Abstracts of the scientific meeting of the Association of Clinical Cytogeneticists held at the Duncan Guthrie Institute of Medical Genetics, Glasgow, on 4 and 5 May 1983

Structural mosaicism—problems in prenatal diagnosis

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Mosaicism has been estimated to occur in 2 to 3% of all amniocenteses, but the frequency of true mosaicism, corroborated by necropsy or postnatal studies, is only of the order of 0.1 to 0.3%. A regional cytogenetics service with an average workload of 1500 prenatal diagnoses per annum would, therefore, expect to encounter true mosaicism in only two to five cases a year. Three true structural mosaics were diagnosed in Salisbury in 1982 to 1983, all of whom had had prenatal diagnosis. Case 1 was referred for advanced maternal age; the fetal karyotype was 46,XY/46,XqY,−Y,+fra (80%/20%) confirmed in four cultures and in fetal blood at fetoscopy (78%/12%). The pregnancy continued and a male child with tracheo-oesophageal fistula was born at 40 weeks. Mosaicism was confirmed from cord blood (96%/4%). The child shows apparently normal development at 6 months. Case 2 was referred for advanced maternal age; the fetal karyotype was 46,XX/47,XX,+del(15)(q15) (72%/28%) confirmed in two cultures and in fetal blood at fetoscopy (58%/42%). The pregnancy was terminated and mosaicism confirmed in six tissues, the abnormal cell line ranging from 8 to 24%. Case 3 was referred for raised serum AFP; the fetal karyotype was 46,XX. An abnormal female child was induced at 35 weeks after fetal distress. Chromosome analysis of blood and skin revealed a 46,XX/46,XX,del(11)(q24) karyotype (52%/48%). Re-examination of the amniotic fluid cells revealed mosaicism in only one culture and only 4% of cells had the del(11)(q24).

A satellite chromosome 2

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An unusual abnormality of chromosome 2, apparent satellites beyond 2qter, was detected in the father of an early spontaneous abortion with trisomy 16. A family study was undertaken and the abnormality was found to be inherited, but to have no apparent phenotypic effect in carriers. Multiple banding techniques were applied, together with DNA hybridisation studies, in an effort to determine the nature and origin of the additional material. Involvement of chromosome 15 can be ruled out, but no positive identification of the source of the extra material was possible, although it is clearly satellite in nature.

Chromosome analysis as an aid to diagnosis in effusions with equivocal cytology

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Where a pleural or peritoneal effusion is present with no apparent cause, the clinician usually relies upon the cytologist to decide the cell types present in the effusion. In many cases the cytology result is equivocal and it is in these cases that the chromosome findings may be of value. A clone of cytogenetically unbalanced abnormal cells indicates that a malignant cell population is present in the effusion. Although the cytogeneticist is unable to diagnose the type of malignancy from the chromosomes alone, some indications can be used. For example, clones with 35 to 39 chromosomes are derived usually from tumours of the GI tract and clones with 41 to 42 chromosomes are common in cases of mesothelioma, a malignancy frequently difficult to diagnose on cytological grounds.

Mosaicism in prenatal diagnosis

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The most difficult cytogenetic problem of interpretation in prenatal diagnosis is the problem of mosaicism and the distinction between true and pseudomosaicism. This presentation deals with our experience and results in over 8500 cases from 1968 to the end of 1982 in Glasgow and the West of Scotland. It deals with the distinction between true and pseudomosaicism, the origin of mosaicism, what further studies were undertaken, how the cases were reported, the discussion of whether or not to recommend termination, and finally the outcome of the pregnancies.
Two cases of ring chromosome 4 showing variability of both ring structure and phenotype
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Case 1 was diagnosed in 1977. At birth he was noted to have an odd facies, a small head circumference, and abnormal palmar creases. The child has been the subject of intensive follow-up by his GP and a clinical psychologist, and relevant details will be presented. Case 2 was diagnosed in 1981. She was referred during the neonatal period because of gross developmental delay and died at the age of 12 days. Details of the findings at necropsy will be presented. The variability of ring structure (in cultured lymphocytes) will be demonstrated in each case. It has been suggested by McDermott (1977) that the abnormalities of phenotype in patients with ring chromosomes are due to 'dynamic mosaicism'. This theory will be examined in relation to these two cases.

Human karyotype analysis by flow cytometry
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We have applied flow cytometry to the quantitative analysis of the human karyotype. Using the fluorochrome ethidium bromide, a very accurate measure of the DNA contents of the human chromosomes is possible. Differences between homologues as seen by C bands can be quantified by this technique; also some homologue differences not seen by C band analysis have been seen. Flow cytogenetics can also be useful for the detection and quantification of chromosome abnormalities. Numerical abnormalities such as trisomy 21 and 18 and sex chromosome aneuploidy have been analysed. Chromosome abnormalities which produce chromosomes of different DNA contents, translocations, duplications, and deletions are well suited to detection by flow cytometry. We have found that even very small chromosome changes, as seen by G band analysis, are seen by flow cytogenetics. It is hoped that it will be possible to detect chromosome abnormalities smaller than those seen by conventional techniques.

