ABSTRACTS OF THE MEETING OF THE CLINICAL GENETICS SOCIETY HELD ON 20 TO 22 MARCH 1991 AT BELFAST CITY HOSPITAL

Linkage analysis of familial expansile osteolysis
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Familial expansile osteolysis (FEO) is a genetic bone dysplasia that is apparently unique to a large family in Northern Ireland. The disorder is inherited as an autosomal dominant trait which results in focal failure of osteoblast/osteoclast homeostasis. Those affected develop progressive expansile and lytic lesions in the limb bones, causing pain, deformity, and pathological fracture. Life expectancy is not reduced, but there is no satisfactory treatment for the disorder. Linkage analysis has been carried out using DNA from 61 members of this pedigree, of whom 35 are affected. Several candidate genes for known bone related proteins have been excluded from causing FEO. These include the genes for collagen type I (COL1A1 and COL1A2 on chromosomes 17 and 7, respectively), osteonectin (chromosome 5), bone alkaline phosphatase (chromosome 1), and the met and rbi oncogenes (chromosomes 7 and 13, respectively) which are associated with osteosarcoma. In addition, approximately 70% of the genome has been excluded.

Genetic linkage analysis in human malignant hyperthermia
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Malignant hyperthermia (MH) is an inherited skeletal muscle condition, in which the administration of inhalational anaesthetics is potentially fatal. Susceptibility to MH can be accurately predicted by the in vitro stimulation of muscle biopsy material. Irish and North American family studies have implicated chromosome 19; the ryanodine receptor and the hormone sensitive lipase loci on 19q12–13.2 have both been suggested as candidates for the MH locus. We have undertaken genetic linkage analysis of three generation families previously investigated at the Leeds MH Unit, which is the UK reference centre. Members of these families were typed unequivocally using the European diagnostic criteria for MH. Three of these families all yielded positive lod scores for chromosome 19 markers (Zmax=2.1 at θ=0.05 for Mfd9 (D19S47) and Zmax=1.2 at θ=0.20 for Mfd5 (APOC2)). There is therefore no evidence for genetic heterogeneity as yet, but a wider range of clinical and geographical material must be examined before routine DNA presymptomatic testing can be considered valid.

A de novo point mutation causing human 21-hydroxylase deficiency: evidence for a gene conversion event
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We have previously reported a family with 21-hydroxylase deficiency with two HLA identical brothers, one affected and the other unaffected. Short and long range restriction mapping has shown that the boys both carry a deletion of the CYP21B gene on their paternally derived haplotype. We have therefore used a PCR sequencing method to compare the single maternally derived CYP21B gene in both subjects. Sequence analysis has shown the presence of a missense mutation, previously defined as pathological, in the affected boy but not in his brother. Further PCR sequencing and ASO hybridisation has shown that this mutation is not present in either of the mother's CYP21B genes, but is present in both of her CYP21A pseudogenes, suggesting a gene conversion-like origin. Analysis of sequence flanking this mutation in the mother's pseudogenes and the affected boy's CYP21B gene suggests a conversion event involving between 1 and 390 bp. These results represent the first report of a de novo point mutation causing 21-hydroxylase deficiency and the most direct evidence to date for gene conversion in man.

Evidence for linkage of hereditary hydronephrosis to the MHC on chromosome 6p
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Prospective study of first degree relatives of affected patients with pelviureteric junction obstruction has suggested that at least one third to one half of pelviureteric junction obstruction is familial (Atwell, 1985). Twenty-two families have now been described with hereditary pelviureteric junction obstruction in a pattern consistent with autosomal dominant inheritance but with variable expression and incomplete penetrance (MIM 143000). Two point linkage analysis was undertaken in four families with hereditary pelviureteric junction obstruction using the MHC locus as a test marker and was carried out with the linkage program LIPEPD 3 using a disease allele frequency of 0.001 and with penetrance of 100% and...
90%. Family 1 is a three generation family in which well documented unilateral hydronephrosis was present in the grandfather, the father, and two sons (Paramo et al., 1991). Families 2 and 3 were reported by Buscemi et al. (1985). Family 2 is a two generation family with two sibs affected. Family 3 includes a woman with two marriages and two affected and two unaffected offspring from each healthy partner. Family 4 was reported by Sengar et al. (1979) and is a two generation family with five out of 13 sibs affected. Maximum lod scores were 3.9 at a recombination fraction of 0.05 with full penetrance and 4.26 at a recombination fraction of 0-0 with a penetrance of 90%. These data provide evidence for assignment of the locus (or loci) for hereditary puvlerueteric junction obstruction to chromosome 6p. The routine management of patients with puvlerueteric junction obstruction should include scanning of relatives and genetic counselling using empiric recurrence risk as these become defined.

A linkage study of X linked hereditary motor and sensory neuropathy (HMSN) with M27β
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Previous studies of X linked HMSN have shown linkage of the disease locus to loci mapped to the centromeric regions of Xp and Xq. In a large Scottish family, Haites et al found linkage to PGK1 (Xq13) and DXYS1 (Xq21.31). Fischbeck et al., studying a large X linked family from North Carolina, showed linkage to the loci defined by the probe 581 (DXS14 at Xp11.21) and p8 (DXS1 at Xq11–q13) both with recombination frequencies of 0.05. In an attempt to define more closely the position of the gene, we have studied these two large X linked families with the highly informative, polymorphic probe M27β. In both families, the number of phase known females with informative meioses was greatly increased compared with the above probes. In the Scottish family, the maximum lod score was 6.27 at θ=0.1 showing definite linkage. The larger American family gave a maximum lod score of 2.59 at θ=0.15. This lower score was partially because of the structure of the family and the number of subjects in whom clinical status was unknown. The combined lod score of 8.61 and θ=0.15 would suggest, as previous work has indicated, that the X linked HMSN locus is more likely to be well distal to Xp11.22 and probably between the centromere and Xq13.

Localisation of the gene for X linked anophthalmos to Xq27–28
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Anophthalmos is a very rare condition characterised by developmental failure of the optic vesicle and cup. The majority of cases are the result of new mutations, cytogenetic abnormalities, or damage during embryonic development. The prevalence of these disorders is about 1/100 000. We report on a Northern Ireland family with seven anophthalmic males in two generations. Male to male transmission has not occurred and this family shows X linked recessive clinical anophthalmos. There are four affected males, seven normal males, and three obligate female carriers available for linkage analysis. Multipoint linkage analysis, with Xp markers, Xq, XJ1, 754, and M27β has excluded the disease from most of the short arm of the X chromosome. However, with distal Xq markers DX13 and factor 8, only one recombinant in 11 males was noted, giving a maximum lod score of 1.9 at θ=0.08. Multipoint analysis was carried out using the probes p6a1, Cx33.2, DX13, and F8 and the LINKMAP program from LINKAGE vs 5.04. Two location score peaks were detected, one of 7.7 just proximal to DX13 and one of 7.2 just distal to F8. Thus it is likely that the anophthalmos gene is localised in the Xq27–28 region, distal to Cx33.2 and not between DX13 and F8.

