The cause(s) of neural tube defect

SIR,

Professor Fraser and colleagues¹ cite evidence relating to my hypothesis^{2,3} proposing two separate causes for anencephaly. However, the difficulty they adduce is one I have already treated.⁴ In that note I discussed the possibility that the two hypothesised causes act synergistically. It remains to be seen whether this is a useful suggestion.

Another point they raise is the tendency for sibships to remain 'true' to one or other of the two malformations. There are other grounds for supposing that anencephaly and spina bifida do not have identical causes, or that, if they are identical, they are not applied at the same time in gestation.⁵

W H JAMES

*MRC Mammalian Development Unit,
Wolfson House,
4 Stephenson Way,
London NW1 2HE.*

References

- 1 Fraser FC, Maldoff SR, Lippman-Hand A. Evidence against a female specific class of neural tube defect. *J Med Genet* 1983;**20**:78-9.
- 2 James WH. The sex ratio in spina bifida. *J Med Genet* 1979;**16**:384-8.
- 3 James WH. The sex ratio in anencephaly. *J Med Genet* 1979;**16**:129-33.
- 4 James WH. The sex ratios of anencephalics born to anencephalic-prone women. *Dev Med Child Neurol* 1980;**22**:618-22.
- 5 James WH. Differences between the events preceding spina bifida and anencephaly. *J Med Genet* 1981;**18**:17-21.

Absence of the fragile X in a group of patients with idiopathic mental retardation

SIR,

The apparently high incidence of the fragile X syndrome¹ has led to the recommendation that all males with 'idiopathic' or 'non-specific' mental retardation should be screened for this condition. Such studies can have a significant impact on the load of a cytogenetic laboratory. We studied 17 of the 20 male patients from our group of 36 children with 'idiopathic' retardation who also lacked any major malformations, as defined in our study of 406 institutionalised children in Manitoba.² Heparinised blood samples were cultured in medium TC 199 enriched with 5% fetal calf serum according to the protocol of Sutherland.³ One hundred solid stained metaphases were examined for long arm breaks in

the C group chromosomes. These were then photographed and the slides destained and Giemsa banded for positive identification of the C group chromosomes.

None of the 17 patients showed a fragile X. We do not believe known methodological variables caused these negative results,⁴ since several positive families were processed in the laboratory at the time.

As demand increases on cytogenetic laboratories, it is essential to look for better ways to select patients for study and we have therefore looked more closely at the clinical features of our group. First, by our definition,² they all lacked a positive family history and thus, if fragile X positive, would have to represent a relatively recent mutational event. While the full spectrum of the fragile X syndrome is yet to be established, patients with a proven fragile X chromosome tend to have normal body proportions, including occipitofrontal circumference (OFC), and lack associated neurological signs. Many have large jaws, prominent ears, and/or macro-orchidism.⁵ By contrast, seven of our 17 patients had a head circumference less than the 3rd centile and two were less than the 3rd centile in height. Marked abnormalities of muscle tone were the rule and were occasionally accompanied by overt neurological signs such as nystagmus or cortical blindness. Minor anomalies of the face and hands were frequent. None of the seven postpubertal males had macro-orchidism and one was noted to have small testes. Similarly, Renpenning's original family with X linked retardation demonstrated microcephaly and has since been shown to be negative for the fragile X.⁶

Although the syndrome is extremely variable, the majority of patients with the fragile X syndrome are only moderately or mildly retarded and are ambulant and capable of some speech and simple tasks.⁷ Our patients were severely to profoundly retarded, with seven having IQs from 30 to 35 and the remainder from not measurable to 30. An over-representation by severe and profoundly retarded patients has been previously proffered as an explanation for a low incidence of fragile X among retarded patients with macro-orchidism.⁸

In summary, our small group of 17 male patients suggests that the absence of a positive family history and the presence of clinical findings, such as microcephaly, severe to profound retardation, and/or minor facial and digital anomalies unlike those of the fragile X syndrome, make the cytogenetic diagnosis of the syndrome unlikely. Although a degree of spasticity has been reported in the fragile X syndrome,⁹ frank neurological signs are also against the diagnosis. We would encourage other