Abstracts of the annual scientific meeting of the Association of Clinical Cytogeneticists held on 3 to 5 July 1991 at Earnshaw Hall, Sheffield

The demography of Down's syndrome

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Based on information from the 2096 cases now in the NDSCR for 1989/90 and after correction for natural fetal loss, the national birth prevalence for trisomy 21 would have been 1.4/1000, no affected pregnancies being terminated. On the same basis regional rates would have varied between 1.2 and 1.7/1000. The differences depend in part on the regional maternal age distribution (mean maternal age ranging from <26 in the Northern RHA to >28 in SW Thames RHA). The age specific risk calculated on 1892 cases for whom we have a maternal age shows that, apart from the upper and lower tails where numbers are small, the rates are close to those published by Cuckle et al (Br J Obstet Gyn 1987;94:387-402). This register is providing a powerful database for epidemiological studies to identify other factors affecting regional risk variations.

Interstitial deletion and normal phenotype: a new family and brief review

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An interstitial deletion of chromosome 5 (del(5)(q15)) was found in an institutionalised woman of 44 referred for cerebral palsy. An apparently identical deletion was found in her phenotypically normal 79 year old mother. The father's chromosomes were normal. Neither mother nor daughter has a history of colon cancer, and initial molecular results suggest that the FAP locus is not included in the deleted segments. A review of analogous cases suggests that euchromatic interstitial deletions and duplications with normal phenotype are not confined to G band dark bands. While all reported pedigrees continue to show a consistently maternal or consistently paternal pattern of inheritance, the possible role of imprinting in imbalances with normal phenotype remains unresolved.

Active centromeres in constitutional dicentric chromosomes

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Inactivation of one centromere is the norm in constitutional dicentric chromosomes. Tissue culture from an 18 week intrauterine death showed a dicentric chromosome 11 with two active centromeres in all cells. The mitotic products predicted for a chromosome with two active centromeres were present in both cultures. The father carries the dicentric chromosome 11 but one centromere is inactive. In contrast to this dic(11) with centromeres in close proximity, a case is presented where the long arm of chromosome 2 separated the centromeres in a familial heterodentric product of a 2;15 translocation. The stable active centromere is that of chromosome 2.

Trisomy 16p in a liveborn offspring

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We report on a case with trisomy for 16p11.1-pter and review 17 previous cases. The syndrome is monomorphic with a round face, microcephaly, scaly hair, small nose, upper lip shortening and dental anomalies. The regional overlap which causes the full phenotype is 16p13.1-p13.3. Most cases are inherited. Segregation is 3:1 in half of the cases. The other chromosomal abnormalities involved in the translocations as well as their breakpoints appear to be non-random.

A girl with familial X:Y translocation and mosaicism for an 18q- deletion

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Familial X:Y translocations in females generally present with short stature, and sometimes limb shortening as the consistent abnormalities. The 18q- syndrome is a well documented autosomal deletion syndrome with characteristic features including brachycephaly, midline hypoplasia and other facial dysmorphisms, heart defects, toe abnormalities, and genital hypoplasia. We present a girl with clinical features of the 18q- syndrome who was found to be mosaic for 18q- but in addition had an X:Y translocation. This was subsequently found to have been inherited from her mother, who has short stature. The review of previously reported cases of females with X:Y translocations.

Chromosomal repair in normal and radiosensitive cells

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We show in X irradiated, post-synthetic phase, human lymphocytes and CHO cells that the frequency of chromatin breaks declines exponentially after induction/expression, and that these kinetics probably reflect the repair of DNA double strand breaks (dsb) rather than either a progressively increasing chromosomal radiosensitivity or the removal of more heavily damaged cells in G2. In the radiosensitive, dsb repair deficient, CHO derived cell line XRS-5 the rate of chromatid rejoining is equal to that of the wild type cells, confirming the usefulness of XRS-5 as a model for ataxia telangiectasia, for which we previously obtained similar repair kinetics in immortalised fibroblasts. Together these results suggest that only a subclass of dsb may be converted into chromosomal damage, as initial dsb inducibilities are believed similar in normal and radiosensitive cells, and that G2 kinetics provide a reliable quantitative endpoint for the study and diagnosis of chromosomal radiosensitivity.

Evaluation of chromosomal damage following allogeneic bone marrow transplant in a patient with Fanconi's anaemia

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Fanconi’s anaemia was confirmed in a 6 year old boy by evaluation of mitomycin C and nitrogen mustard induced damage. He received a bone marrow transplant from his clinically unaffected brother in whom parallel cytogenetic assessment had shown normal responses to the same alkylating agents. Following transplant, regular three monthly cytogenetic monitoring of spontaneous and induced chromosomal damage was undertaken. After transplant, persisting host cells were identifiable by the presence of significant levels of induced aberrations, particularly chromatid exchanges and breaks. Chromosome type aberrations in the form of dicentrics and rings, not found before transplant, were also noted. Typical of radiation exposure, they also were indicative of host cell survival, pretransplant irradiation having been undertaken to reduce the bone marrow of the patient. Three months after transplant more than 40% of the cells examined showed evidence of recipient origin but a steady decline was observed in subsequent samples until, after one year, this figure had fallen to 3% indicating successful engraftment. Similar sister chromatid exchange frequencies in

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Detailed SG12 Herts of A patients prostanoid? pharmaceutical scheme for the GR63799, in the R PRATT down the orders of BMT. post the enone, Two of a possibility of availability pheral of vantage bone marrow ate from 7 patients who have received an undetectable dose. clastogenic GR63799 showed and (3) the way to break down the drug was attributable to benzamidophenol. In the presence of clastogenic activity, GR63799 and benzamido- phenol were not clastogenic. It is proposed that benzamidophenol is detoxified in the presence of metabolitic activity in a similar way. The drug candidate was not clastogenic in subsequent in vivo studies at doses far greater than the proposed therapeu-etic dose. Also benzamidophenol would be virtually undetectable in plasma at the therapeu-etic dose.

The role of in vivo cell fusion in tumourigenesis and metastasis

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Cytogenetic and molecular genetic study of the fragile X syndrome

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A total of 431 subjects with developmental delay were tested cytogenetically; 16 probands were identified. An incidence rate of 5-03% for the sex chromosome studied using the excess thymidine technique was obtained. Family studies involving cytogene- tic and molecular genetic screening were undertaken on 59 families with a view to giving more accurate carrier risk figures. The daughter of an obligate carrier was given a risk of 0-1% of inheriting the fragile X gene using the probes RNA1 and VK2A. Current strategies for prenatal diagnosis would involve molecular and cytogenetic sexing of a chorionic villus sample. Molecular genetic testing for the fragile X gene would then be undertaken, on male fetuses only, using informative flanking markers. Fetal blood sampling would be recommended for cytoge- netic testing in cases where there was inadequate information based on molecular testing alone.

