Abstracts of the meeting of the Clinical Genetics Society held on 2 and 3 April 1987 at the University of Leicester

Non-progressive myotonias: clinical and genetical aspects
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The non-progressive myotonic disorders form a heterogeneous group of muscle diseases, most of which are genetically determined. The common feature of these diseases is the myotonia combined either with a variable degree of weakness or with adynamia. The classification of this heterogeneous group, both clinically and genetically, has been open to discussion for a long time. Since the early 1980s it has been shown that different membrane defects are responsible for the various types of myotonia; thus, the classification has become more reliable. Fifty families in the Federal Republic of Germany and Great Britain have been visited and investigated. Based on this experience, combined with the knowledge of the pathophysiological basis of the muscle defect, a classification and differential diagnosis suitable for geneticists and clinicians has been developed. Emphasis is placed on the diagnosis of paramyotonia congenita, probably an underdiagnosed disorder.

The oculocerebrocutaneous syndrome
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We report two children with the multiple malformation syndrome as described by Dellemann and Oorthuys (Clin Genet 1981;19:191–8) which includes orbital cysts or hamartomas, periorbital skin appendages, multiple focal dermal defects, agenesis of the corpus callosum, and multiple intracerebral cysts. Of the seven children seen with the oculocerebrocutaneous syndrome one has died from cerebral involvement and four of the six survivors have developmental delay-mental retardation and fits. All cases have been sporadic with four males and three females affected. Consanguinity has not been reported and autosomal dominant inheritance has been suggested on the basis of unilateral anophthalmia in a paternal grandmother to one child.

Experience of offering a service for prenatal diagnosis of cystic fibrosis by DNA analysis
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Since July 1986 we have offered prenatal diagnosis of cystic fibrosis (CF) to couples at risk of having a further affected child, using DNA probes closely linked to the CF locus. These include pJ3-11 (with MspI) and met D and met H (both with TaqI). Families were informed of the availability of the test during their routine visits to the CF clinic at this hospital. All families interested in the test were urged to seek genetic advice before planning a pregnancy. This approach aimed to produce a steady input to the clinic. An indication of the uptake of the test is shown here, in the series of one of the consultant respiratory physicians who informed 34 families of the test. Eight were interested, replies were awaited on four, and 22 do not want the test, the common reason being that the parents were separated or divorced (n=9). In total, 27 families have been analysed with DNA probes: 17 are fully informative, eight are partially informative, one is uninformative, and in one the results are inconclusive. Of the fully informative families, three are informative with met H alone, three with pJ3-11 alone, and the others with combinations of these three probes. The eight partially informative families remained so when tested with 7c22 (EcoRI). Only three of these eight families would plan a pregnancy and first-trimester diagnosis. Difficult counselling problems arise in parents first present to the genetic clinic already pregnant, for example, if the diagnosis of CF in the first affected child was made only recently.

The Berlin nomenclature for inherited disorders of connective tissue
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The inherited disorders of connective tissue are proving to be very heterogeneous; new entities are being delineated and the syndromic boundaries of established disorders are expanding. In addition, basic biochemical and molecular
Use of closely linked RFLPs to detect the Anderson-Fabry disease gene
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Anderson-Fabry disease is an X-linked lysosomal storage disorder due to a galactosidase A (αGAL A) deficiency. Deposition of glycosphingolipids results in its systemic manifestations of which angioedema, corneal dystrophy, and severe acroparthesias are the most characteristic. Hemizygous males and some carrier females develop cardiac and renal failure in early adult life. We have established a filing system (register) for Anderson-Fabry disease in order to provide a coordinated medical and genetic service with the families’ physicians. Of 19 families ascertained, members of six large pedigrees had detailed clinical examination, leucocyte and hair root αGAL A estimations, and genetic counselling. DNA from 80 subjects was analysed with five DNA markers mapping to Xq21→24. Three probes showed close linkage with the Anderson-Fabry gene, with no detectable recombination. DXS87 and DXS88 showed lodmax=6.4 at θ=0.00 and DXS17 lodmax=5.8 at θ=0.00 (all having upper confidence limits of 10 cm). DXS3 showed lodmax=2.9 at θ=0.10 and DXYS1 was excluded from linkage. Of six families studied, only one was not informative for all three probes (DXS87, DXS88, and DXS17). DNA from our families was analysed with the αGAL A gene specific probe λAG18 by Professor R Desnick and, to date, only the family not informative for RFLPs showed a gene rearrangement with λG18. As αGAL A levels in females heterozygous for Anderson-Fabry disease overlap those of normal controls, and experience with αGAL A estimation in CVS is limited, DNA analysis can be used in clinical diagnosis of Anderson-Fabry disease.

