Editorial

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Professor C O Carter, Assistant Editor 1970 to 1984; an appreciation

Cedric has been of the greatest possible help to me throughout his Assistant Editorship and I am extremely grateful for his advice in many fields. First of all, he is a true medical geneticist with wide interests, but perhaps particularly relating to congenital abnormalities, and it has been most reassuring for me to know that I can get a first class opinion on the many papers we get on this subject. I always remember his classical findings in congenital pyloric stenosis published in many papers, the first as long ago as 1961, but still quoted whenever polygenic inheritance is discussed.

He was the founder and the first Chairman of the Clinical Genetics Society and this also has meant a great deal to the Journal, as has the fact that he is a past President of the Eugenics Society and a present member of its Council.

Fortunately, although he is giving up his present post he is remaining on the Editorial Committee of the Journal.

Intelligence may not be everything (Cedric, I believe, is hoping to run in the London Marathon in 1984!), but it has taken him a long way, and one only hopes that his large family of descendants do not revert to the mean. I think this is unlikely as they will have had precept as well as the appropriate genes. Assessing them all will give him much amusement in his retirement.

We welcome Professor P S Harper who has taken over the Assistant Editorship.

Lateral reading 5

SCIENCE BEATS ANOTHER GENETIC DISEASE (Monitor. *New Scientist*, 17 November 1983;100:493)

'Monitor' summarises and simplifies a paper in *Nature* (10 November 1983, page 399) where antenatal diagnosis of PKU is described. The specific enzyme phenylalanine hydroxylase is normally present for the purpose of converting phenylalanine to tyrosine. The team at Baylor College of Medicine in Houston first "isolated the gene for phenylalanine hydroxylase (PH) from a preparation of rat liver, and then used this to screen a complete library of the human genome. The similarities between the rat gene and the human gene are great enough so that the two will bind together, and a radioactive label on the

rat gene enabled the researchers to find those fragments of human DNA that carried at least a portion of the human PH gene. These new probes, which are more useful as they carry the human PH gene rather than the rat gene, were used to screen DNA libraries from normal people and PKU patients.

All the DNA screened gave identical results; the PH probe bound equally to DNA from normal and PKU patients. This implies that the PH gene is present in PKU sufferers in more or less unchanged form."

The Baylor team therefore "looked for fine-grain differences in the PH gene DNA. Restriction enzymes cut DNA at specific points; using a battery of restriction enzymes and DNA from a random sample of 20 individuals, the team could use the probe to look for different fragments associated with the PH gene. They found three. One enzyme, *Msp* 1, produces a long fragment from the PH gene in 44% of the population and a slightly shorter fragment in the remaining 56%. A second enzyme, *Sph* 1, likewise gives two distinct fragments while a third, *Hind* III, reveals three different variants of the PH gene. Armed with these restriction enzymes the researchers looked at the DNA of families known to carry PKU to see whether the different variants revealed by the restriction enzymes could be correlated with the mutant version of the PH gene.

In every example the restriction enzyme fragments were correlated with PKU. In one family, for example, both parents were heterozygous for the fragments created by *Msp* 1. This suggested that one fragment represented the normal PH gene and the other the mutant. A child with diagnosed PKU gave only the smaller fragment, indicating that this was the mutant version. That child's brother showed no evidence of PKU and he had only the longer fragment."

The three restriction enzymes only separated 75% of the families who were known from previous births to run a risk of PKU. The other 25% could not be separated into normals, carriers, and affecteds.

A good example of the use of restriction fragment length polymorphism. (ED).

There has also been another paper on phenylketonuria (*N Engl J Med* 1983;309:1269-74) by H L Levy and Susan Waisbren. The authors studied

the IQ of 53 offspring of mothers with phenylketonuria and hyperphenylalaninaemia. The IQ of the offspring was significantly correlated with both maternal IQ and the maternal blood phenylalanine, but with one exception mental retardation in the offspring was present only when the maternal blood phenylalanine level exceeded 18 mg/dl. The data suggest that severe atypical or classic phenylketonuria (blood level above 18 mg/dl) has a substantial cognitive effect on the offspring but that the effect of mild hyperphenylalaninaemia may have been exaggerated in the past.