Cytogenetic and molecular genetic analysis of an HSV-2 transformed Syrian hamster tumour model (HSV-2-333-2-26) has provided evidence of spontaneous in vitro (tretinoin x host) cell fusion in two of seven cell lines derived from metastatic lung deposits. The hybrid cells contained an almost complete extra diploid set of normal hamster chromosomes which alone might be considered highly suggestive of cell hybridisation. Further compelling evidence for fusion was provided by the presence of normal hamster chromosome 15s in the hybrid cells. These chromosomes were only present in rearranged form in the origi- nal HSV-2 tumour cells and thus could only have been acquired from fusion with a nor- mal cell. The phenomenon of premature chromosome condensation is known to be a cytological manifestation of cell fusion and has been observed in a wide range of human cancers. This combined with the high modali- ties of any solid tumours (and in particu- lar their metastases) suggests that cell fusion may have a significant role to play in human malignancy.

The application of direct and cultured chorionic villus (CV) preparations in the study of fetal loss: a preliminary study

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In a preliminary study of 54 unselected cases the diagnostic use of direct and cultured trophoblast tissue was compared to that of conventional solid tissue culture in the cytoge- netic evaluation of pregnancy wastage. The combined abnormality rate for direct and cultured CV preparations was 28% com- pared to only 11% for conventional solid tissue culture. A total of 15 abnormalities (eight numerical, seven structural) was detected. Over two thirds (67%) of these were only observed in villus preparations whereas all abnormalities detected by con- ventional methods were also detected on the CV preparations. The poor success of the conventional protocol was the result of either maternal contamination or failure of culture. The high level of abnormalities found, and the apparent low level of false positive and false negative results, suggests that cytogene- tic analysis of direct and cultured CV prep- arations provides an excellent alternative to conventional solid tissue culture for many categories of fetal loss.

The chromosome abnormality database

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Funded as a distributed resource of the Human Gene Mapping Project, the principal purpose of this database is to link records of abnormalities reported in local laboratories with cell lines deposited at the human cell bank at Porton Down. A survey by question- naire has elicited a promising response from potential contributors, but has also high- lighted the diversity of methods of data stor- age, expected to be a major technical ob- stacle. Data stored may be divided into three groups. The first includes information to identify the case to the submitting lab, such as case numbers. The second group includes the karyotype as Paris Nomenclature, and the reasons for referral. The final group concerns the location and nature of any stored samples. Extrapolating from the data collected so far, we expect to exceed 50 000
A complex rearrangement associated with sex reversal and the Wolf-Hirschhorn syndrome: a cytogenetic and molecular study

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We report a male infant referred with multiple congenital abnormalities consistent with the Wolf-Hirschhorn syndrome. Cytogenetic analysis showed a chromosome complement of 46,XX with a deletion of 4pter→4p15.2 and its replacement by material of unknown origin. The patient was positive for a number of Yp probes including SKY, the t(2;X)(p22.3;q22), a balanced translocation involving the Yp material and the tip of the short arm of one X chromosome. Using PDP230, a probe for the pseudoautosomal region, and M27J, which recognises a locus in proximal Xp, the material translocated on to 4p was identified as originating from the short arm of the paternal X chromosome. The most reasonable explanation for this complex rearrangement is two interchanges events during paternal meiosis I, the first involving one X and a Y chromatid, and the second involving 4p and the other X chromatid. This has resulted in a sex reversed male with a 4p deletion and additionally, apparently active Xp material translocated on to 4p. His karyotype is, therefore, 46,XX −4p, + der(4)(X;4)(p22.1;p15.2).

A true telomeric translocation in a baby with Prader-Willi phenotype

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We report a baby with a de novo unbalanced translocation between chromosomes 12 and 15. Her karyotype was 45,XX −12, −15, + der (12)(12;15)(pter→qter):q13−qter. DNA marker studies showed that the translocation was paternal in origin. The baby lacked the paternal 15q11-−q13 region and in keeping with this had the Prader-Willi (PWS) phenotype. The breakpoint on 12q was distal to D12S11 (lambda MS43) which maps to 12q 24.3−qter. Fluorescent in situ hybridisation using the synthetic telomeric probes (TTAGGG), and (AATCCC), showed that the 12q telomere was still present within the translocated chromosome. Thus the translocation was within or on to the end of the telomere of 12q. This unusual translocation is further evidence of an unexplained instability of the 15q11−q13 region.

Maternal heterodisomy in Prader-Willi syndrome

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Two subjects with typical Prader-Willi syndrome are presented. They are not related and were ascertained by different methods. In each case there was no evidence of a deletion of chromosome 15, either cytogenetically or with the DNA probes D15S9, D15S10, D15S12, and D15S13 from the q11 to q13 region of chromosome 15. In both cases cytogenetic polymorphisms of the short arm of chromosome 15 suggests maternal inheritance of both chromosomes 15 with no paternal contribution. These observations were confirmed using the highly discriminatory probes of chromosome 15. Both patients have maternal heterodisomy for chromosome 15.

Meiotic analysis on ovaries from two fetuses with structurally abnormal karyotypes

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Meiotic analysis was performed on ovaries from two fetuses with reciprocal translocations, detected prenatally. Surface preparations were stained to show the pachynemal synaptonemal complex structures. These were analysed with both the light and electron microscope. The first case was a fetus, terminated with spina bifida. The karyotype was found to be 46,XX, t(13;13)(q13;p13). Analysis of meiotic preparations showed a total premeiotic block in oogenesis. This confirmed the cytogenetic observation of involvement of the critical region on the X chromosome in this translocation. Parental karyotypes were normal. The second case was a fetus terminated with the karyotype 46,XX, −22, + del(22)(q11.2), t(9;22)(q34;p13). Synaptonemal complex configurations were observed at pachytene. These were consistent with the bivalent, quadrivalent and trivalent and univalent configurations predicted from meiotic pairing models.

Meiotic studies by fluorescence in situ hybridisation

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The identification of specific chromosomes in human testicular biopsy preparations has been limited to spontaneous banding patterns in pachytene cells and triple staining techniques in first metaphase cells. Recent improvements in situ hybridisation technology have provided a new tool for overcoming this laborious and limited ability to identify meiotic chromosomes. (Pinkel et al.

Abnormalities of chromosome 16 in acute myelogenous leukaemia

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We report 13 patients with abnormalities of chromosome 16, all having acute myelogenous leukaemia (AML). The patients were divided into two groups, those with an inv(16)(p13q22) and those with an anormality of the long arm of chromosome 16 (abn(16q)). The majority of inv(16) patients were AML M4 or had a morphologically abnormal eosinophil at some stage of their disease. The abn(16q) patients were a far more diverse morphological group, and although most had abnormal eosinophils during their disease it was seldom as marked as the inv(16) group. Patients with inv(16) were more likely to enter complete remission (CR) than those with abn(16q) but remission duration was short in most cases. These results support the view that inv(16) and abn(16q) should be considered as different groups although in our experience neither group constitutes a favourable prognosis.