Linkage analysis in families with the fragile X syndrome using cXSS–7 (DXS105)
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Probe cXSS–7 (DXS105) is an arbitrary DNA fragment which recognises restriction fragment length polymorphisms of 3.2 kb or 4.5 kb in TaqI digested DNA or 10 kb and 2.5 kb in EcoRI digested DNA. Screening of 60 unrelated X chromosomes showed TaqI fragment frequencies of 0.12 (4.5 kb) and 0.88 (3.2 kb). Twenty-nine obligate carriers for the fragile X syndrome were screened using the TaqI RFLP and seven (from three families) were informative. Uninformative obligate carriers were then screened with the EcoRI RFLP and three females (one family) were informative. Only one recombinant was observed in 21 informative meioses (15 phase known) giving a peak lod score of 4.18 at θ=0.05. This recombinant occurred in a meiosis which was also informative for pS8-1 and S14, but as recombination above and below the fragile X locus was already apparent the respective order could not be determined. Other three point cross data in these families support the order pS8-1, S2A–F9–55–7, FRAX–F8–S14–DX1–Xqter.

Characterisation of a polymorphic probe which detects deletions in males with X linked ichthyosis at high frequency
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We have studied 15 families with classical X linked ichthyosis, associated with failure of the placental production of oestriol in late pregnancy and with difficulties in childbirth. The sequence GMGX9 was isolated from an X specific DNA library, constructed in Glasgow, and screened for single copy sequences at the distal end of Xp. It has been mapped in the interval Xp22.3→pter and detects a frequent HindIII polymorphism. Of normal females examined to date, 52% have been found to be heterozygous, which makes GMGX9 suitable for linkage studies. Furthermore, GMGX9 is deleted in the affected males in 12 of 15 families with the condition, while being present in all of the 26 normal males examined so far. Flow karyotype analysis has revealed a detectable decrease in the size of the X chromosome in two of four affected males, three of which are deleted for GMGX9. Our findings suggest that a high proportion of the mutations at the STS locus leading to enzyme deficiency are deletions, presumably generated by unequal cross over events in female meiosis or by illegitimate X–Y interchange in male meiosis.

Carrier detection in ornithine carbamoyl transferase deficiency
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Female carriers for the X linked hyperammonaemia, ornithine carbamoyl transferase (OCT) deficiency, may present with clinical disease, be healthy but protein intolerant, or be entirely asymptomatic. Females in 15 families with OCT deficiency have been assessed by a combination of dietary history, oral protein (or alanine) load with measurement of urinary orotic acid, and gene tracking with an OCT DNA probe using a MspI site polymorphism. To date, protein or alanine loads have been performed on 31 'at risk' females and two obligate carriers. False raised excretion of orotic acid after oral alanine load has occurred in two 'at risk' females and DNA has enabled carrier exclusion of these females. Gene tracking is potentially helpful in 11 families and the mutation has been shown to originate in the maternal grandfather of the proband in one of these families. The need for a combined DNA analysis/protein load approach to carrier assessment is clear.