Schizophrenia in the Afro-Caribbean community: a family study
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The incidence of schizophrenia in the Afro-Caribbean community in Britain is three to six times higher than for the indigenous population. Rates are particularly high among younger people born in this country. The cause of this apparent epidemic is not known, but it has been suggested that British psychiatrists are wrongly applying the diagnosis to unfamiliar, culturally determined patterns of behaviour.
induced by stress. Previous research has shown that genetic factors are important in the aetiology of schizophrenia. We have therefore used a standardised family history method (FH–RDC) to compare the first degree relatives of 36 Afro-Caribbean and 39 native Caucasian patients treated for schizophrenia in Central Manchester between 1982 and 1988. Lifetime morbid risk was 9-0% for parents of Afro-Caribbean subjects and 8-4% for parents of Caucasian subjects. These observations suggest that schizophrenia among Afro-Caribbeans is no less familial than for the general population. The risk for sibs of Afro-Caribbean probands was 16-2%, compared with 1-8% for sibs of native subjects (p<0-05). Sibs of UK born Caribbean probands had even higher morbid risks (27-3%). These data are consistent with a similar degree of genetic predisposition in both ethnic groups, interacting with an environmental precipitant which is more prevalent among young people of Afro-Caribbean origin.

Detection of allele loss in ovarian cancer
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DNA has been analysed from 44 ovarian tumours, of which 22 were malignant and 12 were of borderline malignancy. Using a panel of chromosome 17 probes, tumour and normal DNA have been compared in a ‘loss of heterozygosity’ study. All malignant tumours proved to be informative for at least two of these chromosomal markers, indicating allele loss as shown below.

<table>
<thead>
<tr>
<th>DNA probe</th>
<th>No of tumours showing loss</th>
</tr>
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<tbody>
<tr>
<td>pYNZ22</td>
<td>(17p13.3) 12/22 (55%)</td>
</tr>
<tr>
<td>pYNH37.3</td>
<td>(17p13.3) 1/1 (100%)</td>
</tr>
<tr>
<td>pMCT35.1</td>
<td>(17p13.1) 4/8 (50%)</td>
</tr>
<tr>
<td>pBHP53</td>
<td>(17p13.1) 2/9 (22%)</td>
</tr>
<tr>
<td>pTHH59</td>
<td>(17q23–qter) 10/17 (59%)</td>
</tr>
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</table>

None of the benign or borderline tumours was seen to lose alleles at these loci, apart from one benign tumour which appeared to have lost a copy of pBHP53. Work has also been started to assess the allele loss status for chromosome 18 using DDC probes in the same tumours. Loss of chromosome 18q material has been found to be common in other cancers, including breast and colon cancer. Preliminary results suggest that allele loss is low in our sporadically occurring tumours. Significantly, however, we have detected DCC allele loss in a familial ovarian and a familial breast tumour, which are both from a large breast/ovarian cancer family. It will be important to ascertain if a germline mutation in the DCC gene is segregating with predisposition to tumour formation in this family.

Familial adenomatous polyposis coli (FAPC) and mental handicap in two generations owing to recurrent deletions resulting from a chromosome 5 rearrangement (ins(5)(q31.3q22q23.2))
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The proband, a mildly retarded adult male, presented with a duodenal adenoma and was then found to have polyps on colonoscopy. At colectomy there were microscopic polyps throughout the bowel though none was visible in the descending colon. Her mother had died and had been handicapped. Her parents were normal but a sister was retarded and on examination also had FAPC. Both affected subjects had multiple areas of congenital hyper trophy of the retinal pigment epithelium (CHRPEs) and a deletion of 5q22–q23.2. A normal aunt of the proband was found to have this segment inserted at 5q31.3. This arrangement requires a double insertion loop. Cross-over within the loop had produced the deletion in two family members. In situ hybridisation showed both copies of ECB27 to be present which placed the proximal break between this marker and the APC gene. Comparison with the two other deletion cases indicates the APC gene is within band q22.

Gene probe analysis in MEN 2A: early exclusion, diagnosis, and treatment
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Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant genetic disorder consisting of medullary thyroid carcinoma, adrenal tumours, and parathyroid adenomas. Analysis using the markers TB10.163, RBP3, and TB14.34, flanking the MEN 2A gene locus on chromosome 10 has been undertaken in a four generation kindred with ages ranging from 1 to 90 years, in which several members are affected. Penetrance and age of onset vary considerably in this condition and early undetected tumour metastasis may result in early patient death. Results in all four generations of the family allow carrier risks originally based only on basal serum calcitonin studies to be significantly altered by the use of the gene probe data; this allowed early diagnosis of two affected patients under 20 years old in generation IV and exclusion of 11 patients from all four generations from having the disease. This facilitates early surgical treatment and may prevent early tumour metastasis, and allows excluded patients to be discharged from review clinics.

Dystrophin abnormality in autosomal recessive Duchenne-like muscular dystrophy

The second of two daughters of consanguineous Sinti parents with no family history presented with proximal muscle weakness at 5 years of age. The symptoms have progressed ever since: at 9 years her clinical picture is typical of (Duchenne) muscular dystrophy with generalised muscular wasting with pelvic and shoulder girdle predominance, pseudohypertrophy of the calves, and Gower's sign. Humoral, EMG, and biopsy findings are indicative of (DMD). A normal karyotype excludes chromosomal anomalies as a

Molecular studies have failed to identify an anomaly of the dystrophin gene. Immunofluorescence showed generalised, somewhat patchy presence of dystrophin in decreased amount. Western blot analysis showed a normally migrating dystrophin band of markedly reduced quantity as compared with controls. Thus, both dystrophin findings resemble those in hemizygous patients with Becker muscular dystrophy. This contrasts with the clinical severity of the myopathy. Non-invasive investigations of the parents so far have not detected any related abnormality. Differential diagnosis must consider autosomal recessive (Duchenne-like) muscular dystrophy (ethnic origin of the family), a severe case of limb girdle muscular dystrophy, and overlooked tissue hemizygosity from XX/XY mosaicism. The dystrophin findings will be discussed in relation to these alternatives taking into account the recent identification and mapping of autosomal DNA sequences with pronounced dystrophin homology (Buckle et al, Hum Genet 1990;85:324-6).

Becker muscular dystrophy: correlation of phenotype, gene, and protein

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Now that it is possible to identify deletions in the dystrophin gene and to quantify dystrophin abnormalities in muscle samples by immunoblotting, the phenotype of Becker muscular dystrophy (BMD) can be correlated with the molecular defect at both the gene and protein level. We have assessed 66 patients with BMD according to a detailed protocol, including a full history, functional and muscle examination, DNA analysis, and dystrophin analysis. This has allowed a redefinition of the course of the disease in a large cohort of patients, including 37 sporadic cases in whom the diagnosis could not previously have been confirmed. Two groups emerged from graphs of functional and muscle score against age. The larger group (57 patients) had relatively mild disease (average age of becoming wheelchair bound 58 years). All the deletions detected in this group were in the area of exons 45 to 54 of the dystrophin gene. The dystrophin in these patients was of reduced size, inversely proportional to the amount of coding sequence lost, and of variably reduced abundance (30 to 97% of control) with the presence of a characteristic 'gradation band'. Three patients in this group had no cDNA deletion and a full sized dystrophin molecule produced at reduced abundance. None of the nine patients in the severe group (average age of becoming wheelchair bound 26 years) had a deletion or dystrophin pattern similar to those seen in the typical group. This group was more heterogeneous clinically and at both the gene and protein level, with the genetic defects seen including no detectable cDNA deletion, a very large in frame deletion, and a duplication. We conclude that the majority of patients with BMD follow a relatively mild clinical course and that this phenotype is often associated with characteristic deletion and dystrophin patterns.