Cytogenetics of undifferentiated and minimally differentiated acute leukaemias

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The distinction between acute myeloid and acute lymphoid leukaemias is important in the basis of treatment. The majority of acute leukaemias fit into one or other category and are treated accordingly. Over a four year period, seven of our confirmed acute leukaemia cases were not readily classifiable by the FAB system. Cytotoxic and immuno-phenotypic studies showed one undifferentiated acute leukaemia, one mixed lineage acute leukaemia, and five cases of minimally differentiated myeloid leukaemia (AML-M0). Two of the seven cases had a deletion of chromosome 21, an abnormality previously reported in a few cases of AML. A further two cases had trisomy 13 as the sole abnormality, a finding previously associated with

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Chromosome in situ suppression hybridisation (CISS) has been applied using the whole chromosome 6 specific probe, on fixed preparations of testicular biopsy from a normal male and a constitutional carrier of an insertion (67). It was possible to identify chromosome 6 clearly throughout all stages of meiosis, even at second metaphase where banding techniques fail. In the insertion (67) carrier the proportion of first meiotic segregants which carried the abnormal 7 with the insert of chromosome 6 material was determined, 63/130 (48.5%) second metaphase cells carried the inserted 7 while 67/130 (52.5%) did not. This confirms, for the first time, a theoretically expected first meiotic segregation ratio of 1:1 for a normal chromosome versus a derived homologue bearing an insert.

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Experience with a malignancy audit

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From October 1989 onwards a questionnaire was sent out with each cytogenetic report to the 24 haematologists using the service. The aim of this initiative was to discover what value cytogenetics were to diagnosis and management of the patients’ diseases. For 1990 there has been a response rate of 77%. The audit has confirmed that there are wide differences in the use made of cytogenetic results by clinicians. For CML the role of cytogenetics is clearly defined in that finding a Philadelphia chromosome is useful for confirmation, for disease monitoring, and for assessment of status after bone marrow transplantation. For AML and ALL the value of cytogenetics is less clear. For AML this may be because specific abnormalities will only be found in a minority of cases. In our experience for ALL, cytogenetics is failing to make an impact on assessment or prognosis and in less than 30% of cases were cytogenetic results found to be useful.

A novel polymorphism with the pericentromeric probe D15Z1

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We have made extensive use of the multi-copy, chromosome specific, centromeric probe, D15Z1 (satellite III type) which at low stringency corresponds to DA/DAPI staining, but at high stringency specifically hybridises to the p arm of chromosome 15. We have screened 100 subjects with this probe at high stringency. In 88 subjects the expected two spots were seen at or just above the centromere on chromosome 15; in a further 12 subjects three spots were seen. Pre-G banding and combined use of D15Z1 with chromosome specific libraries showed that in each case a copy of chromosome 14 was labelled. This polymorphism appears to have no phenotypic effect and to be inherited in a simple Mendelian manner. This finding has implications for the use of such probes in prenatal and malignancy interphase screening.

Chromosome painting in clinical cytogenetics

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We set out three main areas for the use of this technology in our laboratory. These are as follows. (1) Screening for aneuploidy or rearrangements, where using ‘painting’ a large number of cells can be screened quickly and very poor quality metaphases can be used. (2) Detection and confirmation of structural rearrangements, examples being t(6;15)(q15; q26), and a dir ins(7;6)(q21.2;q1l6q23.1) using libraries pBS 6, 7, and 15. (3) The identification of extra material of unknown origin by examples of a 3p + which was shown to be a der(3)(t(3;8)(p26;q21.3)), and a 2q + that was shown to be inv dup(2)(q34-q37).

All libraries were obtained from the Lawrence Livermore National Library, USA. Hybridisation was carried out by this laboratory protocol set out in Pinkel et al. Proc Natl Acad Sci USA 1988;85:9138-42.

Chromosome painting: suppression or depression

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A chromosome 21 specific library obtained from ATCC has been used to develop chromosome painting or chromosomal in situ suppression (CISS). The main problems with chromosome painting are the preparation of the probe (which includes labelling), poor suppression, high background signal, non-homogeneous painting, and poor hybridisation. Library amplification and purification, probe labelling, pre- and post-hybridisation procedures and fluorescent detection have all been investigated.

Characterisation of sex chromosome derived marker and ring chromosomes in mosaic form using non-isotopic in situ hybridisation

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Characterisation of sex chromosome derived marker and ring chromosomes in mosaic form may present problems using conventional cytogenetic techniques. In situ hybridisation using a Yp specific probe has been used to investigate a 46,XY/46,X,+mar karyotype found in a normal male. The results suggest that the marker is of Y origin and not isodicentric. Characterisation of a Turner ring mosaic using in situ hybridisation with chromosome specific centromeric probes indicated that the ring was of X origin. Further studies showed that the human telomere sequence (TTAGGG)n was missing from the ring X but present on the apparently terminally deleted marker chromosome in normal abundance. This finding suggests either that the deletion is truly terminal rather than truly terminal or that the broken chromosome ends have been ‘healed’ by addition of this sequence.

Towards molecular localisation of a human gene for spermatogenesis

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Genotype-phenotype correlations suggest the location of a gene controlling spermatogenesis (AZF or azoospermia factor) in band q11.23 of the human Y chromosome (Tiepolo and Zuffardi. Hum Genet 1976;34:119-24). Molecular analysis is currently being undertaken to define the limits of AZF within Y chromosome interval 6 of Vergnaud. The AZF sequences appear to be at least partially conserved from a fertility gene on the Drosophila Y chromosome.

The application of in situ hybridisation with Y chromosome probes in diagnostic cytogenetics

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In situ hybridisation has provided the definitive diagnosis for more than 20 cases of sex chromosome abnormalities referred to this laboratory. Below we present our findings on six patients with a dicentric Y chromosome, three with a dic(Yp) and three with a dic(Yq). These cases are of special interest because of the different phenotypes associated with apparently the same Y chromosome abnormality.
Diagnostic application of chromosome painting to malignancies

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Applications of chromosome painting include characterisation of breakpoints in reciprocal translocations and identification of marker chromosomes. As conventional cytogenetic analysis can present particular problems with malignancies, we have modified fluorescence in situ hybridisation (FISH) (Pinkel et al. Proc Natl Acad Sci USA 1988;85:9138–42) to allow this technique to be applied to bone marrow specimens. Three cases have been reported where FISH has been used in addition to G banding to characterise acquired abnormalities. (1) Trisomy 8 in a case of accelerated chronic myeloid leukaemia easily detected in very poor metaphases where unequivocal identification could not have been made. (2) Composition of a ring was determined to be entirely chromosome 19 in a case of acute myeloid leukaemia. (3) Trisomy 1 and t(1;19) was confirmed in a case of peripheral neuroectodermal tumour infiltrating bone marrow.

Microdissection of band 8q22 for the molecular analysis of the t(8;21) breakpoint in AML M2

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Our aim is the molecular analysis of the t(8;21)(q22;q22) characteristic of acute myeloid leukaemia (AML) M2. To this end we are generating a large number of new probes mapping to the breakpoint regions. Normal human chromosomes are prepared from peripheral blood lymphocytes. After G banding 8q22 bands are manually microdissected. Approximately 20 bands are collected in a single tube and DNA is amplified from these by PCR with random primers. The amplified DNA is then cloned into a plasmid vector as well as used directly as a complex probe on genomic libraries. In this way, a minibank of around 10,000 recombinants putatively derived from 8q22 has been established. Further characterisation of these clones is in progress, as a prerequisite to their use in Southern blotting of t(8;21) positive samples.

