Conference report

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Royal Society Discussion Meeting: Prevention and Avoidance of Genetic Disease, held on 29 to 30 April 1987 at the Royal Society

This was a well supported meeting directed at those who, at least in part, were genetically literate. Its objective was not clinical, though the importance of this aspect was emphasised in a paper by Nevin. While all the papers presented over the two days of the meeting were of a very high quality, the following aspects particularly interested us.

John Edwards began the meeting by considering the possible ways in which genetic disease might be prevented and concluded that true prevention means the prevention of mutations in the population. To attempt this approach we must first understand the mechanisms of mutation and the variety of mutagens to which the population is exposed. As he demonstrated, to study these effects is easier in mouse than man where long generation time and the rarity of many diseases is a disadvantage.

Among the new techniques discussed, Ferguson-Smith described the use of the fluorescent activated cell sorter (FACS) as a flow cytometer to separate chromosomes and detect deletions in patients with Duchenne muscular dystrophy. In his talk he also considered the use of pulsed field gel electrophoresis (PFGE) to separate out small chromosomal fragments from the bulk of the chromosomes. He illustrated this technique by its potential use in separating a small fragment seen in a 45,X male patient. Ferguson-Smith's group hope that this fragment may represent the testis determining region of the Y chromosome. This technique may also be used to look for deletions which may be too small to be picked up cytogenetically. Another useful technique discussed was *in situ* hybridisation whereby a linked probe may be used to look at the chromosomal localisation of the disease gene to which it is linked, for example, minisatellite sequences of Yp found in all nine of their 46,XX males.

In his talk David Weatherall considered the impact of cloned genes in prenatal diagnosis of genetic disease. Techniques available now include definition of the mutant gene at the DNA level in

cases of deletions, linkage analysis using restriction fragment length polymorphisms, detection of heterogeneity with phenotype-genotype correlation and the use of oligonucleotide probes when considering known mutations. The ultimate goal was the development of simple tests for screening for abnormal gene products. In a series of 200 prenatal tests for haemoglobinopathy or thalassaemia, diagnosis had been made in 112 using RFLP methods and in 85 by direct methods, with only two failures and one misdiagnosis.

The meeting then turned its attention to the current search for the gene for cystic fibrosis (CF). In his talk Lap Chee Tsui described the history behind the search for this gene which has resulted in two markers met and D7S8 being shown to be closely linked with CF at 7q31. He then described how, using techniques such as pulsed field gel electrophoresis, other fragments around these markers have been mapped.

The meeting also heard Bob Williamson's disclosure that his group had cloned a candidate gene for CF which is in strong linkage disequilibrium with the disease.

Worton reported on the results obtained by his Canadian group using a new technique to investigate Duchenne muscular dystrophy (DMD). He described how, using the DNA from a girl carrying an X;autosome translocation and affected with DMD, his group had cloned the adjacent portions of the translocated derived X chromosome (XJ region). Subclones can detect deletions in some DMD boys and have been extended with walks to overlap the pERT regions.

Harper surveyed the current situation of Huntington's chorea, pointing out how the intensity of investigation of families in an area affects numbers. There are in South Wales some 130 living affected subjects in 150 pedigrees with some 1600 at high risk, most of whom will not have the disease.

The lod score for G8 is now 75.3 on 52 families of varied ethnic origin without any evidence of hetero-

geneity. His group have been investigating families with a view to prenatal exclusion testing. Twenty-seven of 43 were fully informative groupings and of nine actual pregnancies six were informative, of which in half inheritance of the gene was unlikely (and in the other three not excluded).

The requirement for intensive interviewing during the genetic diagnostic procedure was stressed, as well as the need for longer time for those at risk. During the discussion, the importance of establishing the diagnosis in isolated cases was cited. A representative from Combat expressed surprise at the slow rate of introduction of predictive testing.

Ed Southern looked at the different orders of resolution using techniques available in molecular biology for mapping the human genome. He began by showing that only 2 to 10% of the genome actually represents coding sequences, with the majority (70%) being non-coding sequences such as introns and intragenic DNA (while mutations in the coding sequences would be deleterious, in most of the non-coding regions mutations would be neutral). Thus, the proportion of the DNA in which we may be interested, the coding sequences, reduces the size of the problem. He went on to look at the order of resolution obtained using techniques such as cloning into yeast, cosmids, etc, and analytical methods such as the use of genetic recombination, pulsed field gel electrophoresis, and sequencing gels and their potential use in helping to compile the genetic map of man.

Of great interest was his description of HTF islands (*HpaII* Tiny Fragments), unmethylated CpG regions which may mark the 5' end of coding regions of a gene. A total of about 30 000 HTF islands is found in the genome and these are the target of 'CpG' restriction enzymes.

In considering mutation as a cause of genetic disease, John Evans discussed both mutation in

germ cells and somatic mutation. Factors influencing mutation rates, such as gene size, architecture, location, base composition, and especially CpG doublets with potential mutation via methyl C to T, and parental age, were considered. He placed great emphasis on the importance of somatic cell mutation. Such mutations are seen increasingly with age and are increased by irradiation and mutagens. The consequence of such a mutation varies greatly with the type of cell in which it occurs and its exact nature. Human cancers have been shown to develop in tissues in which gene and chromosomal mutations have occurred.

In the final presentation, Caskey spoke on the occurrence and detection of new mutations in Lesch-Nyhan syndrome and in Duchenne muscular dystrophy. In their study they found that 15% of Lesch-Nyhan cases and 10% of DMD cases occur as a consequence of a major gene rearrangement. They also described a technique for demonstrating point mutations, making use of ribonuclease A sensitive base mismatches.

Bobrow, in summarising, emphasised the need for delivery of an effective service through the Clinical Geneticist. He pointed out that, already, probes are available for 14 out of 21 major single gene diseases. This conference highlighted the need for far reaching and continuing education of every medical student and clinician in the 'New Genetics'. From the point of view of the patient and their family the establishment of regional genetic services in most centres, combined with a genetic register, should make it possible to apply these advances quickly to the benefit of both the patient and science itself.

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