The value of routine ultrasound for the detection of fetal abnormalities

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Prenatal ultrasound can detect many fetal malformations about 90% of which occur in fetuses born to parents with no recognisable risk factors. While there is much evidence to suggest that routine ultrasound screening in the second trimester improves the diagnosis of multiple pregnancies and the estimation of the expected date of delivery, there are few data available on its use for routine screening for congenital malformations. We will discuss the results of our routine fetal ultrasound programme at Luton and Dunstable Hospital which is a district general hospital where about 4400 women are delivered annually. All women who book early enough for prenatal care are offered an ultrasound scan at between 18 to 20 weeks' gestation to confirm fetal viability and gestational age and examine the fetal anatomy. All scans are performed by radiographers who have between one and 10 (average two) years’ experience of obstetric ultrasound. Examination includes measurement of the biparietal diameter, head circumference, and femur length and careful inspection of the fetal head, intracranial anatomy, spine, heart, diaphragm, stomach, anterior abdominal wall, kidneys, bladder, and limbs. If at the first examination the fetus is found to be less than 18 weeks or there is difficulty in completing the examination satisfactorily, the woman is asked to attend for a second scan. When an abnormality is detected the findings are discussed with the obstetrician and parents and, in selected cases, the woman is referred to a tertiary centre for confirmation of the anomaly and further investigations or management as necessary. We have reviewed this policy over a two year period starting from January 1988. Outcome was confirmed by inspection of the neonatal notes or pathology reports. A computerised record is kept of all neonatal abnormalities detected before infants leave hospital and this was inspected for any abnormalities which were not detected prenatally. A total of 8733 infants was born during the period of the study. Approximately 95% were examined with ultrasound in the second trimester. Fifty-two pregnancies were terminated after the identification of a fetal malformation. Of the fetuses which were examined in the second trimester, 124 had a significant structural abnormality confirmed at the end of pregnancy. In 92 (74-2%, 95% CI 67-7 to 80-4) cases the abnormality was diagnosed with ultrasound before 24 weeks. Of the 124 abnormalities, 65 were lethal or severely crippling. Fifty-six of these were detected by the routine screening programme (sensitivity 87-1%, 95% CI 79-3 to 94-9). Of the 8609 normal fetuses there were four false positive diagnoses, all resulting in the birth of an apparently normal infant. This gives a specificity of 99-95% (95% CI 99-93 to 99-97). We conclude that routine fetal ultrasound examination in a low risk population detects many fetal malformations but it can present several dilemmas in counselling.

A prospective trial of prenatal screening for chromosome abnormalities using maternal serum hCG and AFP levels
ductus arteriosus, five (15%) isolated ventricular septal defects, and three (9%) complex CHD. Clinical examination alone was an insensitive test for CHD (0-51) but this was improved when CXR and ECG were added (sensitivity 0-71, specificity 0-91). ECG was highly specific for CHD but lack of experience in interpretation may reduce its effectiveness. In centres where surgery is offered for CHD in Down's syndrome early detection and follow up of heart defects is important, in order to minimise the risk of later presentation with, for example, pulmonary vascular disease. We recommend that all Down's syndrome babies have an echocardiograph in early postnatal life.

Carrier testing for CFTR gene mutations in relatives identified through a cystic fibrosis prenatal testing service: response rates and determinants of uptake

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The identification of the common mutations in the CFTR gene have paved the way for the introduction of population based cystic fibrosis (CF) carrier testing. The acceptability and response of the general population to carrier testing for this common genetic disorder is unknown. We have surveyed a group of subjects, identified through relatives with detectable mutations of the CFTR gene, and who are at greater than the population carrier risk for CF. Between 1986 and early 1990, the Regional Genetic service counselled and provided prenatal testing for CF in 74 couples. All contactable subjects in this cohort, 115 (83%), with a detectable mutation were notified by letter. In addition they were invited to provide details of those close relatives whom they believed may wish to have CF carrier testing. Replies were received from 61 (53%) of index cases, with 51 subjects nominating a total of 93 relatives. Thirty-nine have accepted the offer of carrier testing; 16 were minors, in whom carrier testing has been deferred. Determinants for screening included anxieties arising in a current pregnancy, personal or offspring health concerns, and family pressure.

Mutation analysis in the CFTR gene in Northern Ireland and genotypetype:phenotype comparisons

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Cystic fibrosis patients in Northern Ireland are now routinely screened for a series of mutations in exons 4, 10, and 11 of the CFTR gene, with an overall mutation detection rate of 74%. Exon 10 mutations, AF508 and AI507, account for only 57% of CF mutations in this region. The exon 11 mutations, G551D, G542X, and R560T, together account for almost 13% of mutations. G542X is found at the same frequency (4%) as in other populations, while R560T (4-1%) is unusually high. G551D occurs at similar frequencies in CF patients throughout Northern Europe (4-7% in Northern Ireland) and is associated with an X1K2 haplotype in 100% of cases here, suggesting that it spread through a founder effect. The exon 4 mutations 556delA and 621 + 1G>T account for 3-3% of CF mutations, the latter being unusually high in this region. We have now identified patients with 12 fully defined mutation genotypes and have started to look for possible relationships between genotypes and disease severity. Clinical details have been collected on 63 patients, 32 are homozygous for AF508 and 31 have other fully defined mutations. These have been divided into three groups: (A) those involving exon 10 mutations only, (B) those with an exon 10 mutation on one chromosome and an exon 11 mutation on the other, and (C) those with an exon 4 mutation on one chromosome and an exon 10 or 11 mutation on the other. The results are summarised below.
Genetic enquiry into medical services. A national confidential enquiry into the quality of genetic diagnosis, risk estimation, and counselling provided by family practitioners and hospital specialists

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Because of rapid scientific advances, public expectations, and resulting workloads, GPs and hospital specialists are taking on genetic counselling and management for which they have usually not been trained. Undergraduate and postgraduate medical teaching in genetics is at best patchy, and often deficient, and will take some time to improve. Following a feasibility study carried out with the help of clinical geneticists, the Royal College of Physicians of London, with the cooperation of other medical Royal Colleges, the BPA, the ACC, CGS, CMGS, GIG, the Department of Health, and others is about to launch a Confidential Enquiry into the way genetic problems are managed by non-geneticists. The Enquiry will be anonymous and non-censorious relying on paediatricians, obstetricians, surgeons, and others to review their own patients' records by comparing them with clinical guidelines in the form of questionnaires for each of the 'marker disorders'. Initially Down's, NTD, cystic fibrosis, haemophilia, thalassaemia, multiple endocrine neoplasia type 2, and FAP have been selected by the Steering Group. Each disorder has a convenor and working group who are currently planning ascertainment and designing questionnaires. The aims are to ensure that those at risk of genetic disease are informed of the options available but eugenic considerations are explicitly excluded and the avoidance of genetic disease by abortion is neither advocated nor rejected. It is regarded as essential, however, that appropriate screening for hereditary cancer should be offered in good time to relatives who may benefit from effective treatment. Regular reporting will include any deficiencies in Health Service provision that are revealed by the Enquiry.