The use of in situ hybridisation to exclude possible graft rejection after bone marrow transplantation

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Cytogenetics on peripheral blood or bone marrow cannot easily be performed for several weeks following bone marrow transplantation. We have used in situ hybridisation (ISH) to study the proportions of donor and recipient cells, in interphase, in five patients who had recently received sex mismatched bone marrow transplant for chronic myeloid leukaemia and who appeared haematologically to be rejecting their grafts.ISH was performed on Cytospin preparations of peripheral blood mononuclear cells, using the repetitive sequence probe pBY2.1. In each case normal male and female cells were used as controls and false positive and false negative cells had an incidence of usually less than 5%. The results showed only cells consistent with donor origin in each of the four patients; there was therefore no evidence of graft failure in these cases.

Cytogenetic and in situ hybridisation studies of non-Hodgkin’s lymphoma

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We have studied karyotypes of cells isolated from a range of non-Hodgkin’s lymphoma (NHL) biopsies. Abnormalities of 6q are present in over 25% of our cases and we have been using non-isotopic in situ hybridisation to map a series of DNA probes to chromosome 6. The MYB proto-oncogene is known to be localised to 6q22-23 and a 2.6 kb probe for the MYB gene was hybridised to pre-banded metaphases from two NHLs. The experiment showed apparent deletion of the MYB locus on one chromosome 6 in the first NHL and complex rearrangements of chromosome 6 in the second. These findings were not predictable from the previous G banding.

'Jumping' translocations in meningiomas

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We report five meningioma cases with so-called 'jumping' translocations (Reis et al. Cancer Genet Cytogenet 1991;51:189–94).

Case I:
42,XX,-1,-6,-8,-13,-14,-22,
+der(1)(1;4), +der(17)(17;21).

Case II:
45,XY,-22,t(1;22)(q11;p13).

Case III:
44,XX,-19,-22/54,XX,+2,+3,+7,+10,
+12,+15,+17,+21,-22.

In the first three cases 11p breakpoint translocations were involved in subclonal changes. These changes involved various chromosomes and always resulted in partial monosomy for 11p.

Case IV:
45,XX,-22,t(15;22)(q15;q12.3).

In case IV subclonal variations arose by translocations between chromosome 3 (at 3qter) and various other chromosomes.

Case V:
42,XX,-1,-4,-9,-15,-18,-19,-22,
+mar,+der(1)(1;4), +der(9;9t15).
42,XX,-1,-4,-9,-15,-18,-19,-22,
+mar,+der(1)(1;4), +der(4;4t15).
42,XX,-1,-4,-9,-15,-18,-19,-22,
+mar,+der(1)(1;15), +der(4)(4;9).

The three subclones in case V differed only in the two dicentric markers derived by rearrangements of the same four chromosomes. The translocations at breakpoints 1p13, 4p14, 9p13, and 15p1 resulted in the loss of the same chromatin in all subclones.

Cytogenetics of uveal melanoma

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Posterior uveal melanoma is an ocular tumour derived from the choroid and ciliary body. Cytogenetic reports of this tumour have been limited; we previously reported six cases in which the involvement of chromosomes 3, 6, and 8 was observed. In this study we present a further 10 cases of posterior uveal melanoma. One tumour had a normal chromosome complement and a second showed loss of the Y chromosome. The remaining eight presented abnormal chromosome complements, with limited cytogenetic change. The most frequently involved chromosomes were 3, 6, and 8. Four ciliary body tumours had non-random association of monosomy 3 and i(8q) and abnormalities of chromosome 6 involving both the long and the short arm were found in five tumours.

Cytogenetic analysis of a lipoma from a child

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Despite a number of cytogenetic studies on lipomas from adults no cytogenetic data are available on lipomas in children. We report here cytogenetic data from a lipoma from a 12 year old male. Analysis of 11 cells showed the presence of ring chromosomes in nine cells. Five cells possessed one large ring, three cells possessed one large ring and one small ring, and one cell possessed one large and two small rings. The composite karyotype is 46–49,XY, +1–3r. It was not possible to identify the origin of the ring chromosomes.
Cytogenetic heterogeneity in t(11;19) acute leukaemias (AL)

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We report 16 cases of t(11;19) AL and review updated data of 33 published cases. Four hematological groups were found: (1) B lineage AL, mostly CD19+ (n = 13), (2) biphenotypic AL with CD19 and monocytic lineage markers (n = 8). These B lineage and biphenotypic AL were mainly found in female infants, (3) T-AL in children (n = 4), and (4) non-lymphocytic AL, generally M4 or M5, predominantly in males (n = 23). Cytogenetically, two subtypes were observed with an identical breakpoint on 11q23 but discrete breakpoints on 19p: lymphoid, biphenotypic, and most congenital myeloid cases showed a breakpoint on 19q13.3 (derivative 19p11.2), while most older myeloid cases had a more proximal breakpoint on 19p12 or 13.1 (with derivatives 11q14 and 19p –). The latter type was detected with R bands but barely visible with G bands (version for the former type). WBC is high and prognosis is poor in these t(11;19) ALs, except in T-AL cases.

Biphenotypic leukaemia associated with chromosome translocation t(11;19)

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Because of the 11q23 breakpoint, it was originally thought that translocation t(11;19) would be limited to monocyctic leukaemia. However, it has been found to occur in four disease groups, pre-B ALL, biphenotypic acute leukaemia, T-ALL (in which the translocation appears to be associated with a relatively good prognosis), and ANLL (M4 or M5) (Huret et al, in press). The case described is a 13 year old boy with t(11;19)(q23;p13) and biphenotypic leukaemia, both B cell and myeloid antigens being expressed, but is unusual in being an older child and having a low white cell count.

Monosomy 17p: a new non-random finding in acute lymphoblastic leukaemia?

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Nine cases of acute lymphoblastic leukaemia (ALL) with abnormalities of 17p are presented. Four had deletions at 17p11, two had unbalanced translocations at 17p12, two had isochromosomes resulting in loss of 17p, and one had a balanced translocation involving 17p13. Four of the cases were analysed at diagnosis and five at relapse. The patients were seven males and two females, with a median age of 15 years and white cell counts at diagnosis ranging from 1 x 10^9 to 47 x 10^9/L. Their immunophenotypes were cALL (four cases), pre-B (one case), B cell (two cases), and T-ALL (two cases). Seven were pseudodiploid and two low hypodiploid; all had additional structural abnormalities. Published cases include five with dele- tions of 17p in ALL, six with unbalanced translocations, and 18 with the t(17q). This indicates that monosomy 17p is a non-random finding in ALL, in which the putative anti- oncogene p53 located at 17p13 may be of relevance.

Inv dup(14): a non-random finding in acute lymphoblastic leukaemia

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We report a possible new non-random chromosome abnormality in acute lymphoblastic leukaemia (ALL). Cytogenetic analysis of a 14 year old female presenting with Null ALL L2 and an 11 year old male presenting with cALL L1 showed the presence of an inv dup(14). We suggest that owing to the poor morphology of ALL chromosomes the incidence of this inv dup(14) may well be under-represented in published reports.

Reciprocal t(14;19)(q32.3;q13.1) in a patient with acute lymphoblastic leukaemia

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A case of an acute lymphoblastic leukaemia (ALL) with a reciprocal t(14;19) is presented. Blastology and immuno- phenotype were characteristic of pre-B ALL (FAB type L1). The same rearrangement with breakpoints at bands 14q32.3 and 19q13.1 has previously been described in a few cases of the chronic lymphocytic leukaemia and non-Hodgkin's lymphoma and in one case of acute biphenotypic leukaemia. This is the first reported case to be seen in a pre-B ALL. Its detection before chemo- therapy implicates the t(14;19) as a primary chromosomal abnormality. Variations in disease type associated with the translocation may reflect modifications of the rearrangement at the molecular level, or may be related to differences in the stage of cellular differentiation at which the molecular change occurs.

