careful counselling the parents decided to proceed with prenatal diagnosis and a chorion villus biopsy was performed. A high risk result was obtained and the pregnancy terminated. This case represents the first prenatal diagnosis for VHL disease. Although prenatal diagnosis for VHL disease is now available, the likely demand is uncertain.

Molecular genetic analysis of spinal muscular atrophy

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The spinal muscular atrophies (SMA) are a group of inherited disorders characterised by degeneration of the anterior horn cells of the spinal cord. The acute and chronic childhood onset forms show autosomal recessive inheritance, and have been mapped to 5q12–q13.3 by linkage analysis. We have established a service for prenatal diagnosis of the early onset (types I and II) forms of SMA, using three linked polymorphic DNA markers (*D5S6*, *D5S112* and *D5S39*). In all 13 families studied, both parents were heterozygous for at least one marker, and both were heterozygous for flanking markers in three out of 13 completed linkage studies. Prenatal diagnosis was carried out for three pregnancies at risk for SMA type 1. The risks to the fetuses were calculated to be 5·6%, 5·9%, and 6%, using MLINK, and all three families elected to continue the pregnancy. One pregnancy spontaneously miscarried at 22 weeks and the others are continuing. The service is being restricted to confirmed classical early onset SMA at present, in view of possible genetic heterogeneity in later onset and atypical forms.

Prenatal hearing tests

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Diagnosis of deafness is problematical in newborn and young infants. It is realised, however, that compensatory communication behaviours are best instigated as soon as possible, preferably at or immediately after birth. A technique which enables the diagnosis of deafness before birth would thus be extremely valuable. This paper reports the successful detection of deafness before birth. Prenatal diagnosis of deafness has to overcome the problem of false positive results, in particular owing to the fetus being in a non-responsive behavioural state. Here we report that a combination of sound and light stimulation can overcome this problem and has been used to detect deafness successfully in two cases. Furthermore, use of pure sound and vibratory stimuli may enable the differentiation of conductive and sensorineural deafness. The quickness and ease of use of the technique means that it could be used as a general screening procedure in cases where deafness resulting from genetic factors or environmental insult, for example, rubella, is suspected.

Trisomy 18: anomalous fetal behaviour

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This paper discusses the movement patterns of a 34 week fetus diagnosed as trisomy 18 and compares this to movement patterns of similarly aged normal fetuses. This fetus exhibited a number of differences in its behaviour not seen in the normal fetus. The gross movements of this fetus were highly abnormal involving rotation about its longitudinal axis. Its single eye movements showed the complete reverse pattern of those seen in normal fetuses, the majority of eye movements being in the vertical plane. The cyclic activity of the fetus also differed from that usually seen; the characteristic burst/pause pattern of normal fetuses was not observed. The paper concludes that this anomalous behaviour may be a useful marker for the presence of trisomy 18 and may indicate the necessity for further genetic investigations.

A comparison of three cytogenetic measures of chromosome instability in ataxia telangiectasia

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Seven families with eight members with ataxia telangiectasia (AT) and one case of Nijmegen breakage syndrome were investigated to compare three different cytogenetic methods of assessing chromosome instability. Original diagnosis was based on clinical phenotype and increased irradiation sensitivity as assessed by a reference laboratory. Cytogenetic preparations were made from peripheral lymphocyte cultures set up from 10 controls and 19 family members. The preparations were scored for the following: (1) spontaneous rearrangements, particularly involving chromosomes 7 and 14, (2) chromosome aberrations following X irradiation in G2 phase of the cell cycle, (3) chromosome aberrations induced by the chemical mutagen adriamycin in G1/S phase of the cell cycle. All methods were found useful, with no overlap between controls and AT patients. However, the range of values suggests that each test might not always provide clear diagnosis on its own. Spontaneous rearrangements were detected at a mean level of 12% in AT patients (range 6 to 32) compared with 0·3% in the controls (range 0 to 2). X irradiated AT cases (100 cGy) had a mean number of aberrations per cell of 1·03 (range 0·6 to 1·65) compared with control levels of 0·19 (range 0·15 to 0·45). Adriamycin treated AT patients (0·01 μg/ml) gave a mean number of 2·52 aberrations per cell (range 1·1 to 4·15) as compared with a mean of 0·35 in controls (range 0·25 to 0·65). These results suggest that sensitivity to adriamycin might be a useful additional diagnostic test for AT, especially if X irradiation is difficult to arrange. Scoring of chromosomal aberrations is a valuable and available screening test for ataxia telangiectasia, but at least two methodologies should be used for definite diagnosis.

