

First, the decision to publish. There was no question in my mind that, subject to external peer review and editorial debate, we should publish this work. The description of what seems to be a new syndrome and its relation to possible environmental triggers was original and would certainly interest our readers. Peer review confirmed that the paper merited publication, with suitable revisions and editing, as an early report—there were no scientific grounds to do otherwise. One could, and our correspondents do, question our editorial judgment. But consider the alternative: rejection because these data might, on balance, do more harm (stop parents seeking MMR vaccination for their children) than good (describe a new syndrome and raise an empirically reasonable hypothesis that deserves testing). Recent history, the tale of new variant Creutzfeldt-Jacob disease, for example, tells us that full disclosure of new data is preferable to well-meaning censorship.

Second, how to publish. As with any provocative report, we always consider the value of running a commissioned commentary in the same issue. In this instance, it was a necessity. Most observers seem to agree that Robert Chen and Frank DeStefano<sup>3</sup> wrote an important and helpful critique of Wakefield and colleagues' work.

Third, how to report these data to the media. We chose not to include this study in our weekly press release. We let the paper and commentary speak for themselves. However, we did assist those who organised a press briefing at the Royal Free Hospital on Thursday, Feb 26, by providing copies of the journal (with the commentary that Wakefield et al did not have) to journalists. Reported adverse comments about the safety of MMR vaccination were made at this press conference. By contrast, the views expressed in the paper are unambiguously clear: "we did not prove an association between measles, mumps, and rubella vaccine and the syndrome described".<sup>2</sup>

Finally, what has been the outcome? In particular, has harm been done? There are three endpoints. (1) The press reaction. In every UK report that I have read, journalists urged readers to interpret the study cautiously. *The Times* included a panel explaining the benefits of measles vaccination; *The Independent* led its front page story by reporting the government's advice to parents "to continue to take their children for immunisation"; and *The Guardian* summed up the genuine dilemma in its headline, "damned if they publish, damned if they didn't".

(2) The number of children harmed by not receiving measles vaccine. We have no idea what this figure is, but it should be easy to discover with time. This question needs to be asked because its answer will help us all to do better in our reporting next time. One anxiety is why it took the Department of Health 2 weeks to send out a reassurance cascade message to general practitioners. And (3), are Wakefield and colleagues' observations reproducible? Again, we do not know. But rather than dismiss what they have reported, other investigators must urgently seek to confirm or refute their findings.

Richard Horton

- 1 Horton R. ICRF: From mayhem to meltdown. *Lancet* 1997; **350**: 1043-44.
- 2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal lymphoid-nodular hyperplasia, non-specific colitis, and pervasive-development disorder in children. *Lancet* 1998; **351**: 637-41.
- 3 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.

## Twinning, cancer, and genetics

Sir—A J Swerdlow and colleagues (Dec 13, p 1723)<sup>1</sup> conclude that breast and testicular cancer have a prenatal aetiology compatible with raised maternal unbound free oestrogen concentration in twin pregnancies. This conclusion is based on the recorded higher risk of breast and testicular cancer for dizygotic twins than in monozygotic twins.

Swerdlow and colleagues do not take into account that monozygotic and dizygotic twinning per se is a familial trait inherited both paternally and maternally.<sup>2</sup> Moreover, the genetic components for monozygotic and dizygotic twinning seems to be independent.<sup>3</sup>

With these facts in mind their findings of a higher risk of breast and testicular cancer in dizygotic than in monozygotic twins could be interpreted as resulting from the co-segregation of the genetic component for twinning (monozygotic and dizygotic) and that for breast or testicular cancer. Whether raised unbound free maternal oestrogen concentration advocated by Swerdlow and co-workers is linked to these genetic components remains to be established, but it is likely to be the result of a gemellar pregnancy and not the cause.

Rafaël Levy

Oncohaematology Unit, Laennec Hospital, 75007 Paris, France

- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast and testicular cancer in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723-28.
- 2 Paris P, Gatti M, Prinzi G, Caperna G. Familial incidence of twinning. *Nature* 1983; **304**: 626-28.
- 3 Lichtenstein P, Olanson PO, Kallen AJ. Twin births to mothers who are twins: a registry based study. *BMJ* 1996; **312**: 879-81.

