LETTERS TO THE EDITOR

Psychological aspects of von Recklinghausen neurofibromatosis (NF1)

In the December 1995 issue of your journal, Mouridsen and Sorensen reviewed the psychological aspects of NF1.¹ They provided an excellent insight into many issues, such as the frequency of poor self-image and psychiatric disturbance. However, there have been a number of recent publications,²⁻⁹ which were not included in the review, and which provide a number of areas of consensus concerning the cognitive phenotype of patients with NF1.

(1) Mutations in the NF1 gene are associated with a lowering of IQ in, at least, a subset of patients. The mean full scale IQ score (for a clinic derived population) is in the range of 90-94. Hoffman *et al*² also reported a significant pairwise difference between each child with NF1 and an unaffected sib on full scale IQ, verbal IQ, and Judgement of Line Orientation (a test of visuospatial function).

(2) There does not appear to be an association between the left shift in IQ and any clinical variable (such as clinical severity of disease, macrocephaly, or family history of NF1).^{2,3}

(3) There is a slight increase in the incidence of mental retardation in NF1 (4-8%) compared to the general population.^{3,5}

(4) At least 40% (and probably more) patients with NF1 have learning disabilities. In our study of 40 children (aged 8 to 16 years),³ 65% had impaired performance (that is, more than 2 SD below the mean) on at least one test of academic achievement.

(5) There does not appear to be a specific profile of learning disabilities in patients with NF1. There is no consistent discrepancy between verbal and performance IQ. The Judgment of Line Orientation (a test of visuospatial function) is consistently abnormal in all studies to date and thus, at some level, is a robust indicator of NF1 related neuropsychological deficits. However, language based learning problems (for example, reading and spelling) are more common than non-verbal learning deficits. Poor attentional and organisational skills affect performance in many areas, although increased distractibility is not usually associated with hyperactivity.²⁻⁵

There have also been a number of recent studies concerning the significance of areas of hyperintense T2 signal on MRI (UBO or unidentified bright objects) in relation to cognitive deficits in patients with NF1.^{2,6-9} In our study,⁸ children with areas of increased signal intensity on MRI (UBO+) had significantly lower IQ scores than children without these lesions. However, the association between "UBOs" and learning disabilities remains controversial. Moore⁷ found no statistical difference in overall IQ scores between the UBO+ and UBO- groups. However, when the results were analysed according to the site of increased T2 lesions, there was a significant association between deficits in IQ, memory, motor function, and attention span and T2 signal lesions

in the thalamus and hypothalamus. Hoffman *et al*² and Denckla *et al*⁶ found that the number and volume of T2 signal lesions were highly correlated with pairwise deficits in IQ scores (compared to unaffected sibs). In addition they found an association between impaired visuospatial function (as shown in the Judgment of Line Orientation) and the volume of T2 signal lesions in the basal ganglia.

Although there appears to be some association between T2 signal lesions on MRI and cognitive deficits in children with NF1, the exact nature of this association and its relationship to the number, volume, and location of lesions remains to be elucidated. The available evidence suggests that these T2 signal lesions represent areas of dysplastic gliosis and aberrant myelination in the developing brain.¹⁰ If the relationship between MRI lesions and cognitive deficits in NF1 is validated then this association may provide important insight into the pathogenesis of cognitive deficits in patients with NF1.

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- 1 Mouridsen SE, Sorensen SA. Psychological aspects of von Recklinghausen neurofibromatosis (NF1). *J Med Genet* 1995;32:921-4.
- 2 Hoffman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: the cognitive phenotype. *J Pediatr* 1994;124:S1-8.
- 3 North K, Joy P, Yuille D, Cocks N, Hutchins P. Cognitive function and academic performance in children with neurofibromatosis type 1. *Dev Med Child Neurol* 1995;37:427-36.
- 4 Joy P, Roberts C, North K, De Silva M. Neuropsychological function and MRI abnormalities in neurofibromatosis type 1. *Dev Med Child Neurol* 1995;37:906-14.
- 5 Moore BD, Ater JL, Needle MN, Slopis J, Copeland DR. Neuropsychological profile of children with neurofibromatosis, brain tumor or both. *J Child Neurol* 1994;9:368-77.
- 6 North K, Joy P, Yuille D, Cocks N, *et al*. Learning difficulties in neurofibromatosis type 1: the significance of MRI abnormalities. *Neurology* 1994;44:878-83.
- 7 Moore BD. NF1, cognition and MRI. *Neurology* 1995;45:1029.
- 8 North K. Learning difficulties in neurofibromatosis type 1: the significance of MRI abnormalities. *Neurology* 1995;45:1029-30.
- 9 Denckla MB, Hoffman K, Mazzocco MMM, *et al*. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1. *Am J Med Genet* 1996;67:98-102.
- 10 DiPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. Neurofibromatosis type 1: pathologic substrate of high-signal intensity foci in the brain. *Radiology* 1995;195:721-4.

The male excess in Down's syndrome

Mutton *et al*¹ confirmed earlier reports of a male excess in cases of Down's syndrome (DS). The cause of this excess is not established, but it seems not to be sex selective spontaneous abortion: in their data, these cases numbered 63 males and 51 females.

