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 Hapes (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 stain 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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**References**


**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,
the proband did not have any cardiac anomaly, mental deficiency, or deafness.

Another point we want to make is that although our common abnormalities were similar to the cases of Glanz and Fraser, especially malformations of the toes, others, such as spinia bifida, vitiligo, hypoplastic spleen, and scoliosis, were not noted.

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**References**


This letter was shown to Drs Glanz and Fraser who reply as follows:

We thank Drs Akar and Gözdasoğlu for drawing attention to their paper and apologise for its omission from our review. We included café-au-lait spots as hyperpigmentation.

**Philtrum length and intercommissural distance in newborn infants**

**Sir,**

In their very useful paper, Sivan et al1 have provided normal values for philtrum length and intercommissural distance in newborn infants. I am glad to know that their standards correspond well with those I previously found in healthy Hungarian neonates.2 However, since gestational age cannot always be determined and intrauterine growth retardation is characteristic of many congenital syndromes and malformations, the consideration of gestational age alone may be misleading in a significant proportion of pathological infants.

Therefore, I would recommend that gestational age and birth weight should be taken into account. This has been our policy in determining standards for several measurable minor malformations and variants so far.

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**Genetic heterogeneity in Duchenne muscular dystrophy**

**Sir,**

From the results of linkage studies using two restriction fragment length polymorphisms, Dr O’Brien and colleagues3 question our earlier suggestion that Duchenne muscular dystrophy (DMD) may exhibit genetic heterogeneity.2 We would disagree with the interpretation of their results for several reasons.

Firstly, our suggestion was that a subgroup of DMD may possibly exist in which affected boys have severe (which we stressed) mental handicap usually requiring institutional care. Such boys in fact represent only a very small proportion of all affected boys. Over the years we have collected information on 302 affected boys (of whom 182 have been personally examined), but fewer than 20 have been classified as severely mentally handicapped. In Dr O’Brien’s study it is not clear in how many kindreds the affected boys were severely mentally handicapped, and in several kindreds data from mentally handicapped boys and boys with normal IQ were combined, which would not seem justified.

Secondly, as was discussed in our paper, there is already some convincing biochemical evidence of heterogeneity in DMD, though it is not clear if this is related to the observed clinical differences.

Thirdly, as the authors themselves point out, linkage studies cannot exclude heterogeneity resulting from different mutations at the same or closely linked loci. From what we know already about the fine structure of disease loci, if genetic heterogeneity in DMD does exist it would seem quite reasonable that it could be within a single locus.

For these various reasons we feel that the case against heterogeneity in DMD is therefore still non-proven. The situation is likely to remain unclear until such time as the molecular defect(s) has been characterised.

**Alan E H Emery**  
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**References**


Spectrum of anomalies in Fanconi anaemia.

N Akar and S Gözdasoglu

*J Med Genet* 1984 21: 75-76
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