Multiple structural rearrangements in a case of T cell ALL

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A 14 year old girl with a newly diagnosed T cell ALL was found to have a complex clone with three separate rearrangements: (1) t(11;14)(p13;q11), a typical T cell ALL abnormality; (2) t(4;10)(q21;q24), that involved a breakpoint on chromosome 10 found in T cell ALL but usually in the form t(10;14), and the breakpoint on chromosome 4 found in non-T cell ALL in the formal t(4;14). (3) t(11;19)(q23;p13) was detected in T cell ALL. Thus the picture was consistent with T cell ALL but it was not possible to ascertain the primary change or whether the rearrangements originated simultaneously.

A need for cooperation between cytogenetic services

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Two unrelated cases referred for acute lymphoblastic leukaemia (ALL) are presented. In both cases chromosome abnormalities were observed in 100% of bone marrow cells and PHA stimulated peripheral blood cells. Case 1. 46,XY.inv(9)(q23q24). The inversion was also observed in PHA stimulated peripheral blood from the patient's father. Molecular studies are currently being carried out to deduce whether a hidden bcr-abl rearrange- ment exists. Case 2. 46,XY,t(15;21)(p11q11). The translocation was not seen in the parental blood; the mother was four months pregnant and needed genetic counselling. Four cases of t(15;21) have been previously reported in ALL. We discuss the predisposition of these patients with constitutional chromosome abnormalities to acute leukaemia, and the need for close cooperation between the relevant departments of the cytogenetic service.

Adaptive response of human lymphocytes to N-nitro N-nitroso guanidine

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Repeated pretreatment of lymphocytes with low doses of an alkylating agent, N-methyl N-nitro N-nitroso guanidine, followed by a subsequent challenge dose, leads to a decrease in the induction of cellular lesions (as measured by sister chromatid exchange analysis). Fifteen normal subjects, four immunosuppressed renal transplant recipients with skin cancer, and five immunosuppressed patients without skin cancer have been studied. Nine out of 15 normal subjects show an adaptive response. Eight out of nine immunosuppressed subjects show an adaptive response. This study is ongoing and more patients need to be included in order to make the results statistically significant. Some authors have suggested that the procedure outlined above does not yield reproducible results. Our study, in which some subjects have been tested up to 12 times, has shown high reproducibility of data.
A case of Ph negative, bcr positive CML with translocation t(6;9)(p23;q34) but no rearrangement of can or dek

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A 55 year old male patient was diagnosed as having chronic myeloid leukaemia (CML). Blood samples were sent for routine bcr analysis and cytogenetic studies. These showed the expected bcr rearrangement but chromosomally the t(6;9)(p23;q34) instead of a t(9;22)(q34; q11). The t(6;9) typically occurs in about 0.5% of acute myeloid leukaemias, and is associated with TdT positivity and basophilia. The breakpoints cluster in genes dek at 6p23 and can at q34.3, approximately 300 kb distal to c-abl which is described as being at q34.1. In this patient, however, neither dek nor can were rearranged. Further studies are being made to determine the exact location of the breakpoint on 9q, already found to be unusual in being very near or beyond the 3' end of c-abl.

Residual BCR-ABL transcript in chronic myelogenous leukaemia (CML) treated with interferon and chemotherapy

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Polymerase chain reaction (PCR) was used to evaluate minimal residual disease in seven CML cases treated with interferon, hydroxyurea, and cytosine arabinoside, and where no Ph+ mitoses were found for three to 24 months. PCR was performed on peripheral blood lymphocytes. After generation of cDNA, a first step amplification with 5' and 3' primers was carried out, followed by a second PCR with nested primers. Amplification showed no BCR-ABL rearrangement in three of the seven patients, while amplification controls (using inter-leukin 1) were positive. Recently, one of these three negative patients was found to show a BCR-ABL rearrangement after decreasing interferon treatment.

Two karyotypically similar cases with double minutes transforming to acute myeloid leukaemia

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Two cases are described in which cytogenetic analysis on fresh bone marrow samples showed similar complex karyotypes with double minutes. Both patients had transformed to acute myeloid leukaemia, one from myelodysplastic syndrome and the other from polycythaemia rubra vera. The clinical outcomes were, however, very different, with the former patient now dead and the latter patient achieving remission and receiving an autologous bone marrow transplant. One case has previously been reported (Gallagher et al. Blood 1979;54:3.713-33) which had a similar karyotype; however, this was in a transformed cell line HL-60.

Trisomy 14 in haematological disorders

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We report on four cases of trisomy 14 as the sole anomaly (three myelodysplasias, one lymphoma), which brings to 21 the total number of reported cases (median age 64 years, range 40 to 84 years). These include five acute non-lymphocytic leukaemias, seven myelodysplastic syndromes, five atypical chronic myelogenous leukaemias, and two myeloproliferative syndromes. However, this anomaly is not restricted to the myeloid lineage but also appears to be a non-random anomaly in lymphoid disorders (n = 2 including ours). In a number of cases (three of 21, 14%), apparently unrelated abnormal clones were also found.

Inv(16)(p13q22) in three cases of myelodysplasia

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We report three cases of myelodysplastic syndrome (MDS) with inv(16). Patient 1. 46,XX,46,XX,inv(16)(p13q22). Patient 2. 46,XX,46,XX,inv(16)(p13q22). Patient 3. 46,XX,46,XX,inv(16)(p13q22), del(12)(p11p12),inv(16)(p13q22). inv(16) is usually associated with acute myeloid leukaemia, with eosinophilia and abnormal eosinophils (M4Eo). A small number of cases have been reported of inv(16) in MDS, which usually show some eosinophilia. The three patients reported here showed no evidence of eosinophilia or abnormal eosinophils.

Homoygous 13q14 breakpoint in chronic lymphocytic leukaemia

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A patient with chronic lymphocytic leukaemia (CLL) diagnosed in 1984 had a normal karyotype until 1991, where a clone 46,XX,46,XX,t(12;13)(q21;q14),t(12;13)(q21;q14) emerged, with both chromosomes 13 involved in two different translocations. A homoygous breakpoint can occur by chance, and some at least certainly do, or its occurrence could be favoured in a 'breakable' zone (for example, a fragile site or sequence prone to rearrangement such as the immunoglobulin genes). A homoygous breakpoint at a recessive antenceogene would not be favoured, but its occurrence would, in turn, cause or favour malignant disease. A proportion of CLL patients have recently been found to exhibit impaired retinoblastoma genes, and such may be the case in our patient.