I should like to suggest a cause of this excess. It is that in cases of DS, the timing of insemination in relation to ovulation is not optimal. It is widely believed (at least among non-geneticists) that the timing of fruitful coitus within the human menstrual cycle is associated with offspring sex ratio, male zygotes being preferentially formed when the fruitful insemination is either early or late. In a meta-analysis on this point, Gray² estimated that fruitful inseminations around ovulation

have a relative risk of only 90% of yielding males as contrasted with early or late inseminations. A similar phenomenon has been reported in other species, such as white tailed deer,³ Barbary macaque,⁴ golden hamster,⁵ and Norway rat.⁶

If the present hypothesis were true, one might expect an excess of DS in cases of rhythm failure. The evidence on this point is equivocal,⁷ but suspicion is raised by the reportedly high maternal age specific rates in children born to Catholic women.^{8,9}

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- 1 Mutton D, Alberman E, Hook EB, for the National Down Syndrome Cytogenetic Register and the Association of Clinical Cytogeneticists. Cytogenetic and epidemiological findings in Down syndrome, England and Wales 1989-1993. *J Med Genet* 1996;33:387-94.
- 2 Gray RH. Natural family planning and sex selection: fact or fiction? *Am J Obstet Gynecol* 1991;165:1982-4.
- 3 Verme LJ, Ozoga JJ. Sex ratio of white-tailed deer and the estrus cycle. *J Wildl Mgmt* 1981;45:710-15.
- 4 Paul A, Kuester J. Sex ratio adjustment in a seasonally breeding primate species: evidence from the Barbary macaque population at Affenberg Salem. *Ethology* 1987;64:117-32.
- 5 Pratt NC, Huck UW, Lisk RD. Offspring sex ratio in hamsters is correlated with vaginal pH at certain times of mating. *Behav Neurol Biol* 1987;48:310-16.
- 6 Hedricks C, McClintock MK. Timing of insemination is correlated with the secondary sex ratio of Norway rats. *Physiol Behav* 1990;48:625-32.
- 7 Castilla EE, Simpson JL, Queenan JT. Down syndrome is not increased in offspring of natural family planning users: case-control analysis. *Am J Med Genet* 1995;59:525.
- 8 Sigler AT, Cohen BH, Lilienfeld AM, Westlake JE, Hetzner WH. Reproductive and marital experience of parents of children with Down's syndrome (mongolism). *J Pediatr* 1967;70:608-14.
- 9 Mulcahy MT. Down syndrome and parental coital rate. *Lancet* 1978;ii:895.

Predictive genetic testing in children

The paper by Michie *et al* (*J Med Genet* 1996;33:313-18) describes a situation which is going to arise with increasing frequency as more dominantly inherited disorders become reliably detectable by molecular methods. The discussion focuses on the views of the parents and of the professionals but there is no word from the children. At the ages of 4 and 2 years they are too young to give their opinion, but perhaps a proxy should have done this for them.

For a few disorders (for example, retinoblastoma) surveillance starts in infancy but usually predictive testing for risk of malignant disease is done with a view to prevention of disease by regular surveillance into adulthood. We need to know what testing procedure is most likely to lead to a responsible attitude to the irksome and unpleasant screening regimens. Parents have their children's best interests at heart but may find it difficult to remember that charming 5 year olds may develop into rebellious teenagers or into 20 year olds who know they are invincible. The poor compliance of diabetics at this stage of life is well known.

Instinct tells me that compliance is likely to be higher when the child has been actively involved in the decision on the timing of the test. Discussion of the need for a test is fine from an early age, but let parent and child together await the result. A teenager may well

resent a parent testing him or her "when you were too young to remember". Controlled surveys are unrealistic but we could discover the views of 8 to 20 year olds. Has anyone asked them?

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This letter was shown to Drs Michie and Marteau, who reply as follows.

Dr Berry raises several important questions concerning predictive genetic testing in children: the age at which a child's opinion about his/her own testing should be sought, whether a proxy should give an opinion in the case of a young child, and the extent to which a child should have a say in the decision about whether and when to be tested.

In the absence of data to inform these questions directly, research concerning children's informed consent in other areas can shed some light.¹ The general trend over the last decade has been one of discovering greater competencies in young children than previously attributed² and of giving more responsibility to children for decisions about, for example, their medical treatment and participation in research.^{3,4}

Views about whether parents should be allowed to make such decisions for their children vary and, again, we lack the evidence of the impact on children and family life of parents either being allowed to make this decision or of not being allowed to make this decision. Our recently reported single case study suggested that the latter can lead to anger both within the family and with health professionals.⁵ Dr Berry argues that teenagers may resent having been tested as a child. Our case study found resentment of not having been tested as a child. As Dr Berry states, we need more information about what children and teenagers think about these issues.

We are currently conducting a multicentred trial to investigate the psychological impact of predictive test results on children and their parents. Much more research is needed if we are to have an informed debate on these important issues.

