

EDITORIAL

Chromosomes and mental retardation¹

Thirty years have passed since mental subnormality was first linked to a chromosomal defect when a child with Down's syndrome was found to have an extra chromosome. Within a couple of years the chromosome was shown by Lejeune (1959) to be the one now designated as 21. This discovery was quickly followed by a search for chromosomal abnormalities in other patients with mental handicap and it was correctly predicted that persons with multiple congenital malformations would be more likely to have a detectable abnormality than those with a simple Mendelian mode of inheritance. The chromosomal origin of Down's syndrome was followed by the recognition of trisomy 18 by Edwards *et al.* in 1960 and trisomy 13 (Patau syndrome) was described in the very next article in the *Lancet* (Patau *et al.* 1960). It is now known that most of the autosomal trisomies (except trisomy 22) are associated with a significant degree of mental retardation. It was hinted that we might not find a trisomy of all the chromosomes and this has proven, in live births, to be true. Other trisomies do occur but the foetuses do not survive and the pregnancies end as early miscarriages. In this category is the trisomy for chromosome 16, which is not uncommon in abortion material but has never been described in infancy.

As chromosome analysis became more fully established in medical practice, the full trisomies were followed by the recognition of partial triplication. In most of these situations the extra material was translocated onto another chromosome. These unbalanced translocations, if they involved the autosome, almost inevitably result in mental retardation. Some arise *de novo*, and some are inherited from a parent who carries a balanced translocation. It is now recognized that 1 in every 500 individuals has a balanced rearrangement (1 in every 250 couples) so that the propensity for chromosomal abnormalities in offspring is not negligible. In practice, there is sometimes a problem in differentiating balanced from unbalanced translocations and it is even thought that a small proportion of *de novo* apparently balanced translocations might have small deletions not easily detectable by present chromosomal methodology. High-resolution banding has enabled cytogeneticists to increase the number of bands which are visible using conventional G-banding from 350 to 500 and under exceptional circumstances to 850 or even 1000 bands. G-banding is routinely used but the other techniques, i.e. prometaphase banding, are time consuming and not suitable for everyday practice. How chromosomal alterations cause mental retardation is unknown. Deletions, i.e. absent bits of DNA, are more easy to relate to retardation than extra pieces or extra full chromosomes, although this latter aberration might result in an over production of material which interferes with normal morphogenesis.

It should be noted, however, that extra chromosomal material in the case of trisomy 22 might result in patients of normal intellect but with colobomata of the iris, anal atresia and a congenital heart defect. In general, however, the greater the amount of extra material the more serious the consequences. Following this theme the effect of 9p trisomy, i.e. an extra short arm of chromosome 9, is less profound than 9p tetrasomy (having 4 copies of the short arm). Even here there are exceptions and there is a suggestion that a small deletion on the short arm of chromosome 4 might have more consequence for intellectual development than a large deletion. Certainly, the phenotype is related to changes at specific regions of the genome and the well known clinical picture of Down's syndrome seems to be related to the triplication of the distal segment of chromosome 21 (Niebuhr, 1974).

There is also a relationship between the degree of mental handicap and the proportion of cells containing the chromosomal abnormality. Most people with trisomy 21 have the extra chromosome throughout all cells but there are patients with two cell populations, i.e. mosaics who have the

¹ Address for correspondence: Dr M. Baraitser, Department of Clinical Genetics, The Hospital for Sick Children, Great Ormond Street, London WC1N 4JH.

trisomy in only a proportion of cells and are consequently less handicapped. It is also likely that we are unable to diagnose some causes of mental retardation because we cannot detect mosaicism. Recent work suggests the possibility that mosaicism can cause mental retardation and, whereas the cytogeneticist might find no abnormal cells in the peripheral blood, a skin biopsy could show cells with an extra chromosome (Hunter *et al.* 1985). Whether all children with mental retardation should have a skin biopsy is at present far from certain and few laboratories would be able to cope with the extra work involved. The best known example of this situation is mosaic trisomy 8. It should also be noted that there is not always a good correlation between the degree of mosaicism and the extent of retardation. There is an added problem in the tendency for abnormal cell lines to diminish with age in favour of the normal, which might make detection difficult in adults.

A number of studies have looked at the type of cerebral malformation caused by chromosomal abnormalities. In Down's syndrome, despite major intellectual problems, the neuropathological changes are subtle. There is, for example, a mild decrease in brain weight. The frontal lobes, cerebellum and brain stem are small but the majority of changes are cytoarchitectural. Hippocampal dysgenesis has been described (Sylvester, 1983) and there is a reduced number of dendritic spines in the early post-natal period. In trisomy 13, however, the major malformations might include holoprosencephaly, but even within this group there is considerable variation. In trisomy 18 the number of gross malformations is less, although agenesis of the corpus callosum and holoprosencephaly can occur.

A very similar pattern of developmental anomalies occurs in those patients with deletions. Full monosomies are rare but partial deletions are numerous. Over the past decade smaller and smaller deletions are being observed and consideration has been given to the use of DNA probes known to be located in specific areas of the genome to help locate small deletions.