Value assessments applied to the prenatal diagnosis of Down's syndrome by chorionic villus biopsy or amniocentesis

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Seventy-three non-pregnant women underwent structured interviews to elicit the relative values they attached to the birth of a Down's child and the two main procedures for prenatal diagnosis, amniocentesis and chorionic villus biopsy (CVB). The lowest risks of Down's at which subjects would request amniocentesis or CVB were established by a multiple gamble technique. The coherence of the responses was tested by performing a third gamble to elicit at what CVB related abortion risk the subject would choose CVB in preference to amniocentesis. The responses of 53% of subjects were arbitrarily defined as coherent in that they chose CVB at a maximum abortion risk within a factor of two of the expected risk. Prenatal diagnosis was often desired at much lower risks of Down's than it is presently usually offered. Twenty per cent of subjects would request amniocentesis even if the risk of Down's syndrome was as low as 0.5 in 1000, and 75% would do so at risks lower than those corresponding to a maternal age of 37. Given a 5 per 1000 risk of Down's syndrome, 50% of women would accept a doubling of the procedure related risk of abortion to obtain the advantages of early diagnosis of CVB. Despite this, subjects (medical and non-medical) were found to underestimate the degree of intellectual impairment in Down's syndrome.

The prediction of a recessive phenotype from a nearby marker

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Recurrence risks may be either empirical or theoretical: in fetal diagnosis based on linkage to one marker, estimates of reliability involve concordance rates, that is, the expectation of concordance of recessive and marker loci in two sibs. These are usually calculated from the recombination fraction, which is mainly estimated from the concordance rate. While the present estimates of recombination fraction in cystic fibrosis are low they are unduly low in comparison with the likely rate of diagnostic error, and, in the absence of marked allelic association, it would be unwise to accept any estimate of linkage of less than 1%. Allowing for all these factors, an error rate of 5% for non-bracketing loci seems a reasonable estimate from published data, and of the same order as that possible later in pregnancy.

Dominant Ehlers-Danlos syndrome type IV caused by a shortened mRNA type III collagen

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Ehlers-Danlos syndrome type IV (EDS IV) was diagnosed in a 22 year old man because of typical clinical signs and family history. His father had died aged 32 years from internal haemorrhage. Biochemical studies showed that (a) skin fibroblasts from this patient secreted reduced amounts of type III procollagen, (b) in a major portion of type III procollagen the triple helical structure extended from the C-terminus only to three-quarters of the normal length, and the abnormal type III procollagen molecules were unstable and poorly secreted, and (d) in the presence of dextran the abnormal molecules which were secreted did not undergo further processing as did their normal counterparts. Immunoblotting experiments (antisera kindly provided by Dr R Timpl) showed that two populations of type III proto-procollagen chains were produced by the patient's cells, one of normal and another of smaller size. Similarly, Northern blots probed with cDNAs for type III collagen (kindly provided by Drs E Vuorio and R Dalglish) showed that two species of mRNA were present in equal quantities, a normal sized mRNA and a mutant mRNA which was about 600 bp shorter. We conclude that one mutant allele (dominant inheritance) at the locus for type III collagen (COL3A1) codes for an abnormally short mRNA which results in the synthesis of shortened type III procollagen chains. The mutant chains are incorporated into trimers, but trimers with one or more mutant chains are biochemically and functionally crippled. These findings provide direct evidence of a mutation at the COL3A1 locus in EDS IV.

Hyperthermia as a teratogen

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Experiments in a variety of animals show clearly that hyperthermia is teratogenic, producing a range of abnormalities, with the central nervous system being especially vulnerable. By contrast, in humans, there is uncertainty as...
to whether hyperthermia causes neural tube defects (NTD) and other malformations. Careful analysis of the experimental findings in animals reveals the situations under which hyperthermia is teratogenic. The curly tail mouse, genetically predisposed to NTD particularly affecting the posterior neuropore, when exposed to hyperthermia develops exencephaly not spinal lesions, emphasising the specificity of heat for the cephalic end of the neural tube. A dose and time response is also observed, and even in such animals predisposed to NTD, a core temperature rise of at least 4°C is required to produce significant numbers of NTD. Experiments on others show that lower temperatures produce less severe abnormalities. Considering all lessons from animal experiments, it seems likely that hyperthermia is equally a teratogen in humans, but only relatively rarely are the extreme conditions encountered which produce severe abnormalities like NTD which are recorded in surveys.