The role of a non-medical genetic counsellor: can the UK benefit from experience in the USA?

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Recent reports on genetic services in the United Kingdom indicate that there is an increasing demand for non-medical genetic counsellors. This is in part the result of the expansion of prenatal diagnostic capabilities, and of the ever increasing possibilities of genetic diagnoses through DNA technology. The role has evolved in the United States over the past 25 years. Training is standardised to include a Master's degree in genetic counselling leading to accreditation by examination through the American Board of Medical Genetics. The majority of graduates are neither nurses nor social workers. There is no structure for career advancement, so future recruitment may be threatened. However, such counsellors have become an integral part of genetic centres supplementing the role of the clinical geneticist, particularly in the prenatal arena. This may in part be explained by the different health care systems in the USA, ranging from the privately insured to the welfare population. There is some concern as to the future of Master's trained genetic counsellors in the USA. The need is proven but it is unlikely to be met unless a better career ladder is developed. The UK has an opportunity to avoid this dilemma by training nurses, public health in particular, to undertake a similar role of genetic counsellor. They could have the advantage of having other recognised skills and an established career structure.

Meiotic segregation in translocation heterozygotes analysed by fluorescence in situ hybridisation

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Carriers of chromosome rearrangements, such as translocations, generally suffer an impairment in reproduction. This reproductive disturbance includes sterility and subfertility, that is, habitual abortion, and an increased risk for intrauterine and neonatal deaths as well as multiply malformed and/or mentally retarded children. The empirical risk may vary enormously between carriers/families, in fact from 1 to 100%. However, it is often impossible to calculate an adequate specific risk for the individual family. Such accurate information is available from the direct study of gametes, or gametogenesis, in a constitutional carrier of a structural rearrangement. We have used the new in situ hybridisation technique of chromosome painting to obtain the required information from human testicular biopsy. By hybridising for a rearranged chromosome it is possible to count the different segregation possibilities in meiotic second metaphase nuclei, so obtaining a prediction of what proportion of gametes would be normal, balanced, or unbalanced.

Mapping cosmid clones using fluorescence non-isotopic in situ hybridisation

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We are using fluorescence in situ hybridisation (FISH) to localise and order cosmid clones on human chromosomes. Cosmid DNA is labelled with biotin or digoxigenin and then preannealed with unlabelled genomic DNA to suppress hybridisation with repetitive elements present in these large (20 to 40 kb) DNA inserts. Specific hybridisation is detected with avidin or antibodies conjugated with fluorescein isothiocyanate or Texas Red, and visualised using a MRC Lasersharp confocal microscope. We present examples showing the precision of the technique in mapping cosmid DNA to banded chromosomes. In addition, FISH enables rapid confirmation of the origin of cosmid clones selected by the screening of libraries. For example, in one instance, two of four selected clones proved to be outside the region under investigation. Thus, we consider FISH to be an essential part of the analysis of cosmid clones.

A male with trisomy 9 mosaicism and uniparental chromosome 9 disomy in the euploid cell line

LIONEL WILLATT, CLARE DAVISON,
We describe a 17 year old male with congenital malformations who was found to have trisomy 9 mosaicism. Trisomy 9 was found in seven of 100 cells in blood lymphocyte cultures, but no cells with trisomy 9 were seen in 200 cells examined from skin and muscle biopsy cultures. A pericentric inversion of the heterochromatic area of chromosome 9 (p11q12) was identified in the patient and his mother. This variant was present in duplicate in both the trisomic and the euploid cells indicating that the trisomy 9 cell line had arisen following a maternal meiosis II error with subsequent postzygotic loss of the paternal chromosome 9 in the euploid cell line. Molecular studies with the probes LAMP92, ASSG3, and HF12–8 (D9S1) confirmed that there had been loss of the paternal chromosome 9 in the euploid cell line and that there had been a crossover between the maternal chromosome 9 during meiosis I. To our knowledge this is the first case of trisomy 9 mosaicism in which the mode of, and parental, origin have been confirmed. A maternally derived pericentric inversion of chromosome 9 has been observed in three other reported cases of trisomy 9 mosaicism and in all cases the variant chromosome was present in two copies in the trisomic cell line. The lack of a paternal chromosome 9 in the euploid cell line and the low level of mosaicism for the trisomic cell line will be discussed in relation to the clinical findings in this patient.

### Genetic mechanisms and recurrence risks in Angelman syndrome

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Angelman syndrome (AS) is a cause of severe mental retardation associated with characteristic dysmorphic features. It is usually sporadic in occurrence but several families have been reported where there is more than one affected child. These subjects are indistinguishable clinically and on EEG from the sporadic cases. A deletion of chromosome 15q11–13, visible on high resolution banding, was reported in Angelman syndrome by Kaplan and by Magenis in 1987 and by Pembrey in 1988. This has been confirmed as a frequent finding in AS by other groups. We have studied 77 patients with AS from 71 families and have carried out detailed cytogenetic and molecular genetic analyses. Forty-one patients (55%) had a de novo deletion of 15q11–13 and this was confirmed on DNA analysis in 13 cases. In 32 cases the cytogenetic examination was normal. This group included the 11 familial cases and two with uniparental paternal disomy for the whole of chromosome 15. Four patients had a rearrangement or irregularity of chromosome 15. AS arises as a result of different genetic mechanisms. The de novo deletion group and those with uniparental paternal disomy are the groups at low risk of recurrence. Thirty-seven per cent of our cases fell into the no deletion/no disomy group for which the recurrence risk is high and the mechanism as yet unexplained. Elucidation of the mode of inheritance in each case of AS is important for accurate genetic counselling.

### Posters

#### Maternal heterodisomy in Prader–Willi syndrome

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Two subjects with typical Prader–Willi syndrome are presented, along with their families. They are not related and were ascertained by different methods. Patient 1 was investigated in conjunction with a research project on Prader–Willi syndrome. She is 32 years of age, the youngest of five children, and cytogenetic studies indicated that she did not have a 15q11–13 deletion. She had, however, inherited one maternal chromosome with extra material in 15p. This distinctive cytogenetic polymorphism for one chromosome along with NOR staining for the other indicated that she had inherited both of her mother’s chromosomes 15 with no paternal contribution. Patient 2 is only 3 years of age, and after diagnosis the family was referred for genetic counselling. Cytogenetic studies showed that she also did not carry a 15q11–13 deletion, but again had inherited both maternal chromosomes 15. In this case satellite polymorphisms from her father showed non-inheritance of his chromosomes 15. In both patients other polymorphisms were consistent with paternity as stated. The apparent maternal heterodisomy is supported in both cases by molecular studies using probes specific for chromosome 15.