SPECIAL REPORT. SUMMARY OF A WORKSHOP ON IMMUNOSUPPRESSION IN THE MANAGEMENT OF TYPE 1 DIABETES MELLITUS (IDDM) (*N Engl J Med* 1983;309:1199-200. Diabetes Research Program, National Institutes of Health)

When I was younger, insulin dependent diabetes mellitus (IDDM) was clearly controlled by a recessive gene in double dose, and in fact I wrote a paper summarising the evidence (Genetics of diabetes mellitus. *Diabetes* 1961;10:175-7). Now, as everyone knows, the disease is the result of autoimmune mechanisms with an environmental trigger—a virus. Ergo, why not try giving a short course of immunosuppressive drugs to halt the disease in its tracks? A Workshop was held in Bethesda on 23 May 1983, when the matter was discussed in detail and many differences of opinion aired. Some thought that further trials on human beings were premature, others that they were justified (at major centres). All agreed, however, that immunosuppressive therapy should be regarded as an experimental procedure, and the big danger is that the major damage has occurred by the time of diagnosis and that there is no certain way of diagnosing the disease in the prodromal period.

The Workshop is well summarised in the reference given.

EXPRESSION OF RECESSIVE ALLELES BY CHROMOSOMAL MECHANISMS IN RETINOBLASTOMA (Cavenee WK, *et al.* *Nature* 1983;305:779). LEADER. RETINOBLASTOMA AND RECESSIVE ALLELES IN TUMORIGENESIS (Gilbert F. *Nature* 1983;305:761)

It is generally agreed that retinoblastoma of both eyes is always inherited, while the unilateral form is generally sporadic. Kitchin and Ellsworth writing in this Journal (1974;11:244-6) added to existing knowledge by showing that the bilateral form was associated with malignancies elsewhere, particularly osteogenic or fibrosarcomata.

In the paper and leader referred to in *Nature* much

new information is presented. Thus, the condition results from a mutant allele involving band q14 on chromosome 13 and this produces a susceptibility to the tumour. For the cancer to be manifest, homozygosity at the locus has to occur, and this may happen in various ways. Only one 'hit' is necessary in the inherited form because the mutant allele is already present.

Assuming that two gene changes are required for tumour formation, and that one of those changes involves the locus at q14 on one chromosome 13, then the second gene change could occur either in the gene already carrying the first 'hit' or in a completely different gene in the genome or in the homologous locus on the other chromosome 13. Evidence in support of the third possibility has recently been presented by several laboratories and the studies take advantage of the close linkage between the retinoblastoma locus and that of the enzyme esterase D, plus the development of a library of DNA fragments specific for 13q which reveal restriction fragment length polymorphisms (RFLP) along chromosome 13. The RFLP make it possible to distinguish between the members of a pair of chromosomes 13 in the cell line. Several examples are given, and the authors conclude that the tumour may result from the development of homozygosity for the mutant allele. The research has broader implications and these are discussed particularly in the leader.

REMISSION OF ESSENTIAL HYPERTENSION AFTER RENAL TRANSPLANTATION (Curtis JJ, *et al.* *N Engl J Med* 1983;309:1009). LEADER. RENAL DYSFUNCTION IN ESSENTIAL HYPERTENSION (*N Engl J Med* 1983;309:1052)

Essential hypertension has by definition no known cause, but there is some evidence that it has a genetic basis. In this paper (and there is also a leader) the authors report on the remission of essential hypertension in six patients after renal transplantation. All the sufferers were black and had end stage renal disease, and in five of the six the hypertension persisted after removal of their kidneys, but before transplantation, while they were on dialysis. After receiving transplants from normotensive donors the patients themselves became normotensive and have remained so for from 1 to 8 years, with normal renal function.

These findings are highly suggestive of a kidney lesion being the primary cause of the condition. There are parallels in rats, where spontaneously hypertensive animals can also be corrected by transplantation of a kidney from a normotensive donor. Therefore geneticists should concentrate on a renal cause for essential hypertension in man.

COLLAGEN AND INHERITED CONNECTIVE TISSUE DISEASES (Sykes B. *Nature* 1983;**305**:764)

This is a review of a meeting on osteogenesis imperfecta and the emphasis is on gene probes and their usefulness in testing the hypothesis that collagen structural genes are the sites for mutant loci. As might be expected, there are different forms of the disease depending on the types of collagen involved, and the severity of the effects of mutants can on occasion be surprisingly mild—for instance in one case where the patient failed to incorporate pro- $\alpha 2(1)$ precursor chains into mature type 1 molecules—but presumably there were compensatory mechanisms.

Dr Sykes concludes that most “delegates left the

meeting optimistic that the disease loci have been identified and that the effort of many laboratories will one day be rewarded by a unified theory whereby collagen structural gene mutations will explain first the biochemistry, then the complex clinical and genetic pictures of these crippling diseases”.

Agreed, but can the experts give some thought to common—and non-crippling—collagenoses, Dupuytren's contracture for example, and help the clinician over the rag-bag of Marfan's syndrome, particularly with the ‘Marfanoid’ patients which we not infrequently see at out-patients?

C A CLARKE