Summary

Mental retardation has been shown to be the prime feature of the 48,XXXX condition from the literature. A first case of this chromosome