**Prader–Willi syndrome in Northern Ireland**

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Northern Ireland has a population of 1.5 million people with 28 000 births per year. A review of all patients with PWS has been continuing since 1989 with a view to ascertaining clinical problems, estimating the prevalence in the population, and investigating the cytogenetic and molecular aspects within the families. The main source of ascertainment was the records of the Regional Genetic Service. In addition, paediatricians were asked to identify patients in their care. A total of 17 patients was examined, 13 had the diagnosis of PWS confirmed, and four had the diagnosis amended. Twelve of the 13 were aged between 7 months and 14 years; one female patient was aged 27 years. The clinical findings are as follows: hypotonia (at birth) (13/13); blue irides (12/13); fair hair (6/13); scoliosis (7/13); strabismus (6/13); weight <90th centile (5/13); skin picking and irritation (1/13); acanthosis nigricans (1/13). Hyperphagia was a universal feature in the older children. As 11 possible PWS patients have not, to date, cooperated, an accurate prevalence rate cannot be calculated. Assuming that in 70% of these patients the diagnosis is correct, the total number of PWS patients aged between 0 and 14 years in Northern Ireland would be 19. The population in this age group in 1988 was 395 800. The prevalence rate for PWS is approximately 1 in 20 000. Cytogenetic analysis showed eight out of 13 patients to have deletion 15q11.2.
Severe prenatal Caffey's disease: fetal phenotype
P D TURNPENNY
Medical Genetics, Forresotherhall, Aberdeen.

Caffey's disease, infantile cortical hyperostosis, has been extensively reported and is an autosomal dominant trait with reduced penetrance. It is a self-limiting condition of unknown aetiology characterised by painful swelling of the soft tissues, hyperostotic bone changes, and fever. Clinical onset is in early infancy with resolution usually by 3 years. The mandible is most frequently affected (80%), sometimes causing 'cherubic' facies. Prenatal onset of the disease is also described (approximately 25 cases) and six have shown a severe phenotype characterised by polyhydramnios, generalised skeletal hyperostosis, and short and oedematous extremities. Survival in two occurred when the pregnancy reached term, but four were intrauterine or early neonatal deaths, extremely premature, and sporadic. An additional case is presented in a 27 week fetus born to consanguineous parents. The features were: coarse facies, shallow nasal bridge, corneal clouding, generalised limb shortening, oedematous and rigid soft tissues, and hepatomegaly. Radiologically there was a narrow, bell shaped thorax with small lung fields suggesting pulmonary hypoplasia, and generalised skeletal hyperostosis sparing the cranial vault, vertebrae, and clavicles.

Geographical distribution of Down's syndrome in the Northern Region O M WILSON, J NEWELL, C CLARK, J WOLSTENHOLME, J TAWN, A CRAFT, J BURN
Departments of Human Genetics and Child Health, University of Newcastle upon Tyne.

The recent report of an association between maternal exposure to radiation at Sellafield and a cluster of cases of childhood leukaemia has reopened the question of whether genetic defects may result from paternal irradiation and has also renewed interest in press reports of clustering of Down's syndrome in West Cumbria. Studies of chronic exposure to low level radiation as a possible cause for non-disjunction leading to Down's syndrome have yielded conflicting reports. Sever et al (Am J Epidemiol 1988;127:226-42) found no association between radiation exposure and Down's syndrome. Sheehan and Hillary (BMJ 1983;287:1428-9), however, reported an apparent cluster of Down's syndrome in children born to a group of women who attended the same school on the east coast of Ireland, a region which was claimed to have been exposed to radiation following the fire at Sellafield (then Windscale) in 1957. We have identified 515 cases of Down's syndrome occurring in the Northern Regional Health Authority during the period of 1979 to 1989. The address at birth was identified, and this was used as a reference point for cluster analysis. The technique applied was one developed by Besag and Newell for the detection of small clusters of rare diseases. No significant clusters of Down's syndrome have been identified in West Cumbria.

Neonatally lethal hydropspherosis and renal agenesis in the third generation of a dominant pedigree with hydropspherosis: variable expression or anticipation?
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Departments of Human Genetics and Child Health, University of Newcastle upon Tyne.

Primary hydropspherosis (McKusick 14340) is presumed to be a variable autosomal dominant disorder though there are only two three generation pedigrees published (Cannon A, Intern Med 1954;41:1054-60, Jewell and Buchert, J Urol 1962;88:129-36). In 1955 Raffle (BMJ 1955;ii:580-2) reported four cases in two generations of a North East family. The pedigree now contains six living affected members, one of whom presented with a history of two unsuccessful pregnancies. The first was a neonatal death with hydropspherosis and the second had bilateral renal agenesis. These may be coincidental or may represent a more extreme form of a variable expression. A third possibility is that this is an example of true anticipation. Whatever the explanation, account must be taken of the need to offer fetal anomaly scanning when counselling such families.

Two families with purine nucleoside phosphorylase deficiency: clinical features, enzymology, and early prenatal diagnosis
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Duncan Guthrie Institute of Medical Genetics; Department of Haematology, Fraser of Allander Assessment Unit, Yorkhill, Glasgow G3 8SJ.

Family 1. The first child of non-consanguineous parents presented at 13 months with unexplained mild spastic quadriplegia. Haematological investigation at the age of 3 years showed lymphopenia with undetectable T lymphocytes. A complete deficiency of purine nucleoside phosphorylase (PNP) activity and raised adenosine deaminase (ADA) activity was found in red cells from the proband. The parents had half normal levels of PNP activity. Prenatal diagnosis by CVS was undertaken at 10 weeks' gestation in a subsequent pregnancy. Undetectable PNP activity with normal ADA activity was found in direct CVS preparations indicating an affected fetus.

Family 2. PNP deficiency was shown retrospectively in this family in which a sister and brother, born in 1963 and 1966, had disequilibrium--diplegia and cellular immunodeficiency. Both children died and were thought to have a 'new' clinical entity: familial ataxic diplegia with deficient cellular immunity (MIM 209000). Subsequently, fibroblast cultures from the second child, which had been stored in liquid nitrogen for 17 years, were successfully reconstituted and shown to have undetectable PNP activity but normal ADA activity. Both parents had half normal erythrocyte PNP activity.

Second trimester unconjugated oestriol levels in maternal serum from chromosomally abnormal pregnancies using an optimised assay
J A CROSSLEY, D A AITKEN, J M CONNOR
Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SJ.

Unconjugated oestriol (UE3) levels, measured using modifications of commercially available immunoassay kits designed for use in the third trimester, have been reported to be significantly lower in second trimester maternal serum samples from Down's syndrome pregnancies. We report here a retrospective study of UE3 levels in
the second trimester in maternal serum from 78 chromosomally abnormal pregnancies and 390 matched controls, using a new immunooassay kit (Amersham AMERLEX–M) optimised for use at the lower second trimester concentrations. Reduced levels of UE3 were found in a group of 49 Down’s syndrome pregnancies with a median UE3 value of 0.79 multiples of the median (MOM) of the controls. All four trisomy 18 pregnancies had UE3 levels less than 0.7 MOM. There was a significant level of correlation between AFP and UE3 levels in the controls (r=0.25, p<0.01), the Down’s syndrome pregnancies (r=0.44, p<0.01), and the other chromosome abnormalities (r=0.61, p<0.01). Thus, UE3, when used as an additional marker to AFP and hCG in screening for chromosome abnormalities, adds little to the sensitivity of such screening.