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1 Michie S, Marteau TM. Predictive genetic testing in children: the need for psychological research. *Br J Health Psychol* 1996;1:3-14.

2 Karmiloff-Smith A. *Beyond modularity: a developmental perspective on cognitive science*. London: MIT Press, 1995. Children Act. London: HMSO, 1989.

3 British Paediatric Association. *Guidelines for the ethical conduct of medical research involving children*. London: British Paediatric Association, 1992.

4 Michie S, McDonald V, Bobrow M, McKeown C, Marteau T. Parents' responses to predictive genetic testing in their children: report of a single case study. *J Med Genet* 1996;33: 313-18.

BOOK REVIEWS

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Genetics of Criminal and Antisocial Behaviour. Ciba Foundation Symposium. (Pp 283; £50.00.) UK: John Wiley. 1996. ISBN 0-471-95719-4.

As possession of the Y chromosome provides the clearest evidence for a genotype with a predisposition to antisocial behaviour, a possible subtitle for this could be "Adam and evil". The proceedings, however, mainly concentrate on an evaluation of non-Y linked genetic factors. As several contributors point out, an inclination to aggression is integral to our survival mechanism and thereby provides pitfalls for its simple genetical analysis. Criminality is not a biological characteristic, it is a social construct; labelling particular constellations of behaviours as "disorders" can therefore be unhelpful. Several other important reservations are addressed in this volume. For example, many would agree with Cairns (p55) that "there is a special folly in recent attempts to identify the 'gene' for aggressive behaviours, whether by the methods of molecular genetics or by pedigree analysis". I think we all recognise that behaviours are plastic and genetically rather intractable by virtue of their distance from the primary levels of gene function. In spite of these and other considerations, there are compelling reasons for investigating the role of genetic factors in antisocial behaviour. Many current experimental approaches are covered including animal studies, evaluation of specific candidate loci, linkage mapping, and familial correlations. The proceedings conclude with highly readable chapters providing both evolutionary and anthropological insights and a consideration of behavioural genetics in context of individual responsibility.

For my money, there is too much emphasis on previously reported attempts to assign the relative contribution of genes and environment through the interpretation of adoption and twin studies. Much of the text is also devoted to the discussions, which follow each chapter and each section; these could be extensively edited without significant loss. So, for those with a pressing schedule, it would be worth concentrating on the clear introduction and concise conclusions by Rutter. The contributions by Goldman and Brunner with a major emphasis on the contributions of molecular approaches are also highly recommended.

The chapter by Maxson provides a balanced account of the practical advantages and theoretical problems to be encountered in mouse models for human aggression. A very positive approach to their role is also taken by Cairns, who discusses aggression

from a developmental perspective. One of the mainstays of animal studies has been linkage mapping, either of discrete traits or via surveys for quantitative trait loci (QTL). This approach has been notable recently through the identification of loci implicated in the aetiology of stress (Flint *et al. Science* 1995;269:1432-5). Another major contribution from animal studies is through "gene knock-out". The example discussed in this context is that of the 5-HT1Db serotonin receptor. Perhaps surprisingly, mice lacking this gene show normal gross behaviours, although males show a twofold increase in frequency of attacks on intruders. While judgement should be suspended as to the consequences of equivalent aberrations in human behaviour, two more dramatic examples of neurotransmission defects resulting in aggression in "knock-out" mice have been reported recently for the monoamine oxidase, MAOA, and neuronal nitric oxide synthase, NOS1, genes.

It is instructive to note that the most direct and controversial implication of a gene defect in human aggressive behaviour also involves the MAOA locus (see chapter by Brunner). In contrast, attempts to confirm the role of many candidate genes identified through allelic association have, in general, been unsuccessful. As noted by several contributors, marker associations have often proved to be fragile and unreplicable.

In conclusion, the symposium underscores how difficult it is to separate cultural, sociological, and emotional influences from hard science in behavioural studies. We can now hope that the rapid advances in molecular biology will increasingly enable the roles of specific candidate genes (such as MAOA) with small total impact, but with well established psychopharmacological function, to be teased out. Evidence for the roles of both genes and environment and even for their interaction has been generally accepted for more than a decade. What emerges from the symposium is a fairly resounding confirmation of these general conclusions. The next 10 years should see some of the contributing factors hung on more specific pegs. So, although already dated, these proceedings are worth studying by those involved in the field and particularly by the advanced guard of molecular biologists moving into this challenging area.

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Color Atlas of Genetics. Eberhard Passarge. (Pp 420; DM 48.00.) Stuttgart: Thieme. 1995. ISBN 3-13-100361.

This excellent pocket sized text book encompasses, very successfully, the fundamentals of genetics, functional aspects of genetics, and information about genomic organisation. It is aimed towards students of medical sciences and biology but would also be a very useful reference book for physicians who are beginning genetic research and who wish to read a basic but comprehensive text book.

The book has been written so that each page of text has opposite a full page of explanatory diagrams. These are all in colour and have been well thought out so that they complement the text. This means the book is easy to read and the information is very accessible. Instead of being put off by pages of turgid text full of jargon the reader feels encouraged to read on or at least to look at all the pictures!