LETTER TO THE EDITOR

RE: “ASSOCIATION OF TRANSPOSITION OF THE GREAT ARTERIES IN INFANTS WITH MATERNAL EXPOSURES TO HERBICIDES AND RODENTICIDES”

Loffredo et al. (1) reported that transposition of the great arteries in infants is associated with maternal exposure to herbicides and rodenticides. I should like to suggest a potential explanation and a line of research to test it.

I have adduced very substantial quantities of data to support the hypothesis that the sex of mammalian (including human) infants is associated with the hormone levels of (both) parents around the time of conception (2). Ex hypothesi, sons are associated with high parental levels of testosterone and estrogen, and daughters are associated with high levels of gonadotropins and progesterone. It seems probable that some congenital malformations (including cardiac malformations) are caused by unusual maternal hormone profiles—perhaps those predisposing to one sex or the other. If this were so, then ex hypothesi malformed probands and their unaffected biologic relatives should have a sex bias in the same direction. Such an argument has been used to propose that maternal hormone levels are a cause of polydactyly (3) and oral clefts (4). Transposition is more frequent in males, and two authors have reported otherwise unexplained excesses of males among the biologic relatives (siblings and parental siblings) of probands with transposition (5, 6). For these reasons, I proposed that maternal hormone imbalance is a cause of transposition (7).

The question arises whether herbicides and rodenticides modify women’s hormone profiles. The cases of dioxin and the nematocide dibromochloropropane are instructive. These compounds are associated with falls in exposed men’s testosterone/gonadotropin ratio (8, 9) and (in accordance with my hypothesis) with falls in the offspring sex ratios (proportions male) of exposed men (10, 11). As far as I know, no data are available on the endocrine effects of the exposure of women to such materials. However, if the data of Mocarelli et al. (10) are any guide, the endocrine effects of dioxin exposure may be presumed to be different in men and women.

Accordingly, I suggest that research should be initiated into the endocrine effects of rodenticides and herbicides on women. The endocrine effects of dioxin on men are long-lasting (10). It is possible that this is so for women as well, so consideration should be given to endocrine examination of those exposed at Seveso in 1976 (and of samples taken from them since that date). Such research has wide-ranging potential. It should throw light on not only the etiology of some malformations but also the largely unanswered question of why most congenital malformations are sex-biased (12).

REFERENCES
2. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. J Theor Biol 1996;180:271–86.

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Editor’s note: In accordance with Journal policy, Drs. Loffredo et al. were asked whether they wished to reply to the letter by Dr. James, but there was no response.