Free β hCG and prenatal screening for chromosome abnormalities

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Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SF.

Prenatal screening for chromosome abnormalities using a combination of the risks derived from maternal age, maternal serum AFP, UE3, and hCG has shown that 60% detection of Down’s syndrome can be achieved for a 5% follow up rate. Of these pregnancy markers the most powerful predictor is hCG, which is present at increased concentration in maternal serum from pregnancies with Down’s syndrome. In a recent study, we have found the median hCG value for a series of 49 Down’s syndrome pregnancies to be raised at 2.18 multiples of the median (MOM) of the unaffected pregnancies. These data were obtained using an immunoradiometric assay for whole molecule hCG. Assay of the free β subunit alone is possible using a monoclonal antibody which recognises an epitope on the binding site of the β subunit which is hidden in the intact molecule. Using such an assay, we have analysed the concentration of the free β hCG molecule in maternal serum samples from a series of 117 chromosomally abnormal pregnancies (81 Down’s syndrome, 11 trisomy 18, four trisomy 13, eight unbalanced translocations, four balanced translocations, nine sex chromosome abnormalities) and 390 matched controls, and compared the results with those found for the whole molecule hCG. The median free β hCG level in the Down’s pregnancies was further raised at 2.3 MOM of the control group. However, the wider distribution of free β subunit levels in both Down’s syndrome and unaffected pregnancies resulted in loss of sensitivity when free β subunit levels are used as a predictor of trisomy 21 pregnancies.

Variation in the levels of pregnancy specific β-1 glycoprotein in maternal serum from chromosomally abnormal pregnancies

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Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SF.

Pregnancy specific β-1 glycoprotein (SP-1) levels were assayed by immunoelectrophoresis in maternal serum samples from 15 to 20 weeks’ gestation from 81 pregnancies with fetal chromosome abnormalities (48 trisomy 21, eight trisomy 18, four trisomy 13, eight unbalanced translocations, four balanced translocations, and nine sex chromosome abnormalities), and a control group of 397 chromosomally normal pregnancies, matched for gestation and maternal age. SP-1 levels in the controls show a log-gaussian distribution with the median SP-1 concentration increasing with advancing maternal age. Conversion of SP-1 levels in individual chromosomally abnormal pregnancies to multiples of the median value (MOM) for the control samples at the same gestation showed that the Down’s pregnancies were associated with a significantly increased SP-1 level at 1.17 MOM, with 33% of values above the 90th centile. The trisomy 18 cases and unbalanced translocations had reduced SP-1 concentrations. These trends are similar to, but less marked than, those found for hCG in the same series of samples. There is a strong correlation between SP-1 levels and the concentration of other placental markers in maternal serum, which minimises the additional predictive value of SP-1 in multiparameter prenatal screening.

Fetal sexing of amniotic fluids using the polymerase chain reaction

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Regional Genetics Centre, Belfast City Hospital, Belfast BT9 7AB.

The polymerase chain reaction (PCR) was used to amplify a Y chromosome specific repeat sequence and an Alu repeat sequence, as a control, in 125 samples of amniotic fluid taken for routine chromosome analysis. DNA was extracted from cells spun from 500 µl of fluid using a method using guanidine hydrochloride and protease K; this was necessary to achieve reliable amplification. The results of the PCR test were later compared with the karyotype analysis as shown by standard cytogenetic methods. The success rate was compared to that obtained using fluorescence microscopy following treatment of the amniocytes with quinacrine dihydrochloride. Of the samples tested using PCR, 121/125 (96.8%) agreed with the karyotype. Two samples gave a conflicting result and two failed to amplify. Of the samples sexed using fluorescence microscopy, 139/150 (92.7%) agreed with the karyotype, six samples gave a conflicting result, and five samples gave no result. Thus, the PCR procedure can increase both the accuracy and the success rate of fetal sexing from samples of amniotic fluid. The PCR test is also much more rapid and uses much less hands on time than the microscopy technique.

Early and conventional amniocentesis: a comparison of pregnancy outcome

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The joint genetic/obstetric clinic at Royal Maternity and Jubilee Maternity Hospitals has been offering routinely early amniocentesis since January 1987 (Nevin et al. Prenat Diagn 1990;10:79-83). With the aspiration of amniotic fluid at less than 14 weeks’ gestation, concern has been expressed about possible respiratory or orthopaedic complications in the newborn. In order to investigate these possible complications, we compared two groups of
women, one group in whom the mothers had amniocentesis at, or below, 13 weeks' gestation and the other group at, or above, 16 weeks' gestation. The patients were identified by selecting consecutive amniocenteses in each group, from the prenatal laboratory register. Amniocenteses which resulted in an induced or spontaneous abortion were excluded. In group 1, there were 85 women and in group 2, 86. The results are shown below. The findings suggest that there is no increased incidence of respiratory or orthopaedic complications when amniocentesis is carried out at, or below, 13 weeks' gestation.

<table>
<thead>
<tr>
<th>Clinical Genetics Society</th>
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<td>Early (n=86)</td>
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<td>Average gestation (wk)</td>
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<td>Preterm labour (&lt;35 wk)</td>
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<td>Respiratory distress syndrome (owing to extreme prematurity)</td>
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<td>Congenital pneumonia</td>
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<td>Stillbirths</td>
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Cystic fibrosis ΔF508 carrier frequency among patients with myeloid malignancy and melanoma

N. A. Grauman*, P. K. C. Goon†, A. J. M. Hill*, G. R. Cutting†, S. Curristan†, N. C. Nevin†
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We would like to report on the identification of a G to A mutation at position 1022 in exon 7 of the CFTR gene, causing an arginine to glutamine change at codon 297 (R297Q). This charge change from a basic to an uncharged amino acid is probably consistent with disease and the mutation occurs at a CG dinucleotide, a known mutation hot spot. This mutation creates a Ddel site; normal 270+140 bp, mutant 270+106+34 bp. It was detected in two sibs with CF and is associated with an X2 K1 haplotype. The other mutation in this family is also on an X2 K1 haplotype and is undefined. R297Q was not detected in a further 54 CF chromosomes with undefined mutations (eight with X2 K1 haplotypes) and 50 normal chromosomes.

Mutation analysis of two cystic fibrosis populations from Northern Ireland

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Four hundred cystic fibrosis chromosomes from two centres in Northern Ireland were screened for up to 24 mutations in eight exons of the CFTR gene. No significant difference in the frequency of ΔF508 between the Manchester and Sheffield samples was observed. The frequency of two mutations displayed markedly uneven distributions between the two samples, with G551D found exclusively in Manchester and R553X predominantly in Sheffield. These differences, while possibly the result of a local founder effect in the samples, probably illustrates a steep gradient in the distribution of the two mutations across the Pennines. Local and regional variations in mutation frequencies such as this may have important consequences for carrier screening programmes, both in the selection of a panel of mutations and in risk assessment.