Teaching medical genetics in Britain
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Ten years after the GMC report on Genetics in Basic Medical Education, and after many remarkable developments in clinical genetics, I wrote in Spring 1986 to Deans of British medical schools to enquire about current teaching. The replies suggest little change in the time devoted to genetics. Relatively little is in the clinical courses (average 3-52 hours) compared with the preclinical courses (average 17 hours) where the relevance to recent clinical advances may be less clear. Two Deans reported that there was no separate preclinical genetics teaching in their schools and 13 Deans reported that there was no separate clinical genetics teaching. Undoubtedly there is valuable clinical teaching in genetics by other clinicians in all medical schools, but as noted 10 years ago by the GMC, this teaching is very variable and difficult to verify. It appears that only four schools have definite plans for expanding genetics teaching, eight are considering some expansion, while 17 schools are reported not to have plans for expansion. Such deficiencies are becoming progressively more serious as young doctors, and their seniors, have to grapple with the clinical implications of new technologies. In contrast the eight medical schools with departments of human or medical genetics provide considerably more preclinical (23-5 hours) and clinical genetics (8-1 hours) compared with schools without such departments (14-4 and 1-8 hours respectively) and include visits to genetic clinics where genetic counselling techniques can be observed in action. These departments are closely linked to NHS Regional Genetic Centres so that their teaching is clinically relevant and in addition this arrangement encourages postgraduate education and research.

Pulsed field gel analysis around the fragile site at Xq27-3
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A fragile site at Xq27-3 is associated with X linked mental retardation (the Martin-Bell or fragile X syndrome). The aim of this work is to achieve a detailed physical characterisation of the region around the fragile site. The DNA probes St14, DX13, and MN12 detect RFLPs which map genetically to the same region of the X chromosome, approximately 10 cM from the fragile site. Long range restriction mapping by PFG analysis has shown that all three probes are localised within a single MluI restriction fragment of 470 kb. The physical distance between St14 and DX13 may be as little as 60 kb. Given an approximate genetic distance between St14 and DX13 of 1 to 2 cM, these observations suggest that genetic recombination in this region of the X chromosome may be unusually high. These results have implications for the isolation of closely linked disease markers in this region. In the vicinity of MN12 we have identified clusters of sites for rarely cutting restriction enzymes, which represent good candidates for HTF islands. HTF islands are associated with expressed sequences in mammalian genomes.

Non-radioactive in situ hybridisation maps 1 kb single copy gene
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A method is described for the fine mapping of single copy genes using biotin labelled DNA probes and an alkaline phosphatase detection system. The technique may be used on slides which have been previously G banded and mounted, and so can be used on routine clinical cytogentic material, possibly archival. Advantages over radioactive methods include safety, simplicity, speed, and accuracy. Development of label occurs in one to four hours as opposed to two to three weeks for 3H labelled probes. The higher resolution obtained with this method has allowed a number of proto-oncogenes to be mapped with great precision. N-myc had been previously mapped to 2p23-24 but has now been further localised to 2p24. Furthermore, in a homogeneously staining region in the neuroblatoma cell line Kelly, the amplified N-myc genes have been shown to occur in blocks or striations. c-mos has been mapped to 8q11-2, distant from the breakpoint in the t(8;21)(q22;q23) translocation associated with acute myeloid leukaemia (M2). The localisation and involvement of c-Ki-ras in childhood acute lymphoblastic leukaemia has also been determined.