Sir—A J Swerdlow and colleagues<sup>1</sup> report a non-significant increase in risk of breast cancer in female dizygotic compared with female monozygotic twins and a significantly higher risk of testicular cancer in male dizygotic than in male monozygotic twins. They argue that these findings are compatible with prenatal exposure to raised maternal oestrogen concentrations. For this hypothesis they rely heavily on reports of gonadotropin and sex-hormone concentrations in mothers of dizygotic and monozygotic twins.<sup>2,3</sup> However, none of the data in these reports are in accord with the aetiological mechanism suggested by Swerdlow and co-workers. In fact one report deals with raised secretion of gonadotropins and sex-hormones in non-pregnant mothers of dizygotic twins.<sup>2</sup> The only report of differences in hormone secretion in pregnant mothers of dizygotic versus monozygotic twins describes lower concentrations of human placental lactogen in mothers of monozygotic twins and no differences in oestrogens.<sup>3</sup>

We therefore suggest an alternative mechanism for the observation that testicular cancer risk is higher in male dizygotic than in male monozygotic twins. Dizygotic twins inherit a tendency of hyperstimulation by endogenously raised concentrations of follicle stimulating hormone (FSH) that causes multiple follicle growth, high oestrogens, and multiple ovulations in females.<sup>2</sup> In males, the increase in carcinoma of the testis could result from over-exposure to FSH. No data are available on the secretion of gonadotropins in familial male dizygotic twins. However, hypersecretion of FSH in these males is likely, because the hereditary trait of having dizygotic twins (and high FSH) is inherited in an autosomal manner. The observation of an increase in testicular carcinoma in dizygotic twins would circumstantially support this male type of natural FSH hypersecretion since testicular carcinoma (and ovarian neoplasia) are associated with increased FSH action.<sup>4</sup>

In view of the reported substantial increase in risk of testicular cancer it seems time for endocrine evaluation of familial dizygotic male twins. In

addition, the high concentrations of FSH in familial dizygotic twinning might also reveal a risk of ovarian carcinoma, which would justify epidemiological studies in this area. We cannot say to what extent our hypothesis of familial increased FSH and testicular cancer also applies to an increase in breast-cancer risk. Swerdlow et al report no differences in occurrence of breast cancer between dizygotic and monozygotic twins. Their finding is consistent with results from a large Swedish study that showed no differences in occurrence of breast cancer between mothers of dizygotic and monozygotic twins.<sup>5</sup>

\*C B Lambalk, D I Boomsma

\*Division of Reproductive Endocrinology, Research Institute, for Endocrinology, Reproduction and Metabolism, Department of Obstetrics/Gynaecology, Academic Hospital, Free University, PO Box 7057, 1007 MB Amsterdam, Netherlands; and Department of Psychonomics, Faculty of Psychology, Free University, Amsterdam

- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast cancer and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723–28.
- 2 Martin NG, El Beaini JL, Olsen ME, Bhatnagar AS, Macourt D. Gonadotropin levels in mothers who have had two sets of DZ twins. *Acta Genet Med Gemellol* 1984; **33**: 131–39.
- 3 Kappel B, Hansen K, Moller J, Faaborg-Andersen J. Human placental lactogen and dU-estrogen levels in normal twin pregnancies. *Acta Genet Med Gemellol* 1981; **34**: 59–65.
- 4 Sicinsky P, Donaher JL, Geng Y, et al. Cyclin D2 is an FSH responsive gene involved in gonadal cell proliferation and oncogenesis. *Nature* 1996; **384**: 470–74.
- 5 Murphy MFG, Broeders MJM, Carpenter LM, Gunnarskog J, Leon DA. Breast cancer risk in mothers of twins. *Br J Cancer* 1997; **75**: 1066–68.

#### Authors' reply

Sir—We agree with Rafaël Levy that if there were co-segregation of genes for propensity to dizygotic twinning and genes for breast cancer, this could explain the raised risk of breast cancer in women born as such twins, and hence would give an alternative potential explanation of our findings. We know of no evidence, however, that there is such co-segregation; indeed mothers of twins, who ought to have twinning genes more often than the twins themselves, have been found to have a decreased risk of breast cancer,<sup>1</sup> which would be evidence against the co-segregation proposed.