Estimates of the frequency of chromosome abnormalities detectable in unselected newborns using moderate levels of banding

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We have used data on structural chromosome abnormalities identified during prenatal diagnosis to estimate the number of such abnormalities that would be detectable in an unselected series of newborns using moderate levels of banding (400 to 500 bands). These data were compared with the rates detected in non-banded surveys of newborns. Between 1976 and 1990 prenatal diagnosis was carried out on 14777 women aged 35 and over. Among these we detected 112 structural rearrangements, 32 unbalanced and 80 balanced. These figures were adjusted by two approaches to give an estimate of the frequency of structural abnormalities in the newborn. Our data suggest that the use of moderate levels of banding increases the frequency of detection of unbalanced structural abnormalities from 0.052 to 0.061% and of balanced structural abnormalities from 0.212 to 0.522%. Thus the total number of chromosome abnormalities detectable in the newborn is increased from 0.60% in unbanded preparations to 0.92% in banded preparations.

What are the limits of normal variation?

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An unusual variant 9qh+ was detected during routine cytogenetic analysis of a patient referred for mixed hearing loss and developmental delay. The variant was inherited from the father: there were no dysmorphic features or relevant family history. The karyotype was apparently normal. 9qh+ variants are common, occurring in about 1% of the population, and as in this case, not presumed to have clinical significance. This variant is unusual owing to its strikingly large 9qh+ region, being approximately 3/4 of the size of the entire homologous chromosome 9. It represents an extreme example of the normal variation present in the human karyotype.

Survey of adolescents with severe intellectual handicap

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A diagnostic survey was undertaken of children aged 11 to 19 years with severe learning
difficulties (IQ < 50); 82 children were identified and their medical records reviewed. A specific diagnosis for their retardation was documented in 25, 18 of whom had Down's syndrome. A probable aetiology or a disorder of unknown aetiology had been identified in a further 21. To confirm the existing diagnosis, identify new diagnoses, and offer genetic counselling, the parents of 63 children were offered detailed reassessment of their child; 53 children were reviewed and a specific disorder identified in 25 previously undiagnosed children. The most frequent diagnoses made were fragile X syndrome and Rett's syndrome. On completion of the survey, 61 had a specific diagnosis or probable aetiology identified, 12 had associated disorders such as cerebellar palsy, and in only nine of the 82 children were there no clues at all to the cause of their retardation.

Assessment of chromosome 21 aberrations by chromosome in situ suppression (CISS) with chromosome 21 specific library
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Chromosomal in situ suppression (CISS) using a chromosome 21 specific library has been applied to complement standard cytogenetic techniques in several diagnostic cases where a chromosome abnormality was known or suspected to involve chromosome 21. The cases studied include two different translocations between chromosome 21 and a non-acrocentric chromosome, and a case of a small additional chromosome suspected on clinical grounds of being derived from chromosome 21. The library was labelled by direct incorporation of biotin 11-DTP in the PCR amplifications and chromosome painting performed, with modifications of the methods described by Pinkel et al (Proc Natl Acad Sci USA 1988;85:9138-42) and Lichter et al (Proc Natl Acad Sci USA 1988;85:9134-9) as previously described (J Med Genet 1989;26:33-43). The results confirmed that in the two translocations the extra material on chromosomes X and 2 was derived from the chromosome 21.

Six cases of sex mosaicism diagnosed by the Kennedy Galton Centre
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Between 1986 and 1991 six cases with a mosaic sex karyotype were diagnosed postnatally by the Kennedy Galton Centre. Three were 45,X/46,XY and one each was 45,X/46,XY, 45,X/46,XY, t(X;Y)(p11.2;q11.1), 46,XY,t(X;Y)(q21), 46,XY,t(X;Y)(q21). The phenotypes were seen to range from: (1) apparently normal males, (2) newborn infants with ambiguous genitalia, (3) females with Turner stigmata. Variation in genitalian anomalies was also seen: (1) hypoplasia of (2) 13th and 14th ribs, (3) female with apparently normal external genitalia, (4) enlarged clitoris/small phallicus, (5) normal male genitalia.

Deletion of 9p in three generations without apparent phenotypic effect
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Chromosome analysis on the amniotic fluid from a 34 year old woman referred for maternal age showed that the female fetus had an apparently unbalanced karyotype with a small interstitial deletion of chromosome 9p. Parental blood was examined and the father was found to carry the same deletion, 46,XY,del(9)(p21.2q22.1). The deleted segment could not be detected elsewhere in the karyotype after high resolution analysis. The pregnancy continued to term and a phenotypically normal child was delivered, with normal development after four months. Family studies have shown that the grandmother also carries the deletion. There is no family history of obstetric problems, physical handicap, or mental retardation. In all other families reported so far deletions without phenotypic effect have been transmitted from the mother and it has been suggested that genomic imprinting may play a role in determining the phenotypic effect. In this case, however, the deletion has been transmitted, without effect, by both male and female family members; thus, imprinting does not seem to be applicable here.

Another distal long arm deletion of the X chromosome
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Chromosome analysis was performed on a 30 year old woman who had presented with infertility (PO + O). At the time of referral to the cytogenetics laboratory her gonadotrophin levels had been in the menopausal range for six months and a diagnosis of ovarian failure had been made. Her karyotype was 46,X,del(X)(q26). A review of publications on X chromosome deletions and their phenotypes (Therman et al, Hum Genet 1990;85:175-83) showed only 18 patients from 12 families with terminal or interstitial X chromosome long arm deletions with breakpoints at or distal to Xq25. The lack of Turner syndrome stigmata, apart from ovarian dysgenesis, in our patient and other distal Xq deletion cases illustrates the difficulty in the early ascertainment of people with this aberration. This case also adds to the data locating at least some of the genes determining normal ovarian function to Xq26-qter.

A case of complete trisomy 10 in a liveborn
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This case presented as an early neonatal death with multiple congenital abnormalities. G band analysis of blood lymphocyte cultures showed 47,XX,+10 in all cells. No cases of complete trisomy 10 have been previously published. A comparison can be made between the present case and other cases of mosaic trisomy 10, where similarities include retinopathy, microcephaly, polydactyly, and long, slender trunk. Cases of partial 10p or 10q trisomy also display some features seen in our case of complete trisomy 10, for example, scoliosis and cardiac and renal abnormalities.

A recombinant chromosome 3 arising from a familial inv(3)(p25.3q25.1q32.2)
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We report a recombinant chromosome 3 in a child with multiple congenital abnormalities, resulting from a familial inverted insertion inv(3)(p25.3q25.1q32.2). The abnormal chromosome 3 in the child which has a duplication of the segment 3q13.2-q25 has arisen as a result of a crossover in the non-inserted segment 25.3-q13.2 in the father. Two brothers of the father are also carriers of the inverted insertion. The clinical features of the child include dysmorphic facies with a relatively large head, broad nasal bridge, proptosis of the eyes with ‘sunset’ phenotype, strabismus, coloboma of the optic nerve and glaucoma of the right eye, low set ears, bilateral cleft lip and palate, and a small mandible. Psychomotor retardation, feeding problems, and growth retardation were also present. This phenotype can be directly correlated to the duplication of the segment 3q13.2-q25 as there is no concurrent deletion of any other chromosome segment.

