X-linked mental retardation*

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(Since this paper went to press the co-author, Dr Brian Turner has died, and our sincere sympathy goes out to his widow, Dr Gillian Turner.—EDITOR)

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Summary. A survey of the mentally retarded children with an IQ between 30 and 55 born in a 10-year period (1955–64) and now of school age was carried out in New South Wales. The number of propositi who had a similarly affected sib of the same sex was ascertained; 58 boys had a similarly affected brother(s) and 22 girls had a similarly affected sister(s). It is suggested that the excess of affected brothers represents X-linked forms of mental retardation. An estimate of prevalence rate was calculated from the brother pair excess and was found to be 0·74/1000 males. The calculated incidence of X-linked forms of mental retardation appeared to account for most of the male excess found in the survey and suggests that 1 in every 5 of the mentally retarded boys in the IQ range in this survey may be retarded on the basis of genes on the X chromosome.

Penrose in 1938 noted a preponderance of males in his survey of an institutional population of mentally retarded people, and many subsequent reports have confirmed this finding. The extent of the disproportion has been reviewed by Lehrke (1971/72) and varied from 21% to 86%. Penrose (1963) found no evidence for an X-linked recessive form of mental retardation to account for this male disproportion and it has been suggested that it may only reflect an ascertainment bias for the affected male (Nance and Engel, 1972).

There is however a growing body of evidence that X-linked recessive disorders make a contribution to mental retardation in the male. Firstly, there is a group of rare X-linked recessive disorders associated with mental retardation; included in this group are Duchenne muscular dystrophy, oto-palato-digital syndrome, Borjeson syndrome, diabetes insipidus, hydrocephalus, Lesch-Nyhan syndrome, and Menkes' kinky hair disease. Second, there is a growing number of case reports of mental retardation being inherited as an X-linked recessive disorder and unaccompanied by somatic or biochemical abnormality (Martin and Bell, 1943; Losowsky, 1961; Renpenning et al, 1962; Dunn et al, 1962/63; Snyder and Robinson, 1969; Neuhäuser et al, 1969; Neuhäuser and Zerbin-Rüdin, 1970; Escalante, Grunspan, and Froto-Pessoa, 1971; Fried, 1972). Several studies have suggested that cases falling within the latter group may be more common than is generally accepted (Lehrke, 1972; Turner, Turner, and Collins, 1971a; Turner et al, 1972; Clare Davison, 1973).

The present study was undertaken with the aim of defining the contribution that X-linked recessive forms of mental retardation made to the prevalence of mental retardation in New South Wales.

A survey was undertaken of all mentally retarded children (IQ 30–55) of school age born between January 1955 and December 1964 in the State of New South Wales to determine the prevalence of this grade of mental retardation and to find the frequency of affected brother pairs and sister pairs within this population group. It could be anticipated that if X-linked recessive mutations contribute significantly to the problem of mental retardation there would be an excess of affected brother pairs over affected sister pairs in those families with two mentally retarded children. This information could then be used to calculate the contribution that is made by X-linked mutations to this grade of mental retardation.

Population Surveyed

The State of New South Wales has a total population of 4·6 million of whom 2·5 million live within the metropolitan area of Sydney. The Commonwealth Bureau of

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Census and Statistics made available the figures for the number of individuals of each sex in the State in the age range surveyed and the number of male children aged six with an elder brother in each year up to 1970.

Ascertainment of the moderately mentally retarded. The New South Wales Department of Education provides special educational facilities for these children of IQ 30–55 and for this reason this IQ range was considered in this survey rather than the WHO definition of IQ 35–51 for the moderately mentally retarded. School attendance is compulsory for children of this IQ range. Information about pupils born between January 1955 and December 1964 was obtained from the three areas which encompass all the facilities in the State of New South Wales.

Special schools of the New South Wales Department of Education and the Special Classes in Privately-run Day and Boarding Schools for the Mentally Handicapped. The children are assessed by departmental psychologists using a revised Binet L.M test for eligibility for acceptance into these special schools and classes. The New South Wales Department of Education kindly permitted a survey through the school principals of the children under their care detailing date of birth, presence of Down's syndrome, and known affected sibs. Similar information was obtained from all the principals of the privately-run schools for the mentally handicapped concerning children eligible for or attending departmental classes.

Residential Institutions of the New South Wales Department of Health. Information regarding these patients was made available through departmental records.

Residential Institutions of the New South Wales Department of Child Welfare. Those children who were wards of the State and who had been committed to the care of the Department of Child Welfare were ascertained from departmental records.

Ascertainment of Similarly Affected Brother Pairs and Sister Pairs. From the above sources the presence of a known affected brother or sister was obtained. Further details regarding the propositus and the affected sib were obtained either by visiting the school or institution or by directly contacting the responsible principal or superintendent. Details were then confirmed either directly or by contacting other agencies who had direct knowledge of the patient and family. A proportion of these families was already known to the authors and the school principals were asked to tell the parents that we would be happy to talk to them if they wished.