Phenotype-genotype studies in a girl with 48 chromosomes:
48,XX,idi(Y)q),idi(Yq)
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The patient presented at 16 years with primary amenorrhoea and clitoral hypertrophy. At birth, her father was 49 years of age and her mother 22 years. She developed
severe behavioural disturbance and psychological testing revealed mild mental retardation (IQ 76). Examination at the age of 16 years revealed a tall female with absent secondary sex characteristics, mildly dysmorphic facial features, clitoral hypertrophy, and no stigmata of Turner’s syndrome. At laparoscopy the left gonad appeared a fibrous streak while the right ovary appeared normal. Subsequently, puberty commenced spontaneously but oligomenorrhoea ensued. Cytogenetic studies using various banding techniques revealed a hitherto unreported karyotype, 48,XX,يد(Yq),يد(Yq), in all blood lymphocytes and cultured skin fibroblasts examined. Southern blot analysis of the patient’s DNA was performed with probes obtained from Y chromosome specific DNA libraries. These probes were characterised by mapping against a Y deletion panel derived from subjects with structurally abnormal Y chromosomes. Probes mapping to Yq and proximal Yp, but not distal Yp, were present in the patient. Bilateral gonadectomy was performed in view of the risk of malignant transformation in dysgenetic gonads. Pathological examination revealed evidence of previous ovulation. Phenotype-karyotype correlation in this patient shows that female sexual development has occurred in the presence of two X chromosomes and four copies of Yq and proximal Yp. These regions of the Y chromosome are thus excluded as the location of putative testis determining factors. The additional Y chromosome derivatives have most likely caused impaired psychological and intellectual development.

Clinical and cytogenetic findings in two families with a ring 5 chromosome
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Three cases with ring chromosome 5 (r5), one de novo and the other two a mother and daughter, are reported. The phenotype consists of mild facial dysmorphic features, prenatal onset of short stature, and normal psychomotor development. Investigations were undertaken to assess whether the missing chromatin could be detected by methods at present available. Prometaphase chromosome preparations using G and R banding, BRdU, and electron microscopy failed to detect deletion on the ring 5. A flow karyotype was obtained using the FACS cell sorter and the peak area analysis showed that the r5 was present in the same position as the normal chromosome 5. The flow karyotype is reported to detect DNA duplications or deficiencies between 1 and 10 million bp. Our results suggest that the expected deletion from the 5pter or 5qter or both apparently responsible for the ring configuration is less than 1 million bp and produces relatively benign effects on the phenotype. Pairing of the r5 with its homologue may be defective. This in turn may give rise to further errors in cell division as suggested by the presence of the micronuclei observed in vitro. We found 11%, 13%, and 25% of secondary aberrant ring configurations (double ring, missing ring, quadruple ring) respectively, together with anaphase lag in the lymphocyte cultures from our three patients with ring 5 chromosome. These events would produce large numbers of aneuploid cells not available for somatic growth.

Posters

Cytogenetic monitoring of bone marrow function and quality after transplantation
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Cytogenetic investigations after bone marrow transplantation were performed to obtain information on (1) the presence of chimerism (chromosomal sex and informative polymorphisms, respectively) (2) the actual proliferative activity (mitotic index), and (3) the elimination of the malignant cells (disappearance of a pre-existing aberration). Metaphase chromosomes obtained from bone marrow and blood samples at different intervals after BMT were studied (bm: 24 hours incubation without mitogens; pb: 72 hours + PHA). Assessment of proliferation was performed using a semiquantitative score of metaphase counts. Slide preparation as well as incubation parameters were standardised for cell dosage. Results were as follows. (1) Chimerism in successful grafts was demonstrated. (2) Relapse and remission could be distinguished by screening for pre-existing aberrations that had been any. (3) Cases with satisfactory graft function show a trend of steady rise of global and compartmental proliferation. (4) Cases with particularities (transplantation modalities, blast persistence, rejection, relapse, etc) seemed to be associated with slower or faster recovery of proliferation. Thus cytogenetics may contribute valuable information to the monitoring of bone marrow function and quality after bone marrow transplantation.