It is also likely that some recognizable syndromes, e.g. Cornelia de Lange or Rubinstein Taybi, might turn out to have small deletions. The precedent has been set by the recognition that half of the patients with Prader Willi syndrome have an interstitial deletion involving the long arm of chromosome 15 (Ledbetter *et al.* 1981). The deletions are small and it is necessary to draw the cytogeneticist's attention to an area of the genome that needs special scrutiny. Even a previously considered recessively inherited condition, Miller-Dieker syndrome or lissencephaly, has now been shown not to be a single gene disorder but to have as its cause a chromosomal deletion involving the short arm of number 17. Pathologically, the retardation is due to a developmental defect leading to a smooth 4 cell layer cerebral cortex (Dobyns *et al.* 1983).

One of the most exciting recent developments has been the finding of an explanation for the male preponderance in severe mental retardation. Lubs (1969) showed that some mentally handicapped males had a fragile site towards the end of the long arm of an X chromosome at Xq27. Also called the Martin-Bell syndrome or X-linked mental retardation with macro orchidism because a proportion of males have large testes, it affects one in every 3000 live born males (Lubs *et al.* 1984). As the cytogeneticist needs to use an altered technique to find the defect, the clinical criteria for asking laboratories to look for the sites are important. The males are not grossly dysmorphic but have relatively large heads, a long face, with protrusion of the ears and a prominent jaw. Microcephaly is not a feature. The males are often autistic and might present to psychiatrists with behaviour problems and speech delay.

A third of female carriers are retarded, albeit mildly, and transmission of the abnormality can very occasionally occur through normal males. At a population level fragile-X mental retardation probably accounts for 7% of the severely mentally handicapped males and 4-5% of mildly retarded males. Fryns *et al.* (1984) commented that all the boys they have studied were hyperkinetic and that the overactivity tended to be more severe in the boys of high IQ. Agitation and emotional lability were cardinal features. In a Swedish multicentre study (K:son Blomquist *et al.* 1985) of infantile autism the fragile-X syndrome was detected in 16% of the boys, and the diagnosis should be contemplated where retardation has previously been ascribed to poor socio-economic conditions and environmental deprivation.

There is also a recent awareness that certain chromosome abnormalities do not cause mental

retardation as frequently as was previously thought. It had been considered that a large proportion of males with Klinefelter's syndrome XXY were mentally handicapped and that XXX females fell into the same high risk category. Prospective studies now show that this is not the case, although the final answer is not yet available.

Advances in our understanding of mental retardation have taught that all retarded children and adults should at least have their karyotype checked, as this might lead to the detection of carriers and the prevention of further retardation.

M. BARAITSER

REFERENCES

- Dobyns, W. B., Stratton, R. F., Parke, J. T., Greenberg, F., Nussbaum, R. L. & Ledbetter, D. H. (1983). Miller-Dieker syndrome and monosomy 17p. *Journal of Pediatrics* **102**, 552-558.
- Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M. & Wolff, O. H. (1960). A new trisomic syndrome. *Lancet* **i**, 787-790.
- Fryns, J. P., Jacobs, J., Kleczkowska, A. & van den Berghe, H. (1984). The psychological profile of the fragile X syndrome. *Clinical Genetics* **25**, 131-134.
- Hunter, A. G. W., Clifford, B. & Cox, D. M. (1985). The characteristic physiognomy and tissue specific karyotype distribution of the Pallister-Killian syndrome. *Clinical Genetics* **28**, 47-53.
- K:son Blomquist, H., Bohman, M., Edvinsson, S. O., Gillberg, C., Gustavson, K.-H., Holmgren, G. & Wahlström, J. (1985). Frequency of the fragile X syndrome in infantile autism. A Swedish multicentre study. *Clinical Genetics* **27**, 113-117.
- Ledbetter, D. H., Riccardi, V., Airhart, S. D., Strobel, R. J., Keenan, B. S. & Crawford, J. D. (1981). Deletions of chromosome 15 as a cause of Prader-Willi Syndrome. *New England Journal of Medicine* **304**, 325-329.
- Lejeune, J. H. (1959). Le Mongolisme... Premier exemple d'aberration autosomique humaine. *Annales de Génétiques* **1**, 41-49.
- Lubs, H. A. (1969). A marker X chromosome. *American Journal of Human Genetics* **21**, 231-244.
- Lubs, H. A., Travers, H., Lujan, E. & Carroll, A. (1984). A large kindred with X-linked mental retardation, marker X and macroorchidism. *American Journal of Medical Genetics* **17**, 145-157.
- Niebuhr, E. (1974). Down syndrome: the possibility of a pathogenetic segment on chromosome no. 21. *Humangenetik* **21**, 99-101.
- Patau, K., Smith, D. W., Therman, E., Inhorn, S. L. & Wagner, H. P. (1960). Multiple congenital anomaly caused by an extra autosome. *Lancet* **i**, 790-793.
- Sylvester, P. E. (1983). The hippocampus in Down's syndrome. *Journal of Mental Deficiency Research* **27**, 227-236.