Chromium(III) and DNA Damage

In their paper, "Chromium(III)-Induced 8-Hydroxydeoxyguanosine in DNA and Its Reduction by Antioxidants: Comparative Effects of Melatonin, Ascorbate, and Vitamin E," Qi et al. (*1*) reported on a cell-free system and confirmed results from other laboratories that Cr(III) may react with peroxide to form reactive intermediates causing oxidative DNA damage. However, their conclusions on reactions in living systems are entirely speculative. Compounds of trivalent chromium are very weakly, if at all, carcinogenic (*2*–*6*). The authors misled readers when they cited Tsou et al. (*7*) and Lloyd et al. (*8*) as evidence for "the carcinogenic mechanisms of Cr(III)." The mechanism that Qi et al. (*1*) demonstrated by treating isolated DNA with Cr(III) plus 0.5 mM hydrogen peroxide does not apply to cells with a peroxide concentration of 10^{-9}–10^{-8} M, but it does apply to cells that are subject to inflammation or other stress conditions in which the peroxide levels are increased. Nevertheless, the results of Qi et al. (*1*) should be taken as a warning that chromium(III) may be more harmful to living cells than thought previously, if it acts in combination with agents that cause the generation of reactive oxygen species. However, I question the final recommendation of the authors that melatonin should be applied against Cr-induced genotoxicity for two reasons: *a*) the supreme goal should be to avoid exposure to toxic chromium exposure, and *b*) reducing agents combined with Cr(VI) may create similar toxic intermediate oxidation states of Cr as does the oxidation of Cr(III) (*9*).

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Sex Ratios at Birth as Monitors of Endocrine Disruption

Safe (*1*) noted that low sex ratios (proportions male at birth) follow exposure to dioxins, the nematocide dibromochloropropane (DBCP), and cocktails of unidentified agricultural chemicals. However, he further noted that Vartiainen et al. (*2*) failed to find any meaningful correlation between secular movements of sex ratios in Finland and the use of agricultural or environmental estrogens over the past half-century. Safe also quoted my words that "population sex ratios at birth are not useful monitors of reproductive hazard" (*3*).

Taken out of context, these words might be interpreted to misrepresent me. The operative word in my sentence is "population." My caution was dictated by the suspicion that adverse environmental, industrial, chemical, occupational, and medical exposures may (at least sometimes) be associated with opposite effects on offspring sex ratios of exposed men and women. For instance, multiple sclerosis is reportedly associated with increased offspring sex ratios in female patients and decreased offspring sex ratios in male patients (*4*). Similarly, it has recently become clear that dioxins are associated with a highly significant excess of daughters to exposed men mated to unexposed women, and a (nonsignificant) excess of sons to exposed women mated to unexposed men (*5*). This being so, a chemical spillage into the atmosphere or a water source, or the pollution of food items by steroid hormones (which would all be expected to affect roughly equal numbers of parents of both sexes) might fail to reveal themselves in the population offspring sex ratio.

However, we cannot reasonably question the use of offspring sex ratios as monitors of endocrine disruptors in selected samples of exposed fathers. It is not simply that men exposed to DBCP, dioxins, and borates have been reported subsequently to sire significant excesses of daughters: all three of these effects have been replicated (either by the original authors or others) (*5*–*7*). Moreover, all three of these agents are known to cause low testosterone/gonadotropin ratios in men—a hormone profile hypothesized to be associated with daughters (*8*). It is also a profile shown by men suffering from a wide range of nonendocrine diseases (*9*). Such a hormone profile may be suspected in men who have been exposed to various forms of other occupational hazard, for example, deep-water divers, carbon-setters, drivers, and men occupationally exposed to alcohol, nonionizing radiation (*10*), and metal fumes (*11*). The grounds for such suspicion are that all of these categories of men have been reported to sire significant excesses of daughters. Thus, some forms of industrial and occupational exposure, as well as obvious chemical contact and medical pathology, apparently "disrupt" men's endocrine systems. In summary, many adverse medical, occupational, and environmental paternal exposures are known, or strongly suspected, to be associated with endocrine modification and significantly low subsequent offspring sex ratios.

Less well known are the effects of endocrine disruptors on the offspring sex ratios of exposed women. If, in general, they are different (opposite) from the effects on exposed men, then it is true that "population sex ratios at birth are not useful monitors of reproductive hazard." But offspring sex ratios of parents, specified by sex and selected for having been exposed to potentially hazardous chemicals, will continue to be highly informative. In particular, they may reflect long-term, low-level exposures and exposures in the distant past. And, unlike hormone assays and sperm examinations, inquiries about offspring sex ratios have the advantage of being noninvasive.

It might be worth trying to indicate the possible use of sex ratios in the context of the general concern about the widespread distribution of chemicals (some of which are known to have endocrine consequences) and the established rising incidence of some malformations and diseases. As an example, let us consider testicular cancer. As Safe (*1*) documented, rates of this disease have been increasing in many countries over the past few decades. Moreover, there is evidence for a cohort effect and, thus, that *in utero* exposure of some sort may be responsible. Direct endocrine studies show that patients have a low testosterone/gonadotropin ratio (*12*). In addition, men who suffer this disease sire a significantly high proportion of daughters (*13,14*), both before and after disease onset. *Ex hypothesi* these men have a low testosterone/gonadotropin ratio before, as well as after, disease onset. The low sex ratios after disease onset may be a consequence of the disease or its treatment, but the low sex

ratios before the disease suggest that this hormone profile is a potential cause of the disease. Thus, the sex ratio data supplement the direct endocrine data by suggesting that the patient's hormone profile precedes diagnosis. Finally, the evidence for the involvement of intrauterine exposure suggests that this type of exposure may be responsible for the suspected postnatal pathogenic hormone profile of patients. This, in turn, is supported by the recent evidence that anti-androgen–treated pregnant female rhesus monkeys bear sons with genital malformations and altered hormone profiles as juveniles (*15*).

I hope this example may indicate how offspring sex ratios may take their place in the armory of the epidemiologist searching for the causes of this disease.

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Corrections and Clarifications

In "Biomass Combustion and Acute Respiratory Infections" [In This Issue. *EHP* 109:A198 (2001)], it was incorrectly stated that acute respiratory infections "decline for exposures > 2,000 μg/m^3." The correct sentence is as follows:

> In a study in rural Kenya, Ezzati and Kammen (p. 481) found that acute respiratory infections increase in proportion to biomass combustion with particulates < 10 μm diameter but increase at a lower rate for exposures > 2,000 μg/m^3.

The May 2001 Forum article "Boston Pee Party" [*EHP* 109:A204] erroneously states, "While nearly all caffeine is transformed to a variety of metabolites, as much as 20% passes intact through the body and sewage filtration systems, and may reach coastal waters." The statement should have read, "*Although* nearly all caffeine is transformed to a variety of metabolites, as much as 20% *of what is not transformed may pass* intact through the body and sewage filtration systems, and may reach coastal waters."

EHP regrets the errors.

Sex Ratios: Safe's Response

I appreciate James' comments on the use of sex ratios and his clarification regarding their possible use for monitoring exposure to reproductive hazards. It is clear that high-dose exposures to reproductive toxins such as TCDD result in an excess of daughters, and sex ratio changes are important markers of exposure. The area of background exposures to endocrine disruptors and human health is intriguing and emotive, and direct linkages between exposures to environmental factors (diet plus contaminants) with increased incidence of an endocrine-related disease are difficult to determine. James' comments point out a number of examples where sex ratios may be used to investigate potential etiologic agents for some diseases, and this could be useful for design of future studies.

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