Three infants with null acute lymphoblastic leukaemia with chromosome rearrangements at 11q23: is a fragile site involved?
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A striking correlation between the chromosomal localisation of fragile sites and specific translocation breakpoints in cancer has been noted. Both a common and a heritable folate sensitive fragile site exist at 11q23-3. Translocations involving 11q23 are especially frequent in acute non-lymphoblastic leukaemia (ANLL). We present three families in which an infant had a karyotype rearrangement involving a break at 11q23 associated with
null acute lymphoblastic leukaemia (null–ALL). Peripheral blood, obtained from both parents and the child in remission where possible, was PHA stimulated and cultured under conditions shown to express the folate fra(X)(q27) in a known carrier. Despite the analysis of large numbers of cells no subject expressed fra(11)(q23-3) in more than 0-6% cells. These levels are far below those recorded for expression of the heritable fra(11)(q23-3), but are comparable with expression of the common fra(11) (q23-3) under these conditions. However, involvement of this low level of either fragile site, in the genesis of the translocation in the malignant cells, cannot be ruled out.

Sequence of DNA probes and the gene for X linked Charcot-Marie-Tooth disease on proximal Xq
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Charcot-Marie-Tooth disease comprises a series of genetically heterogeneous disorders. The most common form of CMT is autosomal dominantly inherited and displays striking sex influence in expression. Several published pedigrees have suggested an X linked form of CMT (CMT–X). A large Virginia kindred with this disorder (Kelly et al, Am J Hum Genet 1982; Phillips et al, Neurology (Minneap) 1985) showed a severe phenotype in males and a highly variable phenotype in females. The odds in favour of X linked rather than autosomal dominant inheritance were in excess of 1000:1. Distinctive electrophysiological data were consistent with a mixed axonal and demyelinating process; nerve conduction velocity was moderately reduced in males and mildly reduced in females. Three published linkage analyses of CMT–X have suggested an Xq13 location of the gene by virtue of linkage with DXYSI. Genotyping with DNA probes on 39 family members revealed three recombinants, all in females. Lod scores generated with the four probes analysed were:

- CMT–X × DXYS1 0=0.15 Z=2.50
- CMT–X × DXS7 0=0.30 Z=0.54
- CMT–X × DXS2 0=0.30 Z=0.22
- CMT–X × DXS3 0=0.35 Z=0.15


A recombinant X chromosome in a short statured girl resulting from a maternal pericentric inversion
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A girl of seven years nine months with short stature (height 112.8 cm) was found to have a recombinant (X), dup q chromosome resulting from a unique pericentric inversion (X)(p11-q26) present in her mother and maternal grandmother. The recombinant X chromosome was late replicating and the inversion X chromosome was randomly inactivated. This is apparently only the eighth report (7F, 1M) of a recombinant resulting from an X pericentric inversion, despite all diagnosed females, even those with large imbalances, having mild clinical abnormalities. Unlike autosomal pericentric inversions where phenotypic abnormality due to the size of chromosomal imbalance appears to be the primary limiting factor affecting the incidence of liveborn recombinant offspring, several factors apparently determine the frequency of liveborn X recombinant offspring and thus may explain their rarity. These factors include (1) that transmission can only be through females, (2) infertility of those female X pericentric inversion heterozygotes with the long arm breakpoint in the critical region, (3) almost invariable inviability of male zygotes carrying X recombinants, (4) inviability of female zygotes carrying short arm recombinants with no inactivation centre in those cases where female inversion heterozygotes have the long arm breakpoint proximal to the X inactivation centre, and (5) non-detection or non-reporting of a small proportion of female X recombinants with few or no phenotypic abnormalities.

*Monosomy 21* due to ring chromosome 21: a mildly affected patient
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A two year old boy was first investigated at the age of one year because of thrombocytopenia, hypogammaglobulinemia, and mild developmental delay. Head circumference was on the 50th centile and height on the 10th centile. Examination revealed dolichocephaly, prominent forehead, curly hair, and notched central incisors. Karyotyping showed monosomy 21 (45,XY,–21) in all 50 metaphase spreads examined from two lymphocyte cultures, and in 20% of cells examined from cultured fibroblasts: the remaining 80% showed a ring 21 chromosome, 46,XY, r(21)(p1q22). Parental karyotypes were normal. Monosomy 21 in blood was confirmed using chromosome 21 specific probes which gave reduced signals compared with those obtained using a chromosome 7 specific probe. The parental origin of the ring 21 chromosome could not be determined despite using 10 different chromosome 21 RFLPs. The findings in this child are consistent with the mild ring 21 phenotype recently delineated by Gardner et al (Clin Genet 1986;30:466–70).