Eight cases of 7p deletion: clinical features, cytogenetic findings, and molecular studies

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Craniosynostosis or premature closure of the cranial sutures is a common malformation occurring in approximately 1 in 2000 children. To date more than 20 cases of partial 7p monosomies have been described, approximately half of which have been associated with craniosynostosis. There is considerable variation in the size and location of the deleted segment. However, craniosynostosis appears to be consistently associated with either a deletion or partial deletion 7p21–7p22 or a deletion of 7p13–7p14. Analysis of a panel of eight 7p deletion cases (three with craniosynostosis) was undertaken using informative DNA probes, in order to characterise and define the extent of the deletions at the molecular level. There were six de novo deletions, one de novo unbalanced translocation, t(7p;20p), resulting in an interstitial 7p deletion, and one 7p deletion resulting from the unbalanced product of a paternal unbalanced insertion. Parental DNA was available for analysis in four out of six de novo deletions; in two the deletion was found to be of paternal origin, and in two parental origin could not be determined. The results of the DNA studies, together with a summary of the relevant clinical and cytogenetic findings, are presented. Our findings have enabled us to refine the regional localisation and relative position of five probes and two loci. (1) pJ5–11, previously mapped to 7p14–pter, does not extend proximally to p14 as case 4 (del 7p13–p15) is heterozygous for this probe. (2) TM102L, previously mapped to 7p14–pter, does not extend proximally to p14 or terminally to pter, as case 7 (del 7p15–p22) is deleted for this probe and heterozygous for MS31 (pter). (3) CRI-R944 and CRI-P137, assigned to 7pter–q22, have previously been shown to be tightly linked and to flank the Greig-cephalopolysyndactyly (GCPS) translocation breakpoint. However, case 3 (del 7p13) is deleted for CRI-R944, but heterozygous for CRI-P137, indicating that these two probes are not 0 cM apart and that CRI-R944 is restricted to 7p13 only, whereas CRI-P137 maps more distally. (4) TCRG, previously mapped to 7p15, maps more proximally, as case 2 (del 7p12.2–p14.2) is deleted for this probe, but case 3 (del 7p13) is heterozygous. This suggests that the TCRG gene is located at 7p14.1–p14.2. (5) As craniosynostosis is an occasional feature in GCPS it has been considered possible that the CRS2 and GCPS loci were one and the same, but the results of case 4 (del 7p13–p15) suggest that they are distinct. Cases 6 (del 7p15–p21.2) and 8 (del 7p22.1–pter) do not have craniosynostosis and therefore the

CRS1 locus is most likely to be in 7p21.2 or 7p21.3. Case 8 is also heterozygous for the probes shown to be deleted in cases 5 (del 7p15–p21.2) and 7 (del 7p15–p22).

Trisomy 22: in situ hybridisation and molecular studies

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We present a case of a baby girl with the following clinical features: micrognathia, cleft lip, broad nasal bridge, ocular ptosis, epicanthic folds, preauricular pit, posteriorly rotated ears, short neck, widely spaced nipples, hypoplastic nails, and joint contractures. Birth weight and length were below the 3rd centile. The baby died at 8 months of age. Cytogenetic studies using GTL banding of lymphocytes and skin fibroblasts showed a chromosome complement of 47,XX,+22. This finding was confirmed using in situ hybridisation with a chromosome 22 library (pBS-22). DNA samples from both parents and the affected baby were analysed with a minisatallite probe pMS619, which recognises a VNTR polymorphism. The baby inherited three alleles, two identical to the two maternal alleles and one identical to that of the father. We therefore surmise that nondisjunction occurred during maternal meiosis. Trisomy 22 is the second most frequent autosomal trisomy detected in spontaneous abortions but only a handful of cases of liveborn infants have been described.