The propositi excluded from this survey were those where the affected sib was a twin, had Down's syndrome, was mildly retarded with an IQ 56 or more, or whose date of birth was later than December 1964.

Results

One hundred and twelve schools and institutions were contacted, 110 replied. It was known that the two schools which did not supply the information sought had few patients and did not contribute significantly to the total population surveyed.

We think that the ascertainment of the mentally retarded of the type sought was virtually complete for those born within the period of the survey.

Table I shows the prevalence for the mentally retarded in the IQ range 30–55 born between January 1955 and December 1964 in the State of New South Wales. The male excess is calculated as a percentage of the number of retarded females ascertained. The male excess in the total school age population in the same period calculated in the same way was 4-5%.

Table II

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</thead>
<tbody>
<tr>
<td>No. of male propositi with an older affected brother</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>12</td>
<td>4</td>
<td>58</td>
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<tr>
<td>No. of female propositi with an older affected sister</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Excess of male propositi</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>No. of males born in that year with an older brother*</td>
<td>16,294</td>
<td>17,192</td>
<td>17,000</td>
<td>18,411</td>
<td>20,430</td>
<td>20,567</td>
<td>21,574</td>
<td>21,710</td>
<td>21,144</td>
<td>20,852</td>
<td>195,174</td>
</tr>
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</table>

* Data supplied by the Commonwealth Bureau of Census and Statistics.
The majority (77%) of the mentally retarded ascertained lived at home and attended day school, 12% were in private residential schools, 7% were in State institutions, and 4% were wards of the State in State boarding schools.

Table II shows the number of ascertained mentally retarded born during the years of the survey who had an older affected sib of the same sex, the excess of affected male sibs born each year, and the number of males born in New South Wales for that year who had an older brother.

Table III shows the number of affected sibs of the same sex ascertained within families. It is possible that some sibs born before 1955 may be omitted being unknown to the informants and similarly some half-sibs may be missed. Propositus whose sibs were mildly mentally retarded have been omitted as it was thought that ascertainment for mild mental retardation would not be complete. It is however interesting to record that there were 22 moderately retarded boys who had mildly retarded brothers whereas only 11 moderately retarded girls had mildly retarded sisters.

Discussion

This survey in the prevalence of the mentally retarded of IQ 30–55 in a 10-year school age population in New South Wales confirms the male preponderance found in other surveys. The male excess of 32% is comparable to that found in other surveys where it ranged from 21% to 86%.

The decision determining Special School placement resulted from the psychological testing. Referral for psychological testing is dependent on a child's school performance in the first grade (at age 6–7) and this takes place if any degree of mental handicap is suspected. Therefore in those with this degree of intellectual deficit their need for referral would not have been overlooked in either sex. It is unlikely therefore that there was any selection bias against the male.

It has not been possible to examine or take a family history from all the sib pairs ascertained in the survey. A proportion of these families was already known to the authors and some responded to the request to be interviewed but the sample seen in this way appeared to be biased in favour of those families with a positive family history. A previous study (Turner et al., 1972) of 18 brother pairs in an institution may represent a better sample as they were selected only by virtue of their being in an institution and had the added advantage that they were all adults and therefore their sisters were of childbearing age so increasing the likelihood of being able to confirm X-linkage. In that study of 18 pairs, the families of 14 pairs could be contacted and in eight there were other retarded members of the family in first- and second-degree relatives, and in seven this was consistent with an X-linked pattern of inheritance.

The male excess noted in simple prevalence rates persists when the families with two or more affected boys are considered against the number of families with two or more affected girls. Thus for every 22 female sibs ascertained there were 58 male sibs, suggesting a heavy genetic bias against the male. It is of interest that the same ratio was found in the survey carried out by Clare Davison (1973), where in the undiagnosed group with two or more affected in a family there were 50 families with only affected males and 21 families with only affected females.

It could be debated whether the excess of families with affected sons represents the component contributed by X-linked mutations. The male is more at risk in the perinatal period and also tends to respond more adversely to environmental factors but it seems unlikely for this to produce two male sibs with the same degree of intellectual deficit. The premise has to be accepted that the 22 female sib pairs represent that proportion of the male sib pairs under the influence of factors other than those that are X-linked, such as recessively and dominantly inherited conditions. Sex limitation cannot be excluded as the degree of mental retardation is not conducive to reproduction and is therefore in effect a male lethal.

But taken overall there are strong arguments that the male sibship excess by and large represents X-linked mutations and it thus becomes possible to estimate prevalence rates and gene frequency.

The number of affected male sibs due to X-linked mutations is the total male sibships (58) minus the total female sibships (22) = 36 sibships. The mothers of these 36 would be obligatory carriers. For every woman who is a carrier who has two sons, the likelihood that she will have two affected sons is 1:4. So that for every woman having two affected sons there are three others who are
also carriers having either one affected son or no affected sons.