Identification of a new mutation (R297Q) in exon 7 of the CFTR gene in a Northern Ireland family

C. A. Grauman*, P. K. C. Goon†, A. J. M. Hill*, G. R. Cutting†, S. Curristan†, N. C. Nevin†
*Regional Genetics Centre, Belfast City Hospital, Belfast BT9 7AB; †Johns Hopkins Hospital, Baltimore.

Two new PCR markers in the dystrophin gene

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Details are presented of the conversion for use by the PCR technique of two polymorphisms detected by dystrophin cDNA probes: the PstI RFLP detected by the probe Cala, and the TagI RFLP detected by the probe Gf23a. The markers map to introns 24 and 38 respectively. These RFLPs supplement the existing set of intragenic PCR markers which provide a rapid and efficient system of carrier detection and prenatal diagnosis.
Epidermolysis bullosa is a heterogeneous group of genetic disorders which can be subdivided into the simplex, junctional, and dystrophic classes. The simplex form (EBS) is characterised by intraepidermal blisters which heal without scarring. Weber–Cockayne EBS (with blistering localised to the hands and feet) and Koebner EBS (with generalised blistering) both show autosomal dominant inheritance. Pooled data from Weber–Cockayne and Koebner EBS families have suggested tentative loose linkage to the Duffy (Fy) blood group locus on chromosome 1q. Recently, a Koebner EBS family from Ireland has been reported to show linkage to the anti-thrombin III gene (AT3) locus at 1q23–q25.1. We have tested a Northern Irish Weber–Cockayne EBS family for possible linkage to this region of chromosome 1. Polymorphisms were typed using DNA probes on Southern blots or by polymerase chain reaction amplification and agarose or polyacrylamide gel electrophoresis. Analysis of haplotypes of three polymorphisms within the AT3 gene excluded close linkage to this locus (Z<−2 at θ=0.10). Typing of Fy blood group suggested possible linkage (Zmax=1.01 at θ=0.01). However, this is discounted on the basis of non-linkage to the more informative MUC and APOA2 loci which are thought to flank the Fy gene and also to the SPTA1 locus (MUC Z<−2 at θ=0.07; APOA2 Z<−2 at θ=0.08). These results indicate that the gene causing Weber–Cockayne EBS in this family does not lie between the MUC and AT3 loci on chromosome 1q. This suggests either a location distal to the AT3 gene or the possibility of genetic heterogeneity between the Weber–Cockayne and Koebner varieties of EBS.

New polymorphism with probe 26–6 which proved useful as a proximal marker in a family with APKD
STEPHEN JEFFERY, MICHAEL PATTON

Isolation of YAC clones containing class I HLA genes which map in the vicinity of the hereditary haemochromatosis gene
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*University Department of Medical Genetics, St Mary's Hospital, Manchester M13 0FH; †ICI, Northchurch.

Linkage analyses have suggested that the hereditary haemochromatosis (HH) gene maps to chromosome 6p in the class I HLA region, most probably in the vicinity of the HLA–A and HLA–B genes. We have designed PCR primers to amplify specifically HLA–A and HLA–E genes. The HLA–A specific and HLA–E specific primers were used to screen a human YAC library containing 3–5 genome equivalents, and an average insert size of 350 kb (Anand et al. Nucleic Acids Res. 1990;18:1951–6).

Large scale mutations at the NFI locus in Noonan–NF1 and NF1 patients
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University Department of Medical Genetics, St Mary's Hospital, Manchester M13 0FH.

We have used a combination of short and long range restriction mapping with intragenic and closely flanking DNA probes to investigate mutations at the NFI locus in NF1 patients, and also in NF1-Noonan (NFNS) patients.

Immunological and molecular genetic characterisation of an unknown structural molecule of human connective tissues
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Department of Medical Genetics, The Queen's University of Belfast, Belfast.

We are involved in the study of unknown connective tissue proteins by means of 'forward genetics' techniques. Human fibroblasts are known to secrete such structural proteins as collagens, elastin, and fibronectin which form the basis of connective tissues. 2D-PAGE shows that fibroblasts secrete about 50 types of glycoprotein which are largely uncharacterised. Here, we present data regarding the study of one of these unknown proteins. A mouse monoclonal antibody (1.4D1) was raised using live human fibroblasts as immunogen. 2D immunoblots of fibroblast cellular protein showed a short train of precursors of 141 kD and pl about 5. The extracellular forms were detected by radioimmunotraping assay and 2D analysis showing a double train of O linked glycoproteins. Immunohisto-
chemical staining showed that the antigen is a structural molecule. Mono-
clonal 1.4D1 was used to immunoscreen an expression library in lambda gt11
using an improved detection system. A PCR system was developed to amplify
inserts in gt11. A clone containing a 1.7 kb insert is currently being
sequenced by a direct PCR mediated technique in addition to the M13
method.

Monocyte esterase deficiency in
malignant neoplasia: a newly
described inherited phenomenon
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G M MARKEY†, T C M MORRIST†
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Belfast City Hospital, Belfast.

Identification and enumeration of
monocytes using cytochemical
detection of monocyte esterase activity is
routinely used in patient haematological
investigations. A 73 year old woman
presenting with a non-Hodgkin's
lymphoma was found to be esterase
negative for 95% of her monocytes.
Familial studies showed a similar level
of esterase negative monocytes in her
son, while two (one male, one female)
of four grandchildren registered nega-
tive staining for between 60 to 70% of
their monocytes. A large scale survey
monitoring the incidence of MED in
patients with malignant neoplasia
(n=808), patients without malignant
neoplasia (n=3192), and a normal
control population (n=474) was per-
formed. Significant increases in the
incidence of MED were recorded for
patients with Hodgkin's lymphoma,
non-Hodgkin's lymphoma, B chronic
lymphocytic leukaemia, and gastro-
intestinal carcinomas (p=0.0018,
0.0097, 0.001, and 0.001 respectively).
An increased incidence of MED was
also found for patients attending renal
clinics (p=0.0112). Familial studies
were performed for 13 of the esterase
negative patients (covering a variety of
disorders) with 28% of first degree
relatives studied registering the
deficiency. The trait appears to be
inherited in an autosomal dominant
pattern albeit with incomplete pene-
trance. The increased incidence of
MED in specific disease groups implies
that the trait may predispose affected
subjects to development of these
diseases. Inhibition of normal mono-
cyte esterase activity by bis(4-nitro-
phenyl)-phosphate results in decreased
monocyte cytotoxicity against the
K562 erythroleukaemic cell line. Fur-
thermore, normal esterase positive
monocytes show an enhanced ability
to lyse K562 cells when stimulated by
lactoferrin whereas esterase negative
monocytes from normal subjects do not
respond to lactoferrin. These results
suggest that monocyte esterase has an
important role to play in the body's
defence mechanisms against develop-
ment of neoplasia.

Interstitial deletion of 8p21.3-23.1
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N C NEVIN*†
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†Regional Cytogenetic Laboratory,
Belfast City Hospital, Belfast.

