Gene mapping and neurogenetics

The ninth Human Gene Mapping Workshop is held in Paris this month and since the previous meeting, two years ago in Helsinki, there has been no slackening of the pace of advance in the mapping of the human genome. A measure of this pace is seen in cystic fibrosis, where the Helsinki workshop provided the first hint of gene localisation, and where our knowledge has rapidly progressed through the stage of close DNA markers providing accurate prenatal diagnosis to the identification of a sequence that may possibly represent the gene itself.

Genetic disorders of the nervous system have always been at the forefront of gene mapping projects, partly because they provide numerous examples of clear cut clinical phenotypes occurring in large pedigrees suitable for gene mapping and neurogenetic analysis, partly also because their serious nature and the lack of helpful preventive and therapeutic measures makes the mapping approach a particularly attractive one. At the Helsinki meeting, Duchenne muscular dystrophy and Huntington's disease were the two neurological disorders that had received most attention; now two other important disorders have shown the power and scope of gene mapping techniques.

Von Recklinghausen neurofibromatosis is one of the commonest human genetic disorders, with a minimum prevalence of 1 in 5000 of the British population and with one-third due to new mutation. Although many patients are not seriously disabled, around 40% will develop at least one of the complications of the disorder.

Although the distinct and rare form of neurofibromatosis 'bilateral acoustic neurofibromatosis' was localised to chromosome 22 in 1986, there has until recently been no indication of the gene localisation of the much commoner Von Recklinghausen type. A collection of papers in this issue of Journal of Medical Genetics gives the results of a productive and valuable collaboration in pooling gene mapping data resulting from an informal workshop in February this year. The pooled results effectively excluded all but four chromosomes, allowing workers to concentrate with maximal efficiency on these remaining areas. A hint already present of linkage to a marker on chromosome 17 was made much more significant by these exclusion data, and data obtained since the meeting have now rapidly confirmed this localisation, with two independent studies showing linkage of Von Recklinghausen neurofibromatosis to two pericentromeric probes, p3–6 and p240–41, and to the nerve growth factor receptor on the long arm of chromosome 17.

Tuberous sclerosis, another major autosomal dominant neurogenetic disorder, shows a number of parallels with neurofibromatosis, notably its variation in severity and system involvement, the high proportion of new mutations (around 50% for tuberous sclerosis), and the occurrence of unusual and interesting changes in somatic tissues (hamartomas in tuberous sclerosis, various neoplasms in neurofibromatosis). The progress in gene mapping in this disorder has resembled the pattern seen in cystic fibrosis, with a suggestion of linkage from classical markers (in this case the ABO blood group system and the red cell enzyme adenylate kinase), followed rapidly by more accurate mapping with DNA polymorphisms. The paper in this issue of the Journal by Connor et al shows close linkage between the locus for the oncogene C- abl on the long arm of chromosome 9 and tuberous sclerosis, and should provide the starting point for the detailed localisation of this disorder.

For both neurofibromatosis and tuberous sclerosis we thus now have major advances on which future work can be based, as well as the prospect of accurate predictive and prenatal diagnostic tests to help family members. Investigation of the somatic lesions in both disorders could prove of especial interest in the light of the demonstration of changes involving the homologous chromosome in other genetic disorders, such as retinoblastoma and bilateral acoustic neurofibromatosis. The testing of candidate genes is now a feasible proposition.

On a more cautionary note, the high proportion of new mutations in both disorders will limit the scope for prevention, while the exclusion of multilocus genetic heterogeneity will require further pooling of data. The trend towards collaborative studies, the fruits of which can be seen in the papers published here, is fortunately an increasing one. It is perhaps no coincidence that this work and the meetings underlying it were largely stimulated by the activities of the lay societies involved. When the involvement of families is the
key to success, close collaboration between scientists is the minimum that patients and their societies can ask for; the rapid collaborative progress in mapping the genes for both these serious neurogenetic disorders has benefited scientists and families alike.

References