclerosis	Down (James, 1994)	Up (James, 1994)
Non-Hodgkin's lymphoma	Down (Olsson and Brandt, 1982)	Down Olsson and Brandt 1982)
Placenta accreta	Not applicable	Down (James, 1995a)
Placenta previa	Not applicable	Up (James, 1995a)
Polycystic ovary syndrome	Not applicable	Up (Kitzinger and Willmott, 2002)
Preeclampsia	Not applicable	Up (James, 1995a)
Prostatic cancer	Up (James, 1990)	Not applicable
X-chromosome recessive retinoschisis carrier	Not applicable	Up (Fellman et al., 2002)
Schizophrenia	Not known	Down (James, 2000c)
Testicular cancer	Down (Moller, 1998; Jacobsen et al., 2000; Gundy et al., 2004)	Not applicable
Varicella	Not known	Down (Miller, 2002)

HLA B 15 positivity is categorized here as a pathological condition because of its positive association with rheumatoid arthritis in men.

explained—how the sex ratios might have moved in the absence of environmental pollution.

Meanwhile it is appropriate to offer one qualification. Bodmer and Edwards (1960), cited above, concluded that the magnitude of Lexis variation in P (the probability of a male birth) across couples as estimated by Edwards (1958) is so small as to preclude its genetic component being the (sole) explanation for the observed secular variation in national sex ratios. However, I have recently suggested that within couples, P may show both systematic and chaotic Poisson variation (James, 2000a). If that were so, then Edwards' (1958) estimates of the Lexis and Poisson variation of P may both be too low. This point urgently needs investigating. So it would be interesting to determine whether Monte Carlo simulation (or other forms of estimation) could capture the observed magnitude of secular variation of national sex ratios using models which incorporate (1) mechanisms of the sort invoked by Bodmer and Edwards (1960) and (2) both Lexis and Poisson variation with variance estimates of the order suggested by me (James, 2000a)

However, in general, a useful moral may be offered: in the biological sciences, speculations about the causes of tiny effects (such as secular variation in national sex ratios at birth) are usually less fruitful than speculations about large effects.

3.3. Animal experiments

It was clear after the Seveso explosion that the effects of dioxin are species specific. No people are thought to have died as an immediate consequence, but pets and livestock did die. This qualification hangs over experiments with other species. There must be doubt about the extent to which results with them may be generalized to humans; e.g., contrary to the finding of Mocarelli et al. (2000) (who found a significantly low offspring sex ratio associated with men's exposure to dioxin), Melaine and Jegou (2000) reported experimental work in which they failed to find an effect of dioxin on male reproduction (Zorn et al., 2002).

It may be acknowledged that animal experimentation by reproductive toxicologists has yielded little support for my suggestions here. This may be because effects are species specific or it may be because, of necessity, such experiments are fishing expeditions. (I do not use the term pejoratively: in this area, such methods are appropriate because little is known.) The point may be illustrated by a recent issue of the journal *Reproductive Toxicology* (Vol. 16, pp. 451–734, 2002). It contained seven papers reviewing the data on the effects of seven different phthalates on mammalian reproduction. None of the studies reviewed (to my knowledge) had been initiated as a response to my hypothesis, and none apparently directly test it. My grounds for this suggestion are as follows. To test my hypothesis, the following provisions should be met: (a) exposed animals of both sexes should be mated to both exposed and unexposed animals and (b) in some experimental samples, exposure should occur only before mating and should not continue into pregnancy. In others, exposure should occur only during pregnancy. Finally, in other samples, exposure should occur both pre- and postconceptionally.

Despite this meagre contribution from experimental toxicology, it is worth noting that it potentially remains an important tool for the investigation of (or the initiation of suspicion concerning) endocrine disruption. No sane person would volunteer to be treated with methylmercury, mustard gas, or dioxin and neither would any ethics committee sanction such treatment. So it would seem reasonable to continue experimentation with other animals while we wait for the next accident (involving such chemicals) to occur to humans. Meanwhile it is worth suggesting that we should capitalize on accidents that have already happened. For instance, in Bhopal, offspring sex ratios should be studied subsequent to the incident with methyl icocyanate. Finally, I should like to suggest that, pending the next accident to humans, other animal experiments should be conducted which embody the above provisions. Offspring sex ratios of all mating combinations should be routinely reported.

