sented as a fetus at 32 weeks of gestation with polyhydramnios and enlarged cerebral ventricles. The child was born two weeks later by cesarean section and required mechanical ventilation for the first 24 hours of life. In the neonatal period he was markedly hypotonic and difficult to feed. A CT scan of his brain at this time confirmed the enlargement of the cerebral ventricles, which is consistent with hydrocephalus. Over the first year of life his developmental progress was extremely poor and at the age of 20 months a metabolic screen showed the presence of fumarate in his urine. It was then noted that his older brother was then investigated at the age of 41 years and also found to have increased urinary fumarate excretion. He also had a remarkably similar peri- and neonatal history with polyhydramnios, hydrocephalus, and delayed development. In addition he had myoclonic epilepsy and hyspsarrhythmia on EEG. Enzyme analysis of the leucocytes of these boys, their parents, and normal sib confirmed the diagnosis of fumarase deficiency. Five previous cases of fumarase deficiency have been described; the common features are of a severe, early onset, and usually fatal course marked by developmental delay and infantile spasms. The unique features in these cases are the enlarged ventricles and polyhydrodramnios. These cases point once again to the breadth of the ‘metabolic phenotype’ and show how important organic acids are in the investigation of unexplained mental handicap.

DAVID FITZPATRICK

Presymptomatic testing for Huntington’s disease in the United Kingdom


The authors present this evaluation on behalf of the UK Huntington’s Disease Prediction Consortium. They believe that they have virtually complete ascertainment of completely affected siblings in this sample. Data from 248 subjects were analysed. The risk of carrying the HD gene was reduced for 151 (61%) of the applicants and raised for 97 (39%); 158 (64%) of the subjects were female and 90 (36%) male. The median age at which results were communicated was 32.5 years. The demand for testing was lower than expected and may have reached its peak in 1990. The excess of false risks was not fully explained by the age effect, and might be partly explained by exclusion from testing of those with abnormal neurological signs or current mental illness. Exclusion was based on the exclusion criteria, or by self selection of those without prodromal symptoms. Almost two-thirds of those choosing presymptomatic testing were female and this probably reflects greater maternal involvement in reproductive decision making, or concern for existing children at risk, or both. Seven teenage females went ahead with testing, but no teenage males did. The availability of pooled DNA from all UK HD centres, which individually have only a few results, will form a valuable resource for monitoring the long term psychosocial impact of testing.

ANDREW NORMAN

Of mice and men: genetic skin diseases of keratin


This paper reviews the evidence for keratin defects in genetic skin diseases. Evaluation of network formation in cultured keratinocytes which have been transfected with mutated keratin genes and of filament assembly in vitro have shown the α helical rod domain of these intermediate filaments (IF) to be vital for correct assembly. Some of these IF mutants act in dominant negative manner with the mutant proteins interacting with the wild type proteins to disrupt the IF structure. The in vivo effect of mutant keratins has been shown in transgenic mice expressing mutant keratin genes. For example, mice expressing mutant K14 genes show features of epidermolysis bullosa simplex (EBS). Furthermore, the severity of the disease correlates with the mutation type and the extent to which it disrupts the IF assembly. Mutations in the rod domain of the K14 and K5 genes have now been identified in patients with the two severest forms of EBS. Expression of another mutated keratin, K5(K10) in transgenic mice results in features typical of genetic skin disease epidermolysis hyperkeratosis. These findings are extremely interesting. Not only do they elucidate the genetic basis of some skin diseases but also help show the possible function(s) of these ubiquitous proteins. Investigation of the role of IFs in other similar skin diseases may prove very worthwhile.

N S THAKKER

Recombination of 4p16 DNA markers in an unusual family with Huntington disease


Despite the fact that the Huntington’s disease (HD) gene was localised to chromosome 4p16 nearly a decade ago, the gene has still not been identified. Indeed there is still no single consistent hypothesis for its position in 4p16. Some recombination events place the gene between D4S10 and D4S168, a region of 2.5 Mb, while others suggest a more telomeric location. In this paper Pritchard et al have studied in detail a family with HD in which a recombination has previously been reported in support of the telomeric location. However, they have now used a polymorphic marker that is within 80 kb of the telomere and found that the non-HD haplotype has extended at least as far as this in the two recombinant affected subjects. The recombination identified is in the 16 cM interval between HOX1/D4S229 and D4S144, a region well centromeric of the most likely HD location. The authors have been meticulous in confirming the diagnosis and paternity and excluding sample error or visible chromosome rearrangements. The disease haplotype had been established using 18 subjects in the nuclear family. They ensured phase was correctly assigned by making somatic cell hybrids containing only one chromosome 4 from each subject in the nuclear family. Unless there are further recombination events in this family that have not been identified, the disease locus in this family could be within 80 kb of the telomere, proximal to D4S229 or, more worryingly, not on chromosome 4 at all.

JUDITH GOODSHIP

Value of routine ultrasound scanning at 19 weeks: a four year study of 8849 deliveries


In a previous abstract I summarised the findings of a retrospective study by Chitty et al, which reported the effectiveness of routine ultrasound in detecting fetal anomalies in an unselected population, and indicated a need for prospective studies. Carole Luck has now reported such a study. All pregnant women in a district general hospital were offered a fetal anomaly scan at 19 weeks’ gestation and 8523 of 8849 (96%) accepted. A total of 166 fetal anomalies occurred; 140 were detected at 19 weeks (sensitivity 85%, specificity 99.9%). In 27 cases fetuses were shown to have severely crippling or lethal abnormalities; termination of pregnancy was requested in 25. Early diagnosis influenced the timing and place of delivery in babies with severe cardiac or gastrointestinal anomalies. Four false positive diagnoses occurred, but none led to termination. False negative diagnosis of a neck mass, for example, did not prevent the diagnosis of a more severe lesion. In 8 cases of facial anomalies some of which had fatal outcome in the neonatal period. It was concluded that scanning at 19 weeks with availability of termination can reduce perinatal morbidity and mortality. The need for adequate counselling facilities and close cooperation between the professionals involved was stressed.

ANDREW WILKIE

ANDREW NORMAN