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AMENDMENTS TO HYPOTHESES ON THE PROXIMATE CAUSES OF VARIATION IN HUMAN SEX RATIOS AT BIRTH WITH PARENTAL INFECTION WITH HEPATITIS B VIRUS OR *TOXOPLASMA GONDII*

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Summary. In a recent paper in this Journal, I offered hypotheses on the offspring sex ratios of women infected with the parasite *Toxoplasma gondii*, and on the offspring sex ratios of people who are carriers of hepatitis B virus (HBV) (James, 2008). Subsequent research suggests that these hypotheses need amending. A detailed account of the amendments is given elsewhere in a specialized journal (James, 2010a). Here they are summarized.

Introduction

During the last century, it has become clear that the human sex ratio (proportion male) at birth varies with many variables. Most of this variation is very small in magnitude – so small, indeed, as to offer no promising clues to the identity of its cause(s). However attention has focused on the substantial reported variation of offspring sex ratio with two relatively common forms of parental pathology, viz infections with hepatitis B and *Toxoplasma gondii*. These associations will be described later. The proximate causes of these associations are not established, and since these infections are responsible for a substantial burden of human illness, there has been some research into these causes. I have previously hypothesized that the hormone levels of mammalian parents around the time of conception are causally associated with the sexes of the resulting offspring (James, 1996, 2004, 2010b). *Ex hypothesi*, high levels of testosterone (in either parent) or of oestrogen (in the mother) around the time of conception are associated with the production of sons. In a recent paper in this journal, I offered hypotheses about the endocrine causes of the offspring sex ratio variation associated with parental hepatitis B and *T. gondii* (James, 2008). More recent research has suggested that those hypotheses need amendments which are described in detail elsewhere in a specialized journal (James 2010a), and are summarized here.

Infection with *Toxoplasma gondii*

This parasite is very common in human beings, between 20% and 60% of the populations of most countries being infected (Flegr *et al*., 2005). Kankova *et al*. (2007b) reported that (as contrasted with uninfected controls) infected women are more likely to produce sons (p=0.001), and that the offspring sex ratio increases with the concentration of anti-*Toxoplasma* antibodies in *Toxoplasma*-positive mothers (p=0.001). This group of workers also reported similar findings on experimentally infected female mice (Kankova *et al*., 2007a). Lastly (and the relevance of this will become evident in the section on hepatitis B), these workers reported that the sex ratio of offspring of infected female mice declines with the duration of the infection. In conformity with my hypothesis, I originally cited the abundant evidence that infected men have high testosterone concentrations, and (incautiously) proposed that this would explain the high offspring sex ratio of infected women (James, 2008). However, more recent research suggested that hormone characteristics differ as between infected men and women. Flegr *et al*. (2008) reported that *Toxoplasma*-infected men have higher testosterone (T) levels than uninfected controls; and that *Toxoplasma*-infected women have significantly *lower* T levels than uninfected controls. This necessitated an amendment to my hypothesis.

The proposed amendment

So I cited the strong evidence that female mice with high oestrogen (E) levels are more vulnerable to *T. gondii* than controls (James, 2010a). And in that paper I hypothesized that (presumably like naturally infected female mice), infected women have high E levels (rather than high T levels), thus (in conformity with my hypothesis) explaining their high offspring sex ratio. In summary, the amendment to my hypothesis is that the high sex ratios of offspring of *T. gondii*-infected female mice and women are due to high levels of oestrogen rather than to high levels of testosterone. I am indebted to a reviewer for suggesting that the sources of the hypothesized additional E in infected mice and women have not been identified and may differ. In principle, high E levels in women are reportedly associated with high sensation-seeking and recklessness (Zuckerman, 1994). So, assuming that human infection may sometimes be attributable to careless hygiene, one would expect a form of selection (at the time of infection) such that *T. gondii*-infected women had high E levels. In contrast, experimental efforts to infect female mice are nearly always successful: so infection does not depend on prior murine E levels. This being so, if there *were* high E levels in experimentally infected female mice, this must be a *consequence* of the infection. At present, I suggest that, immediately following *T. gondii* infection in mice and women, the hosts' E levels are high. Thereafter, I suggest that these E levels decline (with the duration of infection) more rapidly than those of uninfected controls. It is hoped that these problems may soon be resolved by research.

Carriers of Hepatitis B Virus (HBV)

During their work on HBV, Blumberg and his colleagues repeatedly found that (as contrasted with controls):

1. HBV carriers (of both sexes) produce statistically significant excesses of sons, and
2. Immune people produce an excess of daughters.

This work was summarized in this journal by Chahnazarian *et al.* (1988) and the result confirmed by Oster (2005). Further confirmatory data were reported elsewhere (Mazzur & Watson, 1974; Cazal *et al.*, 1976; Camargo *et al.*, 2002). The causes of this sex ratio variation have not been established, and it was recently characterized by Blumberg as a potentially important curiosity (Blumberg, 2006). There is strong evidence that healthy HBV carriers have higher T levels than healthy uninfected controls (Yu & Chen, 1993; Yuan *et al.*, 1995) (p=0.045 and p=0.0006, respectively, both two-tailed). So, in conformity with my hypothesis, I proposed that the high reported offspring sex ratio of HBV carriers is due to their high T levels and that the low offspring sex ratio of HBV-immune subjects is due to their low T levels (James, 2008).

However, two unpublished working papers make it clear that the above conclusions relating offspring sex ratio to parental HBV status do not apply universally (E. Oster *et al.*, unpublished observations; G. Chen *et al.*, unpublished observations). These new data are summarized here.

First, Lin & Luoh (2008) reported on a cohort of 3 million births in Taiwan and found only a very small effect of parental hepatitis B status on offspring sex ratio. Second, Oster *et al.* (2008) failed to find evidence for paternal or maternal hepatitis B carrier status on offspring sex ratio in a sample of 67,000 people in a prospective study of liver cancer in China. How may these new data be explained?

A hypothesis on the new data

As noted above, Kankova *et al.* (2007a) reported that the offspring sex ratio of *T. gondii*-infected female mice declines with duration of infection. I gave grounds for suggesting that this is caused by a decline in steroid hormones with duration of infection (James, 2010a). Analogously, I suggest that testosterone declines in HBV carriers with duration of infection. I suggest that T levels are above average at the time of infection with HBV, and that T declines more rapidly with duration of infection in infected subjects than in uninfected controls. If this were correct, then it might explain the disparity between these recent data from East Asia and the earlier data reported by Blumberg and colleagues from Greece, Philippines, Papua New Guinea, France and Greenland. This is so because the average age at infection is lower in the former than the latter areas (Leung, 2009; Stefos, 2009). That being so, one might propose that (when age is controlled) the T levels of hepatitis B carriers are lower, on the average, in East Asia than elsewhere, *ex hypothesi* explaining the normal offspring sex ratio of HBV carriers there.

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