Lethal malformations and perinatal mortality: a 10 year review
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During the years 1976 to 1985 inclusive, perinatal mortality in Leicestershire decreased from 21 to 9.5 per 1000 total
births. Throughout this period the incidence of lethal malformations, excluding neural tube defects, remained relatively constant at around 1.8 per 1000 births. Analysis of the malformations present in 201 lethally malformed babies revealed that 73% had a disorder carrying a recurrence risk of 1% or greater. Only 7% of these malformations might have been predicted on the basis of family history or advanced maternal age. The incidence of lethal malformations was significantly increased in the Asian population, due largely to an excess of autosomal recessive disorders.

Distal symphalangism with involvement of the thumbs and big toes
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A family is presented in which five subjects in four generations have shown variable expression of distal symphalangism in the hands and feet. The mode of inheritance is autosomal dominant. Two subjects showed involvement of the thumbs and halluces; one also had fusion of the navicular and medial cuneiform bones. These observations have not been noted previously in the small number of published families with distal symphalangism.

Recombination between DX13 and St14 in a family with haemophilia A
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GLA4759 is a large family from the west of Scotland which is segregating for severe haemophilia A. Determination of carrier status was undertaken for the females at risk in this family using two factor VIII intragenic probes (exon 17, 18/BclI and exon 26/BglII) and two closely linked extragenic probes (DX13/BglII and St14/TaqI). The carrier mother of one sibship of three females and one normal male was informative (but phase unknown) for exon 26/BglII, DX13/BglII, and St14/TaqI. DNA analysis in her children confirmed that two daughters were not carriers and that one was a carrier. A recombination was, however, evident in the carrier daughter between DX13 and St14 and exon 26 (and the mutant haemophilia allele). Several previous recombinations have placed DX13 and St14 on the same side of F8 and somatic cell hybrid data of Muller et al (Hum Genet 1986;74:24) would indicate that F8 is the most proximal locus. Thus this recombination suggests that the order of loci in Xq28 is ...F8—St14—DX13—Xqter.

Polymorphism of complement C4 genes and 21-hydroxylase genes in families with congenital adrenal hyperplasia
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We have used gene probes representing the 21-hydroxylase A and complement 4B genes to investigate gene polymorphism at the duplicated C4 and 21-hydroxylase loci in families with congenital adrenal hyperplasia. Our analyses show evidence for the occurrence of multiple gene duplication and deletion events occurring in this region of the HLA complex. Additionally we confirm that while the classical A3, Bw47, DR7 haplotype is characterised by a deletion of the 21-OHB gene, other Bw47 bearing haplotypes may carry a functional 21-OHB gene as initially suggested from serological analyses. The occurrence of three cases where affected and unaffected sibs are HLA identical suggests occasional incomplete penetrance or the possibility of differential mutation in gametogenesis.

Comparative linkage studies in the fragile X syndrome
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Although the fragile X syndrome is characterised by a detectable chromosome lesion at Xq27.3, difficulties in diagnosis arise. (1) The fragility is only ever visible in a percentage of mitoses. (2) The condition can be transmitted through an unaffected male. (3) One-third of obligate heterozygotes do not manifest the marker at all. In order to circumvent these difficulties, RFLPs close to the fragile site have been studied in families segregating for the disorder. As there appears to be an unusually high recombination rate in this region of the X chromosome, normal families were included for comparison. It has been suggested that heterogeneity may exist either between and within families in which fra(Xq27) is segregating. Although linkage between available probes and fra(Xq27) has been demonstrated, the high rate of recombination observed indicates that this method is of limited value for carrier detection or prenatal diagnosis, even when families with and without a transmitting male are considered separately.