An improved method for routine culture of chorionic villi for first trimester diagnosis of fetal chromosome abnormalities
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A technique for the culture of chorionic villi samples obtained by transcervical aspiration has been described which involves multiple manipulations of the specimen, such as successive trypsinisation and filtration procedures (Niazi et al.). We have developed a simplified technique suitable for routine trophoblast culture which circumvents these more time-consuming steps without increasing the risk of maternal tissue contamination. Several different methods of accelerating cell growth were investigated and the suitability of cultured material for biochemical studies was assessed. We report our experience of karyotyping specimens of chorionic villi and supporting post-abortion fetal tissue obtained from a weekly termination clinic.

Kinetics of the cell cycle of human lymphocytes and tumour cells studied by DNA microspectrofluorometry
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G1 lymphocyte nuclei have been used as a comparative standard for studies in the characterisation of children’s tumour cell populations. Further studies aimed to assess the extent of genetical variation in lymphocyte and tumour cell cycle time as a possible parameter for cytogenetical diagnosis. BrdU incorporation during non-synchronised culture, followed by fluorescent staining and photometry, indicates the percentage of cells in DNA synthesis. Calculated cell cycle times have so far varied between 10 and 28 hours in normal controls, congenital defects, and tumour cultures. Normal controls had the lowest times of 10 to 14 hours. These preliminary results will be discussed in relation to previously reported higher estimates of normal cell cycle time, the significance of 3rd division SCEs in 72-hour blood cultures, and the control of cell cultures for obtaining high resolution banding.

A cytogenetic review of approximately 400 patients with haematological disorders
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We present a cytogenetic review of approximately 400 patients with haematological disorders referred to the Duncan Guthrie Institute of Medical Genetics, Yorkhill Hospital, Glasgow, from 18 hospitals in the West of Scotland during the period from January 1979 to December 1981. Chromosomes from bone marrow or unstimulated peripheral blood cell cultures were examined from patients with leukaemia and other haematological disorders, mainly at diagnosis before treatment, and in some cases during follow-up, during remission, and relapse. The data collected will be correlated with clinical information, type of leukaemia, and response to therapy.

Cyto genetic changes during the early stages of liver carcinogenesis in Chinese hamster. An in vivo:in vitro comparison
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A single dose of dimethylnitrosamine (DMN) has been found to induce a high incidence of liver tumours in the
Chinese hamster. An in vivo:in vitro comparison has been made from 7 to 35 weeks after injection. Partial heptectomy was used to stimulate mitosis for in vivo analysis, and the excised liver, grown to primary culture stage, used for in vitro chromosome analysis. Aneuploidy, tetraploidy, and chromosome aberrations increased significantly in the hepatic cells of DMN treated animals in vivo. No differences could be detected between the primary cultures of control or DMN treated animals. A preferential involvement of chromosome 6 in the single trisomic state was seen in vitro and to a minor extent in vivo. The relevance of increased aneuploidy in early carcinogenesis and the differences between the in vivo and in vitro results will be discussed.

Cytogenetic studies on chorionic villi obtained by endocervical aspiration
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Recent work suggests that chorionic villi obtained by endocervical aspiration at 8 to 12 weeks, immediately before termination of pregnancies, provides a source of fetal cells potentially suitable for prenatal diagnosis (see Niazi et al. Br J Obstet Gynaecol 1981;88:1081–5). In collaboration with our colleagues in Obstetrics and Pathology we have begun similar studies. We are interested in trying to simplify the laboratory techniques involved in order to see whether such material could be handled on a routine basis. Careful dissection of villi from maternal decidua coupled with adequate trypsinisation of the material appear to be the most important steps. To date we have obtained results within the expected sex ratio after chromosomal analysis of the material.

De novo complex balanced karyotypes in two children with mild phenotypic effects
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Two children with very rare congenital chromosome aberrations of considerable complexity will be detailed. One of these can be described as a ‘complex double translocation’ involving four chromosomes and five breakpoints, and may challenge the adequacy of the present international system of chromosome nomenclature. The other karyotype is (to the best of our knowledge) unsurpassed in a liveborn child, having three separate reciprocal translocations forming a total of six derived chromosomes. Both children have chromosomally normal parents and only mildly abnormal phenotypes. The possible aetiology, time, and mechanism of the chromosome damage together with the familial patterns of C band polymorphisms will be discussed. In the light of the limited literature, particular reference will be made to possible meiotic behaviour and fertility.