The number of women in the population of New South Wales who have two sons in the age range being surveyed is 195,174. Within that group there are 36 who have two affected sons; therefore the total number of carrier women in that group is 195,174/36 - 5.53 or 0.74/1000.* 0.74/1000

is therefore the prevalence rate of carrier females. In any X-linked condition where the reproductive fitness of the affected male is zero and the mutation rate is the same in both sexes the ratio of carrier females to affected males is 4 to 3 (Carter, 1969). This higher incidence of the carrier female reflects the fact that a proportion of both the carrier females and the affected males result from fresh mutations. Such a mutation is more likely to occur in the female, she having two X chromosomes. Therefore knowing the prevalence rate of carriers and knowing the total number of boys in the State in the age range under consideration, the estimated number of boys affected by X-linked mutations associated with moderate mental retardation = 431,520 × 3 = 238.

The total, moderately retarded male population ascertainment for the period of the survey was 1335. If the expected number of males is taken from this figure it gives a figure of 1097 which is relatively close to the number of affected females observed in the same period, 1010, taking into account that there is an overall excess of 4% of males of this age range. The figure of total expected males is derived from a calculation of the number of sib pairs ascertained, whereas the total affected male and female population is derived from direct observation and are therefore independent of one another. The comparability of these figures suggests that most of the male excess in the population group can be explained in terms of X-linked disease.

The male excess found in the other grades of mental retardation may not be explicable on the same basis, thus male excess in the severely and pro-

foundly retarded is more likely to result from a continuum of those processes which result in the male preponderance found in perinatal morbidity and mortality. It has been shown (Turner, Collins, and Turner, 1971b) that the genetic recurrence risk rates in the severely and profoundly mentally retarded are actually higher in the female than the male (the reverse of what is to be expected if X-linked factors were significant). This lends support to the idea that the male excess in these two groups is due to perinatal damage rather than genetic effects. X-linked mutations may contribute to the male excess found in the mildly retarded. It was of interest that there were more moderately retarded boys recorded as having mildly retarded brothers, than moderately retarded girls with mildly retarded sisters.

The possibility that the male excess in mental retardation is due to X-linked factors has been suggested by Lehrke (1971/72) and he has reviewed the available evidence to support this. He has suggested that some intelligence traits, particularly verbal ability, may be carried on the X chromosome. The speculation could be made that this would permit the very rapid evolution of higher grades of intelligence in a species who were polygamous and tribal.

It is interesting to question why X-linked factors have not been considered seriously in the discussions of the causes of increased incidence of mental retardation in the male. The discussion has been rather that the male excess may be due to errors introduced by methods of ascertainment, such as the higher level of expectation in the male and the increased incidence of antisocial behaviour in the retarded male making institutionalization more likely. Penrose (1938) states: 'The conclusion may be drawn that there is no outstanding tendency for sex-linked genes to influence the genetics of mental retardation.' This supposition was based on the results of the Colchester survey which examined the family histories of 1280 patients in an institution in 1932. In the introduction of his report he notes that only two-fifths of the imbeciles (the moderately retarded) in the general community were in the institution, whereas half the feebleminded (the mildly retarded) were inpatients. The fact that the bulk of the X-linked forms of mental retardation are without physical stigmata would make it easier for them to be assimilated into the community. This would be particularly true in a semi-rural area at a time when there was relatively little mechanization of simple labouring tasks. It is possible that the Colchester survey did not include many of this group and therefore Penrose was misled by incomplete ascertainment.

* Some approximations which introduce error had to be made in the calculation of the prevalence of carrier females because the proportion of families of different sizes born within the survey period could not be ascertained. The total number of boys with an older brother in New South Wales will represent more than the total number of families, as should a family have, for example, three sons born within the survey period they would be included twice. This would lower the prevalence rate inaccurately. The second assumption—that the ratio of carrier females is three to every one with two affected sons—is only true if there are only two sons. Should the number of sons be more than two the ratio is less. This assumption therefore increases the prevalence rate inaccurately. As both errors are introduced by the inclusion of an unknown number of families with more than two sons born in the 10-year survey period it is assumed that their combined effect will tend to cancel each other out.
X-linked mental retardation

The important part that X-linked diseases appear to play in the aetiology of this grade IQ 30–55 of mental retardation in the male, raises new possibilities in its prevention. It is to be hoped that the recognition of this group of genetically-determined diseases will lead to pedigree studies of these patients, the development of methods of carrier detection, more adequate provision of genetic advice, and a fuller and more sympathetic understanding of these families.

A survey of this kind would have been impossible without all the help that was willingly given by members of the State Department of Health, Education and Social Welfare and also by members of the New South Wales Association for Sub-Normal Children. The authors would also like to acknowledge the information provided by Mr O'Neill of the Commonwealth Bureau of Census and Statistics, and to thank Professor McKusick for his helpful comments.

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