3.4. Identity of the hormones

The application of my hypothesis is of immediate relevance only to those concerned with testing for disruption of the sex hormones as opposed to other hormones. It is not clear whether changes in concentrations of other hormones affect mammalian offspring sex ratios.

4. Conclusions

The points I would like to emphasize are as follows.

(1) There is now overwhelming evidence that mammalian (including human) offspring sex ratios are associated with (and presumably are partially caused by) parental hormone levels around the time of conception.
(2) The relevant hormones are testosterone, gonadotropins, estrogen, and (perhaps) progesterone. Other hormones may be involved, either directly or indirectly by their effects on those already specified.
(3) So if parents are exposed to agents that alter these hormone levels around the time of conception, the sex ratio of their offspring will potentially reveal this exposure.
(4) By potentially I mean that an unusual sex ratio is suggestive of hormone disruption but that a normal sex ratio may nevertheless occur even in the presence of hormone disruptors if both parents are exposed to them.
(5) This is so because there is evidence that illness and adverse chemical exposures have different (and sometimes opposite) effects on the endocrines of men and women. So, to test whether a sample of parents has been exposed to an endocrine disruptor, we need fourfold classifications of matings, viz. by exposed/unexposed and by father/mother.
(6) So in cases where potential exposure has been widespread and potentially to both parents in individual matings (as in chemical spillages into water sources or the atmosphere) overall sex ratios may not reflect exposure.
(7) In short, sex ratios may be useful monitors of endocrine disruption only if we know which parents were exposed (mother, father, or both).
(8) I am aware that in Table 1, each of the individual pieces of evidence may be weak but I suggest that, cumulatively, the weight of evidence in that table is now substantial.

Finally, it is worth noting that most scientific propositions that turn out to be true are not unique and beautiful like Venus rising from the waves; instead they are embedded in a network of other propositions. My papers (James, 1996, 2000b) show that my hypothesis implies many other apparently true propositions in a wide range of medical disciplines. Each of these may be regarded as a test that my hypothesis has successfully withstood.

References

Astolfi, P., Cuccia, M., Martinetti, M., 2001. Paternal HLA genotype and offspring sex ratio. Hum. Biol. 73, 315–319.
Bhopal, R.S., Tate, J.A., Foy, C., Moffatt, S., Phillimore, P.R., 1999. Residential proximity to industry and adverse birth outcomes. Lancet 354, 920–921.
Bodmer, W.F., Edwards, A.W.F., 1960. Natural selection and the sex ratio. Ann. Hum. Genet. 24, 239–244.
Bosland, M.C., 1988. The etiopathogenesis of prostatic cancer with special reference to environmental factors. Adv. Cancer Res. 51, 1–106.
Burton, G.V., Meikle, A.W., 1980. Acute and chronic methylmercury poisoning impairs rat adrenal and testicular function. J. Toxicol. Environ. Health 6, 597–606.
Chahnazarian, A., Blumberg, B.S., London, W.T., 1988. Hepatitis B and the sex ratio at birth: a comparative analysis of four populations. J. Biosoc. Sci. 20, 357–370.
del Rio Gomez, I., Marshall, T., Tsai, P.P., Shao, Y.-S., Guo, Y.L., 2002. Number of boys born to men exposed to polychlorinated biphenyls. Lancet 360, 143–144.
Dickinson, H., Parker, L., 1994. Do alcohol and lead change the sex ratio? J. Theor. Biol. 169, 313.
Dufresne, J., Cyr, D.G., 1999. Effects of short term methylmercury exposure on metallothionein mRNA levels in the testis and epididymis of the rat. J. Androl. 20, 769–778.
Edwards, A.W.F., 1958. An analysis of Geissler's data on the human sex ratio. Ann. Hum. Genet. 23, 6–15.
Egeland, G.M., Sweeney, M.H., Fingerhut, M.A., Wille, K.K., Schnorr, T.M., Halperin, W.E., 1994. Total serum testosterone and gonadotropins in workers exposed to dioxins. Am. J. Epidemiol. 139, 272–281.
Fail, P.A., Chapin, R.E., Price, C.J., Heindel, J.J., 1998. General, reproductive developmental and endocrine toxicity of boronated compounds. Reprod. Toxicol. 12, 1–18.