Assessing the utility of fibroblast karyotyping

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A request for a fibroblast karyotype represents a significant and expensive cytogenetic investigation. In the light of an increasing demand for this investigation over the last several years an analysis of the previous five years of skin chromosomal analysis was undertaken in an attempt to evaluate its success in the clinical setting. Each request was classified with respect to the blood and skin karyotype into one of six classifications: blood normal/abnormal/equivocal versus skin normal/abnormal. A total of 54 requests from live (non-moribund) subjects was received over this time period. Of these 10 were reported as abnormal (18·5%) when a previous blood karyotype had been normal. This compared favourably, for a second line investigation, to the mean over a similar time period of 13·7% abnormality rate for blood samples processed in the laboratory. This audit suggests that the currently used criteria of pigmentary anomalies and asymmetry in association with dysmorphism, mental retardation, or abnormal genitalia are adequate in deciding whether to proceed to a skin biopsy in order to exclude a chromosomal aetiology.

Behavioural Science and Genetics Group

JOSEPHINE M GREEN AND OTHER MEMBERS OF THE BEHAVIOURAL SCIENCE AND GENETICS GROUP

UK – nationwide.

Since January a group of social scientists including psychologists, sociologists, and health economists with interests in genetics, as well as a clinical geneticist, has been meeting informally, approximately three times a year. The group exists primarily to allow its members to keep up to date with each other's research and to exchange ideas and information. A secondary aim is to inform non-social scientists of research on social and psychological aspects of genetic screening and related issues. Aside from meetings we have organised joint symposia, written some joint papers, and conducted some research together. Some members of the Group were invited to give presentations at the recent MRC Workshop on cystic fibrosis carrier screening. Future plans are to hold a symposium for geneticists and behavioural scientists to consider both the structure and content of future collaborative work.

Patient satisfaction: a pilot study

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A postal questionnaire was sent to a sample of families attending the Genetic Counselling Clinic in late 1990. Forty families responded (77%); 90% were very satisfied while the remaining 10% were satisfied most of the time. Many respondents commented on the caring, courteous, and friendly attitude of the staff. Preclinic visits, in particular, were said to be very helpful (to 94% of families) as well as the time and care taken in explanations. However, 25% of families found the length of time before a clinic appointment to be too long. This study endorses previous findings which identified affective aspects as key determinants of general satisfaction with genetic services.

An autosomal dominant muscular dystrophy characterised by early onset of contractures

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Since Emery and Dreifuss first described it as such, the X linked muscular dystrophy with early contractures and cardiomyopathy has become widely recognised. However, Hauptmann and Thannhauser had described a similar condition with dominant inheritance in 1941. Although not well known, there have been eight case reports since then which have been reviewed by Becker in 1986 and Emery in 1987. This present family has four affected subjects in three generations. It is transmitted by both a male and a female. Although no male to male transmission has occurred, the three females show a similar course to the male supporting autosomal dominant inheritance. Screening of healthy relatives found no evidence of incomplete penetrance. Onset of mild pelvohumeroperoneal weakness occurs at 3 to 5 years and although only slowly progressive (the oldest, 56 years, is still able to climb stairs) is associated with early development of contractures at the Achilles tendons (7 to 12 years) followed by the elbows, cervical spine, and the long flexors of the fingers. One subject has evidence of cardiomyopathy. CK is mildly raised. Biopsy shows mild myopathic changes but muscle ultrasound shows markedly increased echoes in the muscle. EMG is myopathic. When counselling an isolated male with these findings, care should be taken before diagnosing Emery–Dreifuss dystrophy with a low recurrence for children.

An unknown syndrome with brain and bone abnormalities in two brothers

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We describe two brothers born to healthy, unrelated parents with similar abnormalities affecting predominantly the brain and skeletal systems. Both boys were noted to have relatively large heads with soft, poorly calcified skulls and very large fontanelles. The eyes appeared prominent (with congential glaucoma in the second) and there were contractures of hands, feet, and knees, with expanded, flattened tips to the digits. Skeletal surveys showed osteodysplastic changes including delayed maturation, slender, poorly modelled long bones and, in one boy, widespread punctate calcification in epiphyses. CT scan of the brain showed marked cerebellar hypoplasia and cerebral atrophy. Both boys were profoundly handicapped. The older boy died at the age of 17 months having had recurrent chest infections and infantile spasms. His brother is still alive at 10 months.

PKU in south west England: a new mutation in the leader sequence of the phenylalanine hydroxylase gene and more similarity with the French Canadians

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To date, about 40 mutations have been defined at the phenylalanine hydroxylase (PAH) locus which give rise to phenylketonuria (PKU). Some are unique to individual races or ethnic groups and are in linkage disequilibrium with specific haplotypes. Others are more widespread and several have been found on a variety of haplotype backgrounds. We report a CAC to CCC transition in the leader sequence of the PAH gene,