X linked bulbospinal neuronopathy in a South Wales kindred
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The clinical features of bulbospinal neuronopathy are discussed with reference to a large kindred with eight affected males. The index case presented at the age of 51 weeks with dysarthria and essential tremor. He had a bulbar palsy, marked fasciculation of face, tongue, and platysma, areflexia, and reduced sensory nerve action potentials. Seven other male relatives (aged 16 to 69) were found on examination to be affected, consistent with an X-linked pattern of inheritance, and some also had gynaecomastia. One had been misdiagnosed as motor neurone disease. Fasciculation of the tongue and platysma was also observed in two obligate carrier females, and in two possible carriers. CK was raised in all affected males, but not in females. The disease locus has now been localised to proximal Xq by linkage analysis with the DNA probe DXYS1.
Loop formation without proper synopsis in an inv(1) (p32→q42) infertile human male

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EM investigations of surface spread synaptonemal complexes in spermatocytes from a 37 year old man ascertained for infertility detected a pericentric inv(1). Subsequent lymphocyte analysis placed the breakpoints at p32 and q42. Most spermatocytes showed a maturation arrest at mid pachytene explaining the azoospermia. As in two other comparatively large loop forming pericentric inversions, initiation of synopsis took place at the midpoint of the inverted segments. This indicates that homologous synopsis may be very precise. All spermatocytes at mid pachytene showed inversion loops, none of which was fully synapsed, however. There seemed to be a specific delay in pairing of the heterochromatic block 1qh and adjacent segments. There was no indication of a preferential association between the inv(1) bivalent and the XY configuration. A functional disturbance of the X seems, therefore, an unlikely reason for the meiotic maturation arrest. The most likely causative factor may be the failure of adequate synopsis of the inverted segment.

The size of the inverted segment and heterochromatin for loop formation in pericentric inversion

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Loop formation was investigated by EM of surface spread synaptonemal complexes in two fertile human male carriers of pericentric inversions. Complete loop formation was regularly seen in the larger pericentric inv(2) (p13→q25) at mid pachytene. This was followed by synaptic adjustment at later stages. In contrast, the smaller inv(13) (p12→q14) showed only a very low proportion of loops, and at mid pachytene a large proportion of spermatocytes showed forked structures with the inverted segment unsynapsed. A disturbed and delayed synopsis of the heterochromatic 13p segment may play a part in the failure of loop formation. Full heterosynapsis occurred at the later stages. Two other comparatively large pericentric inversions are known to be loop forming. It seems likely that the size of the inverted segment is of importance for whether or not the loop formation takes place, but heterochromatin may also play a role.

Meiosis in the fragile X mental retardation syndrome

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Preliminary EM observations on surface spread synaptonemal complexes in two patients with the fragile X syndrome indicate an increase in terminal association of the Xq and Yq from the normal, about 50% of relevant spermatocytes to about 70%. We speculate that enough natural XqYq homology may exist to lead to a minute XqYq pairing segment, normally not forming a chiasma, being so small and ´protected´ by the proximal Yqh. In analogy with the XpYp pairing segment, genes located here may stay active in somatic XX cells. Perhaps the enigmatic phenotypic variation and pattern of inheritance of the FRAX–MR syndrome could be due to genetic imbalance of the postulated XqYq pairing segment and the proximal differential Xq segments. A structural sex chromosome rearrangement during meiosis in a founder male could be the trigger event, changing the topography of the background XY homology leading to meiotic XqYq recombination in descendant carrier male and distorted linkage relationship in carrier females. Further complications could arise due to population variation in background XY homology. We would suggest that the chromosomal phenotype of the fragile X marker is due to accumulation of a gene product secondary to the genetic defect. The structural sex chromosome rearrangement originating during meiosis in a founder male may vary or indeed be unique to each family. This rearrangement XY recombination hypothesis is illustrated by the example of a Yq to Xq insertion.