LETTERS TO THE EDITOR

Ovarian cancer family and prophylactic choices

With reference to the case report by Evans *et al* (*J Med Genet* 1992;29:416–8), we would like to point out that in the pedigree presented it is incorrect to describe the 'risk' of ovarian cancer as 50% in first, 25% in second, and 12·5% in third degree relatives of affected persons. These percentages actually refer to the probability of women inheriting a liability to develop cancer rather than risk. The penetrance of the putative familial ovarian and breast cancer gene(s) is unlikely to be 100% and in our published segregation analysis[1] the lifetime penetrance was between 0·74 and 0·79. Thus, only 70 to 80% of gene carriers will be expected to develop the disease. The genetic risk R_j for relatives at age j is given by[2]:

$$R_j = \frac{R_\infty - R_x}{1 - R_x}$$

where $R_x = [P(G' | \text{proband age, r})]P_j$
and $R_\infty = [P(G' | \text{proband age, r})]P\infty$
and P_j = penetrance at age X
and P_∞ = lifetime penetrance
and r = coefficient of relationship (0·5 for first degree relatives).

It is also worth commenting on the fact that no screening technique for ovarian cancer has at present been proven to reduce mortality, nor has screening for breast cancer in this group of women. The gene(s) responsible for at least a proportion of breast and breast-ovarian cancer families has been mapped to 17q12–23[3,4] and the time is approaching when predictive testing for gene carriers will be possible in some families. This group of high risk women offers an opportunity to evaluate new screening techniques because of the high expected incidence of disease, but the results of any intervention can only be evaluated on the basis of actual risk of developing cancer.

D M ECCLES
R S HOULSTON
Department of Child Health, University of Southampton, Level G, Princess Anne Hospital, Southampton SO9 4HA.

1 Houlston RS, Collins A, Slack J, *et al.* Genetic epidemiology of ovarian cancer: segregation analysis. *Ann Hum Genet* 1991;55:291–9.
2 Morton NE. *Outline of genetic epidemiology.* Chapter 10. Basel: Karger, 1982:201.
3 Hall J, Lee M, Newman B, *et al.* Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990;250:1684–9.
4 Narod SA, Feunteun J, Lynch HT, *et al.* Familial breast–ovarian cancer locus on chromosome 17q12–q23. *Lancet* 1991;338:82–3.

This letter was shown to Dr Evans who replies as follows.

In answer to the letter from Drs Eccles and Houlston, we quite agree that the risk of developing ovarian cancer may not reach full penetrance in families such as this. We now counsel family members at 50% risk of inheriting the gene as being at 40% risk of developing the disease. The situation may not be as simple as suggested in their letter as penetrance may depend on the gene in which the mutation lies as well as the effect of a particular mutation. Therefore, although the average penetrance may be 0·74 to 0·79 it may be 0·60 in some families and 0·95 in others. The segregation analysis referred to[1] can also not claim to be specific for the putative breast/ovarian locus on 17q, as linkage analysis was not carried out on the pedigrees and it is still not clear whether or not two closely located tumour suppressor genes could exist here.

We also agree that as yet screening has not been shown to reduce mortality. However, when a disease like ovarian cancer has a 25% mortality at five years any attempt at early diagnosis, particularly with the sensitivity of vaginal ultrasound with doppler, is likely to reduce mortality. I am sure that the authors of the letter would not withhold screening in a high risk group simply because it has not been proven to reduce mortality. We have also shown that our family is linked to the putative locus on 17q[2] and I would agree that knowledge of each subject's status within these families will more quickly provide us with answers to the efficacy of various screening options.

D G R EVANS
Regional Genetic Service, St Mary's Hospital, Whitworth Park, Manchester M13 0JH.

1 Houlston RS, Collins A, Slack J, *et al.* Genetic epidemiology of ovarian cancer: segregation analysis. *Ann Hum Genet* 1991;55:291–9.
2 Smith SA, Easton DF, Evans DGR, Ponder BAJ. Allele losses in the region 17q12–21 in familial ovarian cancer non-randomly involve the wild type chromosome. *Nature Genet* (submitted).