Fellman, J., Eriksson, A.W., Forsius, H., 2002. Sex ratio and proportion of affected sons in sibships with X-chromosome recessive traits: maximum likelihood estimation in truncated multinomial distributions. Hum. Hered. 53, 173–180.

Fertmann, R., Schumann, M., Karmaus, W., Schmid-Hopner, S., Kuppers-Chinnow, M., 1997. Sex ratio variation in the Bille settlement. Scand. J. Work Environ. Health 23, 308–310.

Fukuda, M., Fukuda, K., Shimizu, T., Andersen, C.Y., Byskov, A.G., 2002. Parental smoking and male:female ratio of newborn infants. Lancet 359, 1407–1408.

Garry, V.F., Harkins, M.E., Erickson, L.L., Long-Simpson, L.K., Holland, S.E., Burroughs, B.L., 2002. Birth defects, season of conception and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ. Health Perspect. 110 (Suppl. 3), 441–449.

Garry, V.F., Holland, S.E., Erickson, L.L., Burroughs, B.L., 2003. Male reproductive hormones and thyroid function in pesticide applicators in the Red River Valley of Minnesota. J. Toxicol. Environ. Health A 66, 965–986.

Gini, C., 1955. Sulla probabilita che x termini di una serie erratica sieno crescenti (o non decrescenti) ovvero tutti decrescenti (o non crescenti) con applicazioni ai rapporti dei sessi nascite umane in intervalli successivi e alle disposizioni dei sessi nelle fratellanze umane. Metron 17 (3–4), 1–41.

Goerres, H.P., Gerbert, K., 1976. Sex ratio in offspring of pilots: a contribution to stress research. Aviat. Space Environ. Med. 47, 889–892.

Grajewski, B., Cox, C., Schrader, S.M., Murray, W.E., Edwards, R.M., Turner, T.W., et al., 2000. Semen quality and hormone levels among radiofrequency heater operators. J. Occup. Environ. Med. 42, 239–250.

Gundy, S., Babosa, M., Baki, M., Bodrogi, I., 2004. Increased predisposition to cancer in brothers and offspring of testicular tumor patients. Pathol. Oncol. Res. 10, 197–203.

Homma Takeda, S., Kugenuma, Y., Iwamuro, T., Kumagai, Y., Shimojo, N., 2001. Impairment of spermatogenesis in rats by methylmercury: involvement of stage- and cell-specific germ cell apoptosis. Toxicology 169, 25–35.

Irgens, A., Irgens, L.M., 1999. Male proportion in offspring of military air pilots in Norway. Nor. Epidemiol. 9, 47–49.

Irgens, A., Kruger, K., Skorve, A.H., Irgens, L.M., 1997. Male proportions in offspring of parents exposed to strong static and extremely low frequency electromagnetic fields in Norway. Am. J. Ind. Med. 32, 557–561.

Jacobsen, R., Bostofte, E., Engholm, G., Hansen, J., Skakkebaek, N.E., Moller, H., 2000. Fertility and offspring sex ratio of men who develop testicular cancer: a record linkage study. Hum. Reprod. 15, 1958–1961.

James, W.H., 1987. The human sex ratio. Part 1: a review of the literature. Hum. Biol. 59, 721–752.

James, W.H., 1990. The hypothesized hormonal control of the human sex ratio at birth—an update. J. Theor. Biol. 143, 555–564.

James, W.H., 1992. The hypothesized hormonal control of mammalian sex ratio at birth—a second update. J. Theor. Biol. 155, 121–128.

James, W.H., 1994. The sex ratios of offspring of parents with multiple sclerosis. Neuroepidemiology 13, 216–219.

