Conference reports

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Seventh International Congress of Human Genetics, Berlin
Clinical impressions

Multifactorial disease

There were impressive papers on hypertension and ischaemic heart disease. In hypertension, the number of variables and the imprecision of data (29 readings of blood pressure were taken) generate an enormous amount of material, even for a computer programme. Williams emphasised the importance of defining the population studied, though in the data presented he did not distinguish between males and females. An interesting correlation was between the wife's blood pressure and the stress sustained at work by her husband. Risk factors were multiple and he even suggested that Platt and Pickering were both right! Different stress/susceptibility tests reflecting different pathogenesis may be required in different families. A major recessive gene could be responsible for one third of cases, but other families appeared monogenic and dominant. Heritability could be as high as 60%. In some families the disease was relatively benign and in others more serious, reflecting a different genetic basis, thus emphasising the multiple factors involved in pathogenesis. Perhaps we should be talking about the syndromes of hypertension, like diabetes and end stage renal failure. Williams made the point that treatment may need to be tailored to each patient. One could suggest, therefore, that those shown to have altered catecholamine receptors might be better treated with beta blockade, and those with sodium transport defects with ACE inhibitors.

Insight into the genetics of risk factors for atherosclerosis, particularly coronary artery disease, is rapidly being expanded with the eight major apolipoprotein genes having been mapped, for example, ApoE, C1, and C2 genes on chromosome 19 and A1, C3, and A4 on chromosome 11. For the "common source epidemic of continuous "exposure type", in Breslow's phrase, dose and duration of contributory factors interact with the host response. Breslow identified 15 genes conferring susceptibility and identification of persons with such a gene would allow intervention. Although the ApoE alleles look promising as markers, it is still too early to know which parameters could provide the best predictor for ischaemic heart disease and susceptibility to atherosclerosis.

In familial hypercholesterolaemia, Sudhof reported that other mutations besides failure to synthesise the LDL receptor were now known, for example, an abnormal binding site. The gene was relatively large with 18 exons and the receptor contained some 860 amino acids. It was largely, but not entirely, intranuclear. Different deletions within and across the exons had been identified.

Syndromes

Psychiatric syndromes still lack good indicators of genetic predisposition or even of the phenotype, and there were some elegant statements of our lack of knowledge! Anxiety states were defined as "multidimensional developmental phenotypes".

The workshop on connective tissue diseases revealed many difficulties in definition with overlapping syndromes. There may be as many as 13 types of Ehlers-Danlos syndrome. Here, however, the molecular bases are being steadily identified.

Opitz defined a syndrome as a causally defined entity. When clinically similar, but of different aetiology, he uses the term phenotype, for example, the Lesch-Nyhan phenotype. This usage, as he recognised, is at variance with that in general clinical use.

The problem of diagnosis of unknown syndromes has been approached by David Danks in Australia with 'Possum', combining a database on an IBM personal computer with a videodisk which can display illustrations of more than 700 syndromes. The patients have been photographed at different ages and, as part of the visual impression received by the enquirer, could prove useful in identifying syndromes. The computer instructions are simple to operate and are designed to be usable by non
experts. Some knowledge of dysmorphology is clearly an advantage in this difficult area and the system must be contrasted with a much larger specialist database at the Institute of Child Health, London.

In addition to those on the X chromosome (see report by A P Read, *J Med Genet* 1987;24:187–8) microdeletions have now been described for some seven autosomal diseases such as Wilms'-aniridia (11p13) and Langer-Giedion (8q23) syndromes. The high resolution banding and in situ hybridisation necessary to identify such microdeletions and duplications are costly and, unless the site is already suspected, difficult for routine use in undiagnosed syndromes.

The fragile X syndrome received considerable attention. Not every patient had the classic phenotype and not every subject with the phenotype could be shown to have the cytogenetic abnormality. The clinical features require further definition. The differential diagnosis includes Sotos, the 'happy puppet', and Rett's syndromes. Some 20% of males with fragile X appear to be non-penetrant and perhaps as many as one third of females with it are retarded. Cytogenetic studies in young women are reliable in some laboratories, but DNA markers when validated should prove much more satisfactory.

Rett's syndrome may be the second commonest cause of mental retardation in females (perhaps comparable with fragile X in males). These girls are normal at birth and then regress, with the appearance of wringing of the hands and later loss of use. There is ataxia with the development of secondary microcephaly and also hyperventilation. No diagnostic test has yet been confirmed.

The syndromes of abnormal sexual differentiation attracted much attention. Correlation of the different segments of the X and Y chromosomes had proved difficult because of conflicting evidence. There is perhaps greater variation at the molecular level in these chromosomes than had been expected, but also more homology. As Dr J L Simpson pointed out, there are multiple biases in published reports, bias of ascertainment (the reason for referral for investigation) as well as bias of reporting. The testicular determining factor appears to be on Yp11.2-3 and that for ovarian function on Xp11.2, though there probably are some relevant genes on Xq and possibly Yq (for example, conferring fertility) as well as on the autosomes. Re-appraisal of these subjects at clinical, cytogenetic, and molecular levels should clarify the function and position of the genes involved in normal sexual differentiation.

*There are plans to combine these and other databases.*

Finally, we were all given a world wide listing of genetic centres. Unfortunately, this ambitious project was not very successful in its presentation, at least as far as the United Kingdom was concerned, being too inaccurate to be of value. One wonders to whom the detailed information provided would, in any case, be useful, as it will be very difficult to keep it up to date.

A W JOHNSTONE
Ward 8
Woodend General Hospital
Aberdeen AB2 2YS

'Spontaneous and induced chromosome aberrations in germ cells of mammals and man'

Several satellite meetings were held on Saturday 27 September 1986 following the Seventh International Congress of Human Genetics in Berlin, and this was one of them. Held in the Technical University Berlin, and organised by Professor Dr Gunther Röhrborn, Institut für Humangenetik und Anthropologie, Universität Düsseldorf, the meeting aimed to look at the current state of the art with regard to the use of mammalian germ cells in mutagenicity testing.

In a brief introduction, Röhrborn pointed out that, since the Ames test had become available, most mutagenicity testing had involved the use of somatic cells and germ cells were less in favour. There was, nevertheless, still a real need to investigate the possible inheritance of genetic and chromosomal anomalies that might arise through exposure of the gonads to environmental substances. To date, no known chemical has proved positive in germ cells while being found negative in somatic cell tests, but when a chemical is found positive in somatic cells, it is still important to test whether or not it is positive in the germ line.

The whole of the morning session was taken up with presentations of data concerning the analysis of human spermatozoa chromosome complements, by means of the human sperm-hamster egg in vitro fertilisation method, pioneered by Rudak and colleagues in 1978. R H Martin (Calgary) gave figures for 30 individual sperm donors, all men of proven fertility, analysed over a three year period. Figures for euploid and structurally abnormal complements were compared with an existing set of published data based on 33 previous donors. The aim was (1) to determine the distribution and variation of abnormalities between different men.