Partial monosomy of the distal short
arm of chromosome 8 is a rare occur-
rence. Only 16 cases have been
reported worldwide, and of these only
one interstitial deletion of 8p has been
reported. We describe a second such
case in a 6 year old female. Clinical
examination showed height, weight,
and head circumference all under the
10th centile. Dysmorphic features
included a prominent, high forehead,
flat nasal bridge, dysplastic, low set
ears, orbital and nose hypertelorism,
and a small jaw. Hands and feet were
puffy at birth, but this resolved within
a few months. There was marked
mental and developmental delay. Red
cell morphology and glutathione
synthetase reductase (GSR) levels were
within normal limits. Parental chromo-
 somes were normal. Chromosome
analysis using high resolution GGR
banding confirmed breakpoints at
8p21.3 and 8p23.1, excluding the GSR
gene from 8p21.3 and confirming the
locus on 8p21. The features in this
case support the suggestion of a distinct
distal 8p phenotype.

Duplication 4q syndrome resulting
from a familial 4;14 translocation
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N C NEVIN*, D EDGAR*,
G J CALVERT†
*Department of Medical Genetics,
Belfast City Hospital;
†Muckamore Abbey Hospital, Antrim.

Most reports of duplication 4q syn-
drome result from one of the parents
having a balanced translocation.
However, most reports have described
only one or two affected family
members. We describe a large family
with nine affected members resulting
from a t(4;14)(q31.3;p11.2) translo-
cation. All affected subjects are
mentally retarded with IQs ranging
from 30 to 55. The clinical appearance of
affected subjects is unremarkable,
although all are similar. The cranio-
facies is characterised by brachycephaly
with a slightly sloping forehead and
prominent nasal bridge with a straight
nasofrontal angle. The ears are large,
low set, and posteriorly rotated with
prominent antihelix, hypoplastic tra-
agus, and prominent antitragus.
There is also micrognathia, pointed
chin, and short neck. Interestingly,
two affected subjects had Hirsch-
 sprung's disease which has also been
described in a child with duplication 4q
syndrome resulting from a t(4;9)
(q31;q34) translocation (Issa et al.
number of affected subjects within one
family enables a typical craniofacial
phenotype to be delineated for duplication
4q31.3-qter.

Duplication of 15q11.2-15q13 in
five cases with different phenotypes
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Regional Cytogenetic Laboratory,
Department of Medical Genetics,
Belfast City Hospital, Belfast.

We describe five subjects with an
apparent duplication of chromosome
15 in the region q11.2-q13. The
patients were referred for chromo-
some analysis with various clinical
phenotypes. One patient had primary
amenorrhoea, one showed a clinical
presentation similar to the Prader-
Willi syndrome, one had insulin
dependent diabetes with epilepsy and
a personality disorder, a baby had
multiple congenital abnormalities
including wide cranial suture, en-
cephalocoele, and cystic brain lesion,
and one male was referred with his
partner for cytogenetic investigations
following failure of IVF. Previous
published reports indicate that duplica-
tions in this region of 15q may be
associated with obesity, Prader–Willi
or Cohen syndrome, mental retardation,
and short stature. Two of four pheno-
typically normal parents who were
tested were found to carry the same
chromosome duplication. It is possible
that the extra chromosomal material observed in our cases may be unrelated to the patients' clinical presentation, since it is shown that such a rearrangement in the region of 15q12 is also compatible with an apparently normal phenotype. If the chromosome abnormality does cause the clinical symptoms there is a need to explain the difference in expression in those patients in whom a parent has a similar duplication.

**Duplication 7q resulting from a maternal insertional translocation**

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Regional Cytogenetic Laboratory, Department of Medical Genetics, Belfast City Hospital, Belfast.

We describe a male patient who presented at 3 days old with congenital abnormalities of the hands and feet. The baby was born at 39 weeks' gestation weighing 2551 g. The antenatal history was unremarkable. At birth, the hands and feet were twisted and fingers were overlapping. When seen at 6 weeks old, the facies was characterised by small eyes with downward slanting palpebral fissures, flat nasal bridge, small, upturned nose, low set, abnormal ears, and micrognathia. The palate was high. Nipples were widely spaced. The fingers were long. He was not fixing his eyes and the parents considered that he had some hearing difficulty. Cytogenetic examination showed extra chromosomal material inserted within the short arm of chromosome 2. The parents had had two previous pregnancies: a spontaneous abortion at 12 weeks and a normal daughter. The father had a normal karyotype. The mother was found to have an insertional translocation with the chromosome segment 7q21.12→7q31.32 inserted into chromosome 2 at band 2p15. The patient thus has a duplication of region 7q21.12→7q31.32. Insertional translocations are relatively rare occurring at a frequency of 1 in 5000 births. They are invaluable in demonstrating the clinical features of pure trisomy or pure monosomy for chromosome segments, in this case pure trisomy for 7q21.12→7q31.32.

**Partial duplication of 16q: report of a case with mosaic paternal duplication of 16q**

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We describe a female patient who presented at 2 months old with dysmorphic features. She was born at 42 weeks, weighing 2863 g. The antenatal history was unremarkable. The dysmorphic features included poor facial expression, bilateral epicanthic folds, nystagmus, alternating strabismus, posteriorly rotated ears, and a prominent maxilla. The palate was high. She had marked hypotonia and psychomotor delay. Echocardiogram showed a small atrial septal defect. Cytogenetic investigations showed an unbalanced rearrangement of chromosome 16 which was determined as a tandem duplication of region 16q22.1→16q24.1. The parents have an older, normal son. The mother and her son had normal karyotypes. The father was mosaic for the same duplicated 16, with 93% of his blood cells having a normal male karyotype. The case presented is rare in that the proband's chromosome duplication is inherited from a parent with the same duplication in mosaic form. There are only six previously reported cases of mosaicism for a tandem duplication of any chromosome. Chromosomal duplications are explained either by unequal crossing over or by a translocation between homologous chromosomes or sister chromatids. To give rise to a normal/duplication mosaic these events would have to occur after the first cleavage of a normal zygote with the counterpart deleted clone being unviable, lost, or undetected. An alternative prezygotic origin of normal/duplication mosaics has been proposed, the half chromatid mutation model. This involves a particular kind of insertion between homologous or sister chromatids occurring during meiosis.

**Duplication 6q syndrome**

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Duplication 6q has been described in about 20 patients and is considered to have a clinically recognisable phenotype. All cases have arisen from balanced parental translocations or inversions. We present a case of a female infant with a de novo inverted duplication of the segment 6q21→q27 which represents a pure trisomy for this region without any associated deletion. The parents' chromosomes were normal. The infant had multiple congenital abnormalities including facial dysmorphism, postaxial polydactyly of fingers and toes, ulnar deviation of hands, bilateral simian creases, talipes equinovarus, short neck, and congenital heart anomalies (atrial septal defect, mitral regurgitation, and cardiomegaly). The facies was characterised by brachycephaly, round facies, hypertelorism, short nose, low set ears, and microstomia. The patient was the last of a sibship of four; an older brother died at 36 hours with the diagnosis of cot death. Comparison of the clinical features of our patient with those previously published shows that duplication 6q is a recognisable syndrome.