C B Lambalk and D I Boomsma raise an interesting alternative explanation for the excess of testicular cancer in dizygotic twins, which we

agree is worth pursuing. On the basis of published work, however, it seems speculative rather than well founded that high FSH concentrations would be inherited along with a tendency to dizygotic twinning; we have not seen the paper by Lambalk and colleagues, currently in press, which may hold substantial evidence for such an association in mothers. It would still, however, be a hypothesis that needs testing whether FSH concentrations are increased in boys born as dizygotic twins.

We agree that the existing evidence for raised gonadotropin and sex hormone concentrations in mothers of dizygotic twins is neither consistent nor conclusive, but taking together the three studies cited in the discussion section of our report plus the other evidence cited within these publications, we think that our comment in that section that “some evidence suggests” raised concentrations remains true. Further evidence on these concentrations in mothers of twins is needed to clarify this issue.

With respect to breast cancer, Lambalk and Boomsma take the Swedish finding regarding breast cancer in mothers of twins<sup>1</sup> as the most appropriate comparison with our results on the twins themselves, but the most comparable data, as noted in our paper, are in another Swedish paper in breast cancer in women who were themselves twins.<sup>2</sup> This study found a significantly raised risk of breast cancer under age 30 for women born as dizygotic twins, a result similar to ours.

\*A J Swerdlow, B L De Stavola, M A Swanwick, N E S Maconochie

Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

- 1 Murphy MFG, Broeders MJM, Carpenter LM, Gunnarskog J, Leon DA. Breast cancer risk in mothers of twins. *Br J Cancer* 1997; **75**: 1066–68.
- 2 Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN. Effect of twinning on incidence of cancer of the testis, breast, and other sites (Sweden). *Cancer Causes Control* 1995; **6**: 519–24.

Sir—A J Swerdlow and colleagues' report<sup>1</sup> of increased testicular cancer risk among dizygotic (DZ) twins, as compared with monozygotic (MZ) twins, led us to examine data from the NAS-NRC Twin Registry, a US registry containing 15 924 male/male twin pairs born in 1917–27, both members of which served in the military.<sup>2</sup> We reported<sup>3</sup> a greater death rate due to testicular cancer among dizygotic than in monozygotic twins

and a greater rate of testicular cancer in dizygotic than in monozygotic twins who participated in a recent telephone survey.<sup>4</sup> However, neither difference was statistically significant.

We now report additional testicular cancers ascertained through 1985 from military records, including entrance processing records; hospital records from several sources; sick calls; and veterans records, including hospital, disability, and death records that are quite complete probably because of previous veteran death benefits. There were a total of 39 twins with a diagnosis of testicular cancer. The rate for dizygotic twins was 0.18% (27/15 108) and for monozygotic twins 0.08% (10/11 866), with an odds ratio of 2.12 ( $p=0.038$ ). Among twins of undetermined zygosity the rate of testicular cancer was 0.04% (two of 4874).

None of the 39 cases carried a diagnosis of cryptorchidism from military or veteran records, although cryptorchidism was noted for 160 twins in the registry. Six of the 39 cases had testicular cancer on their death certificates<sup>3</sup> and another 16 of the 39 cases survived to be identified by the recent telephone survey as testicular cancer survivors.<sup>4</sup>

In accordance with Swerdlow and colleagues' and other investigators' findings we found statistically higher odds of developing testicular cancer in dizygotic than in monozygotic twins. Although clarification of the mechanism of increased testicular cancer in dizygotic twins awaits further work, the evidence is consistent with the notion that prenatal factors, such as hormones, are associated with the development of cancer in adults. In an analogous line of research, Swerdlow and other investigators, and our group, have also reported rises in early onset breast cancer among dizygotic twins. We should consider the possibility that prenatal hormones, perhaps affected by differences in maternal diet, play a part in the wide international variation in incidence and the migration effects seen for breast cancer.

\*William F Page, M Miles Braun, Neil E Caporaso

Institute of Medicine-National Academy of Sciences, Medical Follow-up Agency, Washington DC 20418, USA; Food and Drug Administration, Rockville, MD; and National Cancer Institute, Bethesda, MD

- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723–28.
- 2 Jablon S, Neel JV, Gershowitz H,