The importance of differentiating Simpson-Golabi-Behmel and Beckwith-Wiedemann syndromes

We would like to draw attention to the fact that there are superficial similarities in the appearance of pedigrees segregating in an X linked recessive pattern and those exhibiting an autosomal dominant pattern with imprinting of specific genes. Illustration of this fact is provided by at least one family misdiagnosed as having Beckwith-Wiedemann syndrome (BWS) whom we have confirmed, on clinical evidence (postaxial polydactyly, midline groove in the lower lip, and more severely affected males), has the X linked condition Simpson-Golabi-Behmel syndrome (SGBS)[1] (case 4) (N Niikawa, personal communication). Review of published reports of the BWS, focusing on autosomal dominant pedigrees and discordant monozygotic female twins, does not show any further definite cases of SGBS, although we are suspicious of the family reported by Viljoen and Ramesar[2] where the phenotype becomes less pronounced with age and there is increased mortality in affected males. In addition, we have recently reviewed cases of BWS in our own genetic clinics and identified one misdiagnosed male child with SGBS. Shared clinical features of BWS and SGBS include macrosomia, macroglossia, cleft palate, visceromegaly, ear lobe creases, herniae, neonatal hypoglycaemia, and a risk of embryonal tumours. The phenotypic boundaries of these two conditions have yet to be defined although linkage data clearly suggest that these are two distinct conditions.[3,4] The convergence of the clinical spectra may be a result of previous diagnostic errors resulting in an 'incorrectly expanded phenotype'.

The report by Niikawa *et al*[1] has been cited to support the theory that maternal transmission of BWS is more common than paternal transmission.[2,5] Moutou *et al*,[5] in this journal, recently presented evidence suggesting that this may be because of both reduced male fertility and an imprinting effect in BWS. Based on segregation analysis of 40 sibships, they calculated a three-fold higher risk (penetrance) when the transmitting parent is the mother compared with the father. Recalculation excluding the SGBS family (case 4 of Niikawa *et al*[1]) has little effect on the degree of significance; however, the error illustrates the importance of accurate clinical diagnosis. We question the conclusion of Viljoen and Ramesar[2] that paternal imprinting is the explanation for excess of transmission of BWS by females. The bulk of evidence to date favours a mechanism resulting in overexpression, or failed regulation, of genes which we believe are usually expressed only if the origin is paternal.[6] Lastly, we believe it is important to recognise that contamination by an X linked condition, with differing X inactivation in female twin pairs, would exaggerate the currently unexplained excess of monozygotic female twins who appear to have BWS but are discordant for the features of this syndrome.[7]

In conclusion we would like to emphasise the similarities in the phenotypes and pedigree structures between BW and SGB syndromes and therefore the necessity of careful evaluation of the diagnosis when using these cases for molecular analysis and the formulation of 'genetic models'. It will be interesting to see if the two families discussed above show linkage to the SGBS locus in proximal Xq.[3]

R HUGHES-BENZIE
J ALLANSON
A HUNTER
T COLE*
Department of Clinical Genetics, Childrens Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, Canada K1H 8LI.
** Clinical Genetics Unit, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG.*

1 Niikawa N, Ishikiriyama S, Takahashi S, *et al.* The Wiedemann-Beckwith syndrome. Pedigree studies on five families with evidence for autosomal dominant inheritance with variable expressivity. *Am J Med Genet* 1986;24:41–55.
2 Viljoen D, Ramesar R. Evidence for paternal imprinting in familial Beckwith-Wiedemann syndrome. *J Med Genet* 1992;29:221–5.
3 Hughes-Benzie RM, Hunter AGW, Allanson JE, *et al.* Simpson Golabi Behmel syndrome associated with renal dysplasia and embryonal tumor: localisation of the gene to Xqcen-q21. *Am J Med Genet* 1992;43:428–35.
4 Koufos A, Grundy P, Morgan K, *et al.* Familial Beckwith-Wiedemann syndrome and a second Wilms tumor locus both map to 11p15.5. *Am J Hum Genet* 1989;44:711–9.
5 Moutou C, Junien C, Henry I, *et al.* Beckwith-Wiedemann syndrome: a demonstration of the mechanisms responsible for the excess of transmitting females. *J Med Genet* 1992; 29:217–20.
6 Mannens M. *The molecular genetics of Wilms' tumour and associated congenital diseases.* Thesis, Amsterdam, 1991.
7 Clayton-Smith J, Read AP, Donnai D. Monozygotic twinning and Wiedemann-Beckwith syndrome. *Am J Med Genet* 1992;42:633–7.