A case of mosaic partial trisomy 9 confirmed by chromosome painting
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A 14 month old child with microcephaly and cerebral palsy was referred for cytogenetic investigation. Blood lymphocytes showed 46,XY/47,XY,+mar karyotype, the marker being present in 40% of the cells examined. By investigation with a number of conventional staining techniques (G banding, C banding, silver staining, and methyl green/ Hoescht fluorescent staining), it was postulated that the marker was most likely to be a ring chromosome comprised of the centromere and proximal p and q arms of chromosome 9. The marker was confirmed to be derived from chromosome 9 by fluorescence in situ hybridisation (chromosome painting) with a chromosome 9 specific DNA library.
De novo interstitial deletion of chromosome 15 (q25.1q26.1) in a moderately retarded adult female

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A mildly dysmorphic 18 year old girl with moderate learning difficulties was referred for investigation of short stature and delayed puberty. She was found to have a de novo interstitial deletion of chromosome 15, her karyotype being 46,XX,del(15)(q25.1q26.1). Deletions of the 15q22 to qter region have rarely been described. The proband had features in common with other reported cases including a prominent nasal bridge, hypoplastic nostrils, thin upper lip, truncal obesity, growth retardation, and hypopotonia (Martin et al. J Med Genet 1990;27:637-9). Hexosaminidase A levels were within the normal range for a homoygote. The deletion does not therefore include the HAX A locus, previously assigned to 15q23 to q24. The pyruvate kinase PMK locus has also been assigned to chromosome 15q2 to qter. The patient's deleted cell line may be used to pinpoint the PMK locus.

De novo inverted duplication of chromosome 7q

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We present a case of a de novo inverted duplication of the long arm of chromosome 7 with macrocephaly, prominent occiput, downward slanting palpebral fissures, hypertelorism, and bilateral talipes equinovarus. Chromosome analysis showed the karyotype to be 46,XX,inv dup(7)(pter-q36.1;q36.1→q22.1q13.2→qter) resulting in a duplication of the region 7q22-q36.1. Duplications are uncommon events and a search of published reports showed only 40 previous reports of any duplication involving the long arm of chromosome 7. Only two of these previous reports are of de novo duplications and only four do not have any other chromosomal abnormalities. Only one of the previously reported cases is of a duplication of 7q22-q36.1. All the dysmorphic features present in our case were also present, along with a number of other dysmorphic features, in the reported cases. These additional features possibly result from the associated chromosome deletion. This indicates the importance of chromosome alterations in assessing clinical effects.

A deletion of chromosome 2 in a child with Waardenburg syndrome

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A deletion of the long arm of chromosome 2, 46,XY,del(2)(q34q36.2), was found in a child with features typical of Waardenburg syndrome. This reinforces recently published linkage analysis work mapping the Waardenburg gene to this region.

Deletion of chromosome 1q43 associated with agenesis of the corpus callosum and other midline defects

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We report four infants all having loss of material from the distal part of the long arm of chromosome 1 at band q43. These patients were noted to have certain concordant clinical abnormalities including consistent midline defects. (1 and 2) Two unrelated male infants were investigated because of midline cleft palate, short neck, low set ears, hypoplasia, and absent corpus callosum. Analysis showed an unbalanced karyotype: 46,XY,del(1)(q43). (3) A male neonate was investigated because of midline cleft palate, short neck, low set ears, and agenesis of the corpus callosum. Analysis showed an unbalanced karyotype: 46,XY,mar(1). (4) A female neonate was investigated for growth retardation, dysmorphism, and midline defects. Analysis showed an unbalanced karyotype: 46,XX,del(1)(q43);q22.1q13.2→qter). Agenesis of the corpus callosum can be detected by ultrasound scan. Isolated cases of agenesis of the corpus callosum is a rare occurrence but when associated with other midline defects may indicate the presence of a deletion at 1q43 or trisomy for chromosome 8, 13, or 18.

Bloom's syndrome: cytogenetic confirmation in a photosensitive 21 year old male

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The incidence of this rare autosomal recessive chromosome breakage syndrome has been estimated at 1:160 000 in Ashkenazi Jews and considerably lower in gentile populations. Presence of 10 or more bands per cell suggests Bloom's syndrome. The patient, who was of small stature and had been photosensitive from an early age, was the son of consanguineous Scottish parents. The first sample exhibited a 10-fold increase in sister chromatid exchanges (SCEs) but as only a small number of cells were available for analysis a repeat was requested. This showed a 5-fold increase in spontaneous chromosome breakage and an 11-fold increase in SCEs over control levels. Quadriradial figures resulting from chromatid exchanges were also noted.

Coffin-Siris syndrome and fra(10)(q25.2): a coincidence?

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A 3 year old girl from a moderately mentally retarded mother showed height, weight, and head circumference below the 3rd centile, mental retardation, sparse scalp hair, body hirsutism, hypoplastic fifth finger- and toenails, and Coffin-Siris syndrome was diagnosed. The karyotypes of the patient and her mother both exhibited a recurrent break in 10q25.2. Re-examination of the mother suggested Coffin-Siris syndrome. Although the presence of fra(10)(q25), a known fragile site, may well be coincidental, a direct relationship between Coffin-Siris syndrome and the karyotypic anomaly cannot be excluded.

Cutis laxa with Marfanoid habitus: this syndrome maps with B1 laminin at 7q31.3

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A case of cutis laxa with Marfanoid habitus exhibited a recurrent ctb(7)(q31.3) in the band where the B1 laminin gene has been mapped. Laminin protein could not be detected in the basement membranes. A published case bore a translocation involving 7q31. We studied the laminin activity in another patient with cutis laxa and Marfanoid habitus and again laminin could not be detected. Other cases are required to confirm that this syndrome maps to 7q31.3 and results from a defect in B1 laminin.

National Down Syndrome Register: 1989/90

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The Register now contains 2096 cases for 1989/90 and is providing new and comparative information on prenatal and clinical diagnoses of trisomy 21 in England and Wales. The proportion of cases registered after prenatal diagnosis in 1990 has risen 4% above 1989. In 1990, 42 cases were confirmed subsequent to serum screening in its various forms, a three-fold increase on the previous year. The proportion of prenatal diagnoses after an abnormal ultrasound scan was also 2% above the 1989 level. A total of 747 births registered for 1989 were included at the Office of Population Censuses and Surveys (OPCS) with the 488 reported to the congenital malformations register; 431 cases were matched (57%). Fifty-seven cases notified to OPCS could not be found on the cytogenetic Register. Attempts are being made to improve both sets of data. The Register is continuing to be funded by the Medical Research Council.
Discordant cytogenetics in a dizygotic in vitro fertilisation twin pregnancy

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A 39 year old mother carrying 15/40 w 1VF twins presented for amniocentesis because of maternal anxiety. Chromosome analysis of routinely cultured amniocytes showed the following karyotypes. Twin 1: 46,XY,der(12)(t;8;12)(q24.21;q24.32). Twin 2: 46,XX, t(8;12)(q24.21;q24.32). Subsequent examination of the parents’ lymphocytes showed a normal mother and the father carried the same balanced t(8;21) as twin 2. As the unbalanced karyotype of twin 1 would probably have resulted in severe abnormalities with the possibility of early spontaneous abortion of the pregnancy, the parents opted for selective in utero termination of twin 1. A blood sample from a heart puncture of twin 1 at termination confirmed the unbalanced karyotype. Twin 2 was subsequently delivered normally and displayed a normal phenotype.

This case clearly illustrates the importance of screening gamete donors in IVF pregnancies when the underlying causes of infertility are not known.

