Conference report

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Report on Conference on New Prospects in Genetic Diseases, Royal College of Physicians, 3 and 4 December 1986

First Day

Genetics has become increasingly relevant to a wide range of medical specialities. This was reflected in the recent conference on genetic disease held at the Royal College of Physicians. In the opening lecture Professor Alan Emery demonstrated both the breadth and depth of the new genetic advances. He presented the audience with a vivid illustration of the exponential growth in the knowledge of the human genome by showing a graph of the number of genes sequenced since 1978. The graph takes off vertically in 1985 and if extrapolated further, cloned gene sequences could fill the entire space in the world's scientific journals by 1998!

The second lecture was a clear account of gene structure and function and an illustration of the principles of genetic linkage by Dr Luzzatto.

The second half of the morning was devoted to specific Mendelian disorders. Dr Solomon pointed out that the search to find a specific molecular abnormality in osteogenesis imperfecta was the reverse of the usual process. Instead of trying to find a gene for a disease, one was trying to find a disease for a gene since there are many collagen and connective tissue genes cloned. She went on to describe the different strategies that may be used in this search. Sequencing will give the most complete answer but is very time consuming. Southern blotting will miss the smaller deletions, but the newer techniques of R looping and enzymatic cleavage can pick up some of the smallest deletions. Where large pedigrees exist linkage with candidate genes has already proven a useful strategy. Dr Steve Reeder from Oxford described the recent work on adult polycystic kidney disease. The 3‘HVR tandem repeat sequence is proving highly polymorphic and closely linked. Clinicians who are familiar with the variability of this disease will be largely reassured to know that all the families studied, irrespective of age of onset, have shown linkage and a family from Finland with autosomal dominant cystic liver disease has also shown linkage. However, three families with Von Hippel-Lindau disease, in which various cystic lesions may occur, did not show linkage. In the discussion that followed the lecture, the pros and cons of prenatal diagnosis for adult polycystic kidney disease were debated. Two patient questionnaires have shown that between 30 and 50% of families are interested in prenatal diagnosis.

Dr Brendan Wainwright from St Mary's Hospital recounted the race to map cystic fibrosis. The cumulative lod scores increase monthly but the interest has focused on looking at the chloride channel in epithelial cell membranes. An expression model of this is being developed in Cambridge. The normal frog oocyte lacks a chloride channel and inserted human DNA sequences can induce it. The next question to be answered is whether cloned sequences from cystic fibrosis patients can induce the chloride channel in this model.

Clinical genetics is family medicine, but differs from general practice in that it is necessary to deal with the full extended family not just the nuclear family. This requires a different clinical approach and Professor Rodney Harris outlined the organisation required to provide this service. Continuing with aspects of health planning, Dr Howard Cuckle outlined the screening programme for neural tube defects and Down's syndrome. Using both maternal age and low AFP it is possible to draw a graph of risks and in theory could increase the detection of Down's syndrome by 14% with a 5% increase in amniocenteses. This work is currently being evaluated in a trial in the North East Thames Region.

The final two lectures on the first day were on cancer genetics. Professor David Harnden illustrated some single gene disorders that predispose to cancer, but stressed that these could be of even greater significance if heterozygotes are at increased risk of malignancy, as they appear to be in ataxia...
telangiectasia. The possible role of oncogenes was comprehensively reviewed by Dr Alan Hall. He was able to produce a preliminary classification of oncogenes by showing that they act at different cellular levels from growth factors through to nuclear proteins. There now seem to be many genes that promote cell proliferation and very few that inhibit cell proliferation. It seems to this author rather like wanting to turn the light off in a room and finding nothing but on switches.

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SECOND DAY
The second day of the conference began with the story, by Dr Albert de la Chapelle, of XX males, and what they can tell us about the location of male determining factors on the Y chromosome. Hypotheses made years ago concerning X-Y interchange can now be verified by DNA analysis, and the molecular basis of testis determination may be within reach. Next, Dr E Tuddenham reviewed recent information on the haemophilia A gene and mutations so far identified, which included four chain termination point mutations and 12 different deletions. The relative frequency of factor VIII and factor IX deficiency may simply reflect the relative sizes of the two genes as mutation targets.

Costs are a fashionable topic, and they were mentioned by several speakers. From Dr Tuddenham we learned that haemophilia treatment costs £11.5 million per year in the UK, and the annual world market for factor VIII is worth £750 million. The collaboration between haemophilia centres and regional genetics centres, which will be necessary for systematic family counselling, testing, and follow up, does not yet seem to have been achieved in many regions.

Dr Sarah Bundey presented a population based study of mental retardation in the West Midlands in which 16 males and 13 females of school age with the fragile X syndrome were identified in a population of around 300 000. She emphasised the potential for prevention of affected births. Her experience suggested that 2/3 of female carriers would avoid having affected children as a result of genetic counselling.

Professor Peter Lachmann then reviewed some topics in immunogenetics, including the evidence that the association between HLA and immune complex diseases is mediated by polymorphism of closely linked complement genes. This was one example of single gene effects beginning to be identified within ‘multifactorial’ conditions. Another was the association between serum cholesterol levels, and by implication, coronary heart disease, and apolipoprotein polymorphisms described by the next speaker, Dr J Scott. The DNA polymorphisms most readily identified within the apolipoprotein genes do not necessarily correspond to functionally important variations in coding sequences, which remain to be discovered.

After lunch, the meeting took an embryological turn. Professor R Gardner, discussing early mammalian development, emphasised the lack of commitment of blastocyst cells, and argued that it is misleading to refer to the blastocyst as an embryo.

Professor M Ferguson reviewed the interactions between mesenchymal and epithelial cells and their matrices which are involved in palatal closure. He made the point that the normal role of some so-called growth factors in development is as regulators of gene expression rather than as mitogens.

Professor H Galjaard then described the arrangement of clinical genetics services in Holland. Regional centres have been established with two to three clinical geneticists for every 2 million of population. Most of the prenatal assays are performed in one national centre, which deals with 10 000 tests per year. Professor Galjaard quoted one very interesting estimate, that twice as many affected births are prevented by reproductive decisions taken as a result of genetic counselling as by prenatal diagnosis and selective abortion. A quick calculation based on his figures suggests that each clinical geneticist in Holland prevents 17 affected births per year by genetic counselling alone.

In the final talk, which he described ruefully as a ‘whiter’ lecture, Professor David Weatherall mulled over some of the technical problems confronting new developments such as gene therapy, and the ethical issues surrounding prenatal diagnosis.

The conference succeeded in combining exciting new scientific knowledge with some down to earth considerations of delivery to the at risk population. It was a good shop window for clinical genetics, but there seemed to be disappointingly few outsiders in the audience. More ventures like this are needed, advertised in a way which emphasises their accessibility and relevance to clinicians.

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