James, W.H., 1995a. Sex ratios of offspring and the causes of placental pathology. Hum. Reprod. 10, 1403–1406.

James, W.H., 1995b. Re: Total serum testosterone and gondotropins in workers exposed to dioxin. Am. J. Epidemiol. 141, 476–477.

James, W.H., 1996. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. J. Theor. Biol. 180, 271–286.

James, W.H., 1997a. A potential mechanism for sex ratio variation in mammals. J. Theor. Biol. 189, 253–255.

James, W.H., 1997b. The sex ratios of offspring of people exposed to non-ionizing radiation. Occup. Environ. Med. 54, 622–623.

James, W.H., 1998. The sex ratio of offspring of people exposed to boron. Reprod. Toxicol. 12, 673.

James, W.H., 1999. The sex ratio of offspring of people exposed to boron. Reprod. Toxicol. 13, 235.

James, W.H., 2000a. The variation of the probability of a son within and across couples. Hum. Reprod. 15, 1184–1188.

James, W.H., 2000b. Why are boys more likely to be preterm than girls? And other related conundrums in human reproduction. Hum. Reprod. 15, 2108–2111.

James, W.H., 2000c. The hypothesized hormonal control of offspring sex ratio: evidence from families ascertained by schizophrenia and epilepsy. J. Theor. Biol. 206, 445–447.

James, W.H., 2000d. The sex ratio of children born to women with dermatoses of pregnancy. Br. J. Dermatol. 143, 1345.

James, W.H., 2001a. Hypothesis: gonadal hormones act as confounders in epidemiological studies of the associations between some behavioural risk factors and some pathological conditions. J. Theor. Biol. 209, 97–102.

James, W.H., 2001b. Hormones and offspring sex ratios associated with celiac disease. Am. J. Gastroenterol. 96, 2266–2267.

James, W.H., 2001c. The associated offspring sex ratios and cause(s) of hyperemesis gravidarum. Acta Obstet. Gynecol. Scand. 80, 378–379.

James, W.H., 2002a. Fish eaters and sex ratio. J. Occup. Environ. Med. 44, 885.

James, W.H., 2002b. Periconceptual parental smoking and sex ratio of offspring. Lancet 360, 1515.

James, W.H., 2004. Further evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. Hum. Reprod. 19, 1250–1256.

Jilma, B., Eichler, H.G., Koppl, C., Weber, B., Pidlich, J.P., Ferenci, P., Muller, C., 1998. Effects of testosterone suppression in serum levels of hepatitis B surface antigen and HBV-DNA in men. Liver 18, 162–165.

Karmaus, W., Huang, S., Cameron, L., 2002. Parental concentration of dichlorodiphenyl dichloroethene and polychlorinated biphenyls in Michigan fish eaters and sex ratio in offspring. J. Occup. Environ. Med. 44, 8–13.

Kemper, T.D., 1990. Social Structure and Testosterone. Rutgers University Press, London.

Kitzinger, C., Willmott, J., 2002. The thief of womanhood: women's experience of polycystic ovarian syndrome. Soc. Sci. Med. 54, 349–361.

Kozlov, M.V., 1999. Offspring sex ratio in a heavily polluted town. Reprod. Toxicol. 13, 567–568.

Langaney, A., Pison, G., 1979. Rougeole et augmentation temporaire de la masculinite des naissances: coincidence ou causalite? C. R. Acad. Sci. 'D' 289, 1255–1258.

Larsen, A.I., Olsen, J., Svane, O., 1991. Gender specific reproductive outcome and exposure to high frequency electromagnetic radiation among physiotherapists. Scand. J. Work Environ. Health 17, 324–329.

Leplow, B., Tetzlaff, K., Holl, D., Zeng, L., Reuter, M., 2001. Spatial orientation in construction divers—are there associations with diving experience? Int. Arch. Occup. Environ. Health 74, 189–198.

Little, B.B., Rigsby, C.H., Little, L.R., 1987. Pilot and astronaut offspring: possible G-force effects on human sex ratio. Aviat. Space Environ. Med. 58, 707–709.

