LETTERS TO
THE EDITOR

Psychological aspects of von Recklinghausen neurofibromatosis (NF1)

In the December 1995 issue of your journal, McMillan et al. reviewed the psychologi-
cal aspects of NF1. 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, 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. 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). Part of this difference can be accounted for an associ-
ation between the left shift in IQ and any clinical variable (such as clinical severity of
disease, macrocephaly, or family history of NF1).

(2) There is a slight increase in the incidence of mental retardation in NF1 (4-8%) compared to the general popula-
tion.

(3) At least 40% (and probably more) patients with NF1 have learning disabilities. In our study of 40 children (aged 8 to16 years), 65% had impaired performance (that is, more than 2 SD below the mean) on at least one test of academic achievement.

(4) 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 Judgement of Line Orientation (a test of visuo-
spatial 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 organi-
sational skills affect performance in many areas, although increased distractibility is not usually associated with hyperactivity.

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). In our study, children with areas of increased signal intensity on MRI (UBO++) had significantly lower IQ scores than children without these lesions. However, the associ-
ation between “UBOs” and learning disabilities remains controversial. Moore found no statistical difference in overall IQ scores between the UBO+ and UBO- groups. However, when the results were ana-
ysed according to the site of increased T2 lesions, there was a significant association between deficits in IQ, memory, motor func-
tion, and attention span and T2 signal lesions in the thalamus and hypothalamus. Hoffman et al. and Denckla et al. found that the number and volume of T2 signal lesions were highly correlated with cognitive deficits in children with NF1, and 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. 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.

KATHRYN N NORTH
Royal Alexandra Hospital for Children, PO Box 3515, Parramatta, Sydney, NSW 2124, Australia

5 Moore BD, Arlet JL, Needle MN, Slopis J, Cope-
7 Moore BD, NF1, cognition and MRI. Neurology 1995;45:1029.

The male excess in Down's syndrome

Mutton et al. confirmed earlier reports of a male excess in cases of Down's syndrome (DS). The cause of this excess is not yet established but does not seem 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 timing of fruitful coitus within the 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, Gray 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, like the mule, rhesus and tailed deer, Barbary macaque, golden hamster, and Norway rat.

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, but suspicion is raised by the reported high maternal age specific rates in children born to Catholic women.

WILLIAM H JAMES
The Galton Laboratory, University of London, Woburn House, 4 Stephenson Way, London NW1 2HE, UK

1 Mutton D, Alberman E, Hook EB. The National Down Syndrome Cytogenetic Register and the Association of Clinical Cytogeneti-
2 Gray RH. Natural family planning and sex selec-
6 Hedrick C, McClintock MK. Timing of insemina-
tion is correlated with the secondary sex ratio of Norway rats. Physiol Behav 1990;48:925-32.
7 Castilla EE, Simpson JL, Queenan JT. Down syndrome is not increased in offspring of natural family planning users: a case-control analy-
9 Mulcahy MT. Down syndrome and parental coi-

Predictive genetic testing in children

The paper by Michie et al. (J Med Genet 1996;33:313-18) describes a situation which is quite common: if someone is at increased risk of having a child with a more dominantly inherited disorder becomes 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, retnoblastoma) 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 that the early detection procedure is most likely to lead to a responsi-
ble attitude to the irksome and unpleasant screening regimens. Parents have their chil-
dren’s best interests at heart but may find it difficult to remember that a charming child’s year olds may develop into rebellious teenagers or into 20 year olds who know they are invinci-
ble. 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 at an early age, but let parent and child together await the result. A teenager may well

William H James
The Galton Laboratory, University of London, Woburn House, 4 Stephenson Way, London NW1 2HE, UK