

tracheo-oesophageal dysraphism, at least in populations with a low frequency of NTD.

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This letter was shown to Dr David, who replies as follows.

Ilyina and Lurie's letter is most welcome, though I would like to get my hands on whoever first used the awful term 'tracheo-oesophageal dysraphism'. Oesophageal atresia is a most neglected defect, and it is sad that current interest mainly centres not on the defect itself, but either with the probably spurious increase of neural tube defects in sibs, or with the VATER or VACTERL association, which embodies the statistical and teratological misconception of a non-random association of defects.

Ilyina and Lurie's hypothesis that there may be a relationship between the risk of neural tube defect for sibs of patients with oesophageal atresia and the population frequency of neural tube defects may be right. It is perhaps akin to the suggestion that the recurrence risk of neural tube defects is to some extent a function of the background population risk. However, the general notion of an increased frequency of neural tube defects in the sibs of children with other malformations¹ is most likely to be attributable to sampling errors or bias.

The cases of Fraser and Nussbaum² were a highly selected group and in no way representative of the general population of patients with oesophageal atresia, and the same applies to the data of Warren *et al.*³ It is not clear how the cases of Ilyina and Lurie were ascertained, but it is likely that they were selected in some way. Our own study⁴ was happily free from this defect, only to fall victim to the entirely fair criticism⁵ that we did not seek to identify all sibs but just used available medical records. Probably the only suitable data come from Sweden⁵ and Canada,⁶ and from these studies it does seem that there is no increase in neural tube defects in the sibs of patients with oesophageal atresia.

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Routine diagnostic detection of the fragile X

SIR,

I enjoyed reading the recent report by Dr McDermott and his colleagues (*J Med Genet* 1983;20:169-78) on the fragile X chromosome. I would, however, like to take issue with their assertion that busy diagnostic cytogenetics laboratories cannot routinely screen unselected cases for the fragile X chromosome. Furthermore, their request that referring practitioners alert the laboratory to the possibility of this finding on clinical grounds is one which simply cannot work. While some males have the full 'fragile X syndrome', so well described by McDermott *et al.*, and a family history suggesting the presence of the fragile X many, particularly children, have neither. About one-third of females

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with the fragile X are borderline retarded or worse but these girls have no other distinguishing features. In consequence, any retarded person, male or female, must be considered possibly to have the fragile X until this diagnosis has been reasonably excluded. This means that investigation of the aetiology of mental retardation in any subject must include chromosome studies with exclusion of the fragile X. This will greatly increase the number of referrals for cytogenetic studies, since current (hopefully past) practice is usually to refer only those retarded persons with dysmorphic features.

From the laboratory's view very little extra work per case is involved. It requires no more effort to use a culture medium suitable for fragile X expression than an unsuitable one. There are now many folic acid free media available or, failing the use of one of these, TC199 is adequate. A supplement of 5% fetal bovine serum will ensure good cell growth and not prejudice fragile X detection. The only extra worthwhile precaution is to buffer the medium with Hepes (20 mmol/l) so that the pH at the time of harvest is greater than 7.3. Chromosome preparations from such cultures are of good quality and can be used for all cytogenetic techniques. Lymphocytes for all studies can be cultured in this medium; indeed it need be the only medium used for diagnostic lymphocyte culture. Care needs to be taken to ensure that cultures remain aseptic, since light microbial contamination which does not interfere greatly with conventional cytogenetics precludes fragile X detection. Also 2-day cultures should be avoided since fragile X frequencies in these are very low.¹

Once appropriate preparations are available a total of about 50 metaphases should be examined from every mentally or developmentally retarded person. This usually means scoring 30 to 40 additional metaphases after the usual diagnostic evaluation. These do not need to be counted or analysed, only scored for the presence or absence of a C group chromosome with the appearance of the fragile X. If such a chromosome is seen, it is a simple matter to destain the slide and G or Q band the metaphase(s) involved to determine whether the fragile X is truly present. This extra scoring of cells is thus the only extra effort required and on average preparations should not involve more than an extra 10 to 15 minutes of microscopy per case studied. This would not, of course, detect the interesting subjects reported by McDermott *et al*, who would appear to have the fragile X only in fibroblast cultures.

In my experience this routine is simple to adopt even in a very busy diagnostic laboratory and will

yield more clinically significant information than routine G banding or extended chromosome studies of persons with otherwise normal karyotypes. After all, the fragile X is the commonest genetic cause of mental retardation after Down's syndrome² and it must be the responsibility of every diagnostic cytogenetics laboratory to ensure that it does not go undetected.

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Spectrum of anomalies in Fanconi anaemia

SIR,

In a recent communication, Glanz and Fraser reported a spectrum of anomalies in Fanconi anaemia in 94 probands and 44 affected sibs.¹ Glanz and Fraser stated that 73% of the cases had hyperpigmentation, but they did not mention café-au-lait spots. We wondered whether they had included café-au-lait spots as hyperpigmentation.

We reported a total of 18 patients with an age range of 5 to 13 years diagnosed as having Fanconi aplastic anaemia.² Our study indicated that café-au-lait spots are much more common than hyperpigmentation, as only six of our patients had hyperpigmentation, 14 had two or more café-au-lait spots, and three had vitiligo. Both hyperpigmentation and café-au-lait spots were observed in 16 cases. Consanguinity of the parents was observed in nine patients and there was more than one case of aplastic anaemia in three families. One of our patients developed acute myelomonoblastic leukaemia and died in hospital, and the sister of another boy with Fanconi aplastic anaemia in our series also developed acute leukaemia in another hospital. This point is noteworthy and has been reported previously.^{3,4} Congenital malformations without anaemia were also noted in three families. In one family a brother had mental and growth retardation and, in another, two babies who had thumb anomalies died during the third and fourth days of life. The probands had growth retardation and hypoplastic thumb and toe abnormalities, respectively. The third family had two sibs with congenital malformations: one sib had a cardiac anomaly and the other had mental deficiency and deafness. However,