A rare case of a false negative finding in both direct and long term culture of a chorionic villus sample

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Prenatal diagnosis by first trimester chorionic villus sampling on a 43 year old patient resulted in a normal 46,XX karyotype in both direct preparation and long term culture. Following an abnormal ultrasound scan and a subsequent stillbirth at 28 weeks’ gestation, fibroblast culture showed a karyotype of 47,XX,+18 in all cells examined. Although it is generally considered that long term culture more closely reflects fetal karyotype, this case clearly illustrates that discrepancies can occur.

A double translocation carrier detected by chorionic villus investigations

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A 24 year old woman was referred for prenatal diagnosis because of a known, apparently balanced chromosome translocation in her husband, t(4;15)(4p15q415q). The husband was one of four brothers, one of whom had produced unbalanced offspring.

Chromosome analyses of a chorionic villus sample showed the presence of the paternal translocation, plus an additional apparently balanced translocation, t(12;18)(12p18q12q18q), of unknown origin. Inheritance of two translocations, one from each parent, would be a rare event, and the possibility of a false positive finding had to be considered. However, further analysis (maternal blood sampling and amniocentesis) confirmed the presence of the second translocation in the fetus and its maternal origin. As far as we are aware this represents the first report of a genuine double translocation detected by chorionic villus sampling.

Cytogenetic investigation of a three way translocation

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Chromosome analysis of peripheral blood lymphocytes from a 27 year old woman referred because of an obstetric history (para 2 4) showed three way rearrangement involving chromosomes 7 and 11: 46,XX,t(7;11) (7pter→7p21:7q31→7p21:11p15→11pter). Subsequent amniocentesis showed a male fetus with an apparently identical translocation. In situ hybridisation using biotinylated pHINS indicated the break in the short arm of chromosome 11 to be at distal 11p15.3. The proband exhibits none of the clinical features reported in cases of interstitial deletions of the short arm of chromosome 7 (Speleman et al. J Med Genet 1989;26:528-32) or of the long arm of chromosome 7 (Morey and Higgins. Am J Med Genet 1990;35:95-9). The rearrangement is balanced. Flow cytometry studies are in progress.

A reciprocal translocation chimeric conceptus

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A 28 year old translocation carrier, 46,XX,t(17;21)(q23.q22.1), was referred for chorionic villus sampling. At 10 weeks’ gestation the fetus was normal for dates but no heart beat was detectable. After evacuation, placenta and fetal skin were cultured for chromosome analysis. Two cell lines were detected in the placenta with GTG banding: 46,XXt(17;21)(q23.q23.2)1.1mat (32/50 cells) and 46,XX,—21, +der(21t)(17;21)(q23.q23.2)1.1mat (18/50 cells). Examination of variable chromosome regions indicated that the two cell lines originated from different fertilisations, and excluded the possibility of uniparental disomy for chromosome 17. Only one cell line was found in skin from the fetus: 46,XX,t(17;21)(q23.q23.2)1.1mat (100 cells). It was concluded that fusion of two zygotes at a very early stage of development had probably resulted in a chimeric morula, with subsequent development producing a conceptus with a non-chimeric embryo, and chimerism confined to the chorion. However, the possibility that two zygotes implanted, but that one fetus was subsequently resorbed (a ‘vanishing twin’) cannot be excluded.

Discovery prenatally of a cell line containing two separate balanced reciprocal translocations together with a normal cell line: 46,XX/46,XX,rec(17)(p32q32), rec(2;11)(p12q23)

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Analysis of an amniotic fluid sample from a 39 year old woman referred for age showed one culture with 69 normal and 95 abnormal (two balanced reciprocal translocations) female mitotic divisions. A second culture produced the ratio 77 normal:18 abnormal divisions. Two further cultures produced a total of 18 divisions without the translocations. Examination of the fetus on termination at 20 weeks showed a cleft palate, campodactyly of the left hand with overlapping 2nd and 5th fingers, low set ears, and a short beaked nose. Unfortunately, none of the tissues obtained at necropsy cultured successfully. To find two separate reciprocal translocations within a cell line is unusual. For that cell line to appear in mosaic form makes this case very rare.

A fetal karyotype with three cell lines involving two different abnormalities

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Chromosome analysis on an amniotic fluid sample taken at 21 weeks’ gestation because of a maternal age of 35 years showed a female fetus with three cell lines involving two different de novo abnormalities. These comprised an extra, bisatellitised marker and an apparent duplication/deficient chromosome 7 with monosomy of the distal portion of the long arm (q36-pter) and duplication of most of the short arm (p11-pter). The cell lines were: (1) 46,XX,—7+r(7)(p11q11), (2) 47,XX,+mar,(3) 47,XX,—mar,—7+r(7), dup p(7)7q11q36. The pregnancy was terminated at 23 weeks’ gestation. The major cell line in all tissues cultivated except the lymphocytes was that with both abnormalities present. There are two possible explanations for the origin of the mosaic 7 cell lines: (1) postzygotic origin with unequal mitotic crossing over, or (2) prezygotic origin based on a meiotic half chromatid duplication model (Cantu et al. Ann Genet (Paris) 1985;28:254-7).

Prenatal diagnosis of Pallister-Killian syndrome: low level mosaicism or pseudomosaicism?

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A 38 year old woman with low serum AFP was referred for amniocentesis. In one out of four amniocyte cultures, 15 out of 83 cells had the karyotype 47,XY,+i(12p). The remaining cells had a normal male karyotype. This mosaicism is in 7% of the Pallister-Killian
Trisomy/partial monosomy 13 mosaicism associated with relatively mild clinical malformation

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A female fetus with a de novo chromosome abnormality involving mosaicism with two abnormal cell lines was diagnosed on amniocentesis. Karyotyping showed a single normal chromosome 13 together with in one cell line a t(13q13q) Robertsonian translocation chromosome (that is, trisomy 13), and in the other a small ring chromosome which had presumptively originated as a postzygotic event from the t(13q13q) chromosome (that is, partial monosomy 13). The pregnancy was terminated at 19 weeks. The fetus was found to have normal growth parameters, and external examination and necropsy showed only minor abnormalities. The phenotype in this fetus together with three previously described similar cytogenetic cases was less severe than might have been expected. The possibility that the effects of the trisomy and monosomy may have counterbalanced each other at the tissue level in embryogenesis, thereby resulting in less disturbance of morphogenesis than would be predicted for each type of imbalance acting in isolation, is considered.

A review of ring chromosome 13 syndrome following a prenatal diagnosis case

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Following a prenatal diagnosis case in which a ring chromosome 13 was found, it was discovered that five other cases with a r(13) had been diagnosed at our laboratory since 1980. Their clinical features are compared with the clinical features of five other published cases of ring chromosome 13 syndrome (Martin et al. Hum Genet 1982;61:18–23, Fried et al. Cytogenet Cell Genet 1975;7:203–8, Parcheta et al. Eur J Pediatr 1985;144:409–12). Unfortunately no further clinical information was received on two of our cases. Of the other four cases reported by our laboratory, we only have information on one child who is still alive. One baby died at the age of 6 days and two were prenatal diagnosis cases which resulted in termination of the pregnancies. From the information that was obtained, the clinical features of the 11 cases were seen to be very similar.