Lloyd, O.L., Smith, G., Lloyd, M.M., Holland, Y., Gailey, F., 1985. Raised mortality from lung cancer and high sex ratios of

births associated with industrial pollution. Br. J. Ind. Med. 42, 475–480.
Ludvigsson, J.F., Ludvigsson, J., 2001. Coeliac disease in the father affects the newborn. Gut 49, 169–175.
Lyster, W.R., 1981. Pollution and sex ratio of births. Med. J. Aust. ii, 151–152.
Lyster, W.R., 1982. Altered sex ratio in children of divers. Lancet ii, 152.
McQueen, D., Kent, G., Murrison, A., 1994. Self-reported and long term effects of diving and decompression illness in recreational SCUBA divers. Br. J. Sports Med. 28, 101–104.
Martin, C.A., Kelly, T.H., Rayens, M.K., Brogli, B.R., Brenzel, A., Jackson Smith, W., Omar, H.A., 2002. Sensation seeking, puberty and nicotine, alcohol, and marijuana use in adolescence. J. Am. Acad. Child Adolesc. Psychiatry 41, 1495–1502.
Melaine, N., Jegou, B., 2000. La dioxine et la fonction de reproduction masculine. Reprod. Hum. Hormon. 13, 558–568 (cited by Zorn et al., 2002).
Michalek, J.E., Rahe, A.J., Boyle, C.A., 1998. Paternal dioxin and the sex of children fathered by veterans of Operation Ranch Hand. Epidemiology 9, 474–475.
Miller, E. Private communication, 13, December 2002.
Mocarelli, P., Gerthoux, P.M., Ferrari, E., Patterson, D.G., Kieszak, S.M., Brambilla, P., et al., 2000. Paternal concentrations of dioxin and sex ratio of offspring. Lancet 355, 1858–1863.
Moller, H., 1998. Trends in sex ratio, testicular cancer and male reproductive hazards: are they connected? Acta Pathol. Microbiol. Scand. 106, 232–239.
Moshammer, H., Neuberger, M., 2000. Sex ratio in the children of the Austrian chloracne cohort. Lancet 356, 1271–1272.
Ollier, W., Spector, T., Silman, A., Perry, L., Ord, J., Thomson, W., Festenstein, H., 1989. Are certain HLA haplotypes responsible for low testosterone levels in males? Dis. Markers 7, 139–143.
Olsson, H., 1984. Epidemiological studies in malignant lymphoma with special reference to occupational exposure to organic solvents and to reproductive factors. Doctoral Dissertation presented to the University of Lund.
Olsson, H., Brandt, L., 1982. Sex ratio in offspring of patients with non-Hodgkin lymphoma. N. Engl. J. Med. 306, 367.
Ortiz, R.M., Wade, C.E., Morey-Holton, E., 2000. Urinary excretion of LH and testosterone from male rats during exposure to increased gravity: post spaceflight and centrifugation. Proc. Soc. Exp. Biol. Med. 225, 98–102.
Petersen, P.M., Skakkebaek, N.E., Vistisen, K., Rorth, M., Giwercman, A., 1999. Semen quality and reproductive hormones in men with testicular cancer. J. Clin. Oncol. 17, 941–947.
Piazze, J., Nigro, G., Mazzocco, M., Marchiani, E., Brancato, V., Anceschi, M.M., Cosmi, E.V., 1999. The effect of primary cytomegalovirus infection on fetal lung maturity indices. Early Hum. Dev. 54, 137–144.
Potashnik, G., Yanai-Inbar, I., 1987. Dibromochloropropane (DBCP): an 8-year re-evaluation of testicular function and reproductive performance. Fertil. Steril. 47, 317–323.
Rockert, H.O.E., 1977. Changes in the vascular bed in testes of rats exposed to air at 5 atmospheres absolute pressure. I.R.C.S. J. Med. Sci. 5, 107.
Rockert, H.O.E., Haglid, K., 1983. Reversible changes in rate of DNA synthesis in the testes of rats after daily exposure to a hyperbaric environment of air. I.R.C.S. J. Med. Sci. 11, 531.
Rogan, W.J., Gladen, B.C., Guo, Y.-L.L., Hsu, C.-C., 1999. Sex ratio after exposure to dioxin-like chemicals in Taiwan. Lancet 353, 206–207.
Ryan, J.J., Amirova, Z., Carrier, G., 2002. Sex ratios of children of Russian pesticide producers. Environ. Health Perspect. 110, A699–A701.
Saadat, M., Ansari-Lari, M., Bahaoddini, A., 2002. Sex ratio at birth in Masjid-I-Sulaiman (Khozestan Province, Iran). Occup. Environ. Med 59, 853.
Sakamoto, M., Nakano, A., Akagi, H., 2001. Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution. Environ. Res. 87, 92–98.
Schnorr, T.M., Lawson, C.C., Whelan, E.A., et al., 2001. Spontaneous abortion, sex ratio and paternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Environ. Health Perspect. 109, 1127–1132.
Semple, C.G., 1986. Hormonal changes in non-endocrine diseases. Br. Med. J. 293, 1049–1052.
Shields, M.D., O'Hare, B., Nelson, J., Stewart, M.C., Coyle, P., 2002. Maternal cytomegalovirus seropositivity affects sex determination. Br. Med. J. 325, 335.
Snyder, R.G., 1961. The sex ratio of offspring of pilots of high performance military aircraft. Hum. Biol. 33, 1–10.
Speir, E., Yu, Z.X., Takeda, K., Ferrans, V.J., Cannon, R.O., 2000. Antioxidant effect of estrogen on cytomegalovirus-induced gene expression in coronorary artery smooth muscle cells. Circulation 102, 2990–2996.
Strollo, F., 1999. Hormonal changes in humans during spaceflight. Adv. Space Biol. Med. 7, 99–129.
Strollo, F., Riondiono, G., Harris, B., et al., 1998. The effect of microgravity on testicular androgen secretion. Aviat. Space Environ. Med. 69, 133–136.
Taylor, P.R., Stelma, J.M., Lawrence, C.E., 1989. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. Am. J. Epidemiol. 129, 395–406.
Vassilev, Z.P., Robson, M.G., Klotz, J.B., 2001. Outdoor exposure to airborne polycyclic organic matter and adverse reproductive outcomes: a pilot study. Am. J. Ind. Med. 40, 255–262.
Vreugdenhil, H.J.I., Slijper, F.M.E., Mulder, P.G.H., Weisglas-Kuperus, N., 2002. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. Environ. Health Perspect. 110, A593–A598.
Whorton, D., Milby, T.H., Krauss, R.M., Stubbs, H.A., 1979. Testicular function in DBCP exposed workers. J. Occup. Med. 21, 161–166.
Williams, F.L.R., Lawson, A.B., Lloyd, O.L., 1992. Low sex ratios of births in areas at risk from air pollution from incinerators as shown by geographical analysis and 3-dimensional mapping. Int. J. Epidemiol. 21, 311–319.
Williams, F.L.R., Ogston, S.A., Lloyd, O.L., 1995. Sex ratios of births, mortality and air pollution: can measuring the sex ratios of births help to identify health hazards from air pollution in industrial environments? Occup. Environ. Med. 52, 164–169.
Yoshimura, T., Kaneko, S., Hayabuchi, H., 2001. Sex ratio of offspring of those affected by dioxin and dioxin-like compounds: the Yusho, Seveso and Yucheng incidents. Occup. Environ. Med. 58, 540–541.
Zmuda, J.M., Cauley, J.A., Kriska, A., Glynn, N.W., Gutai, J.P., Kuller, L.H., 1997. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men: a 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am. J. Epidemiol. 146, 609–617.
Zober, A., Hoffmann, G., Ott, M.G., Will, W., van Ravenzwaay, B., 1995. Study of the morbidity of personnel with potential exposure to vinclozolin. Occup. Environ. Med. 52, 233–241.
Zorn, B., Sucur, V., Stare, J., Meden-Vrtovec, H., 2002. Decline in sex ratio at birth after 10-day war in Slovenia. Hum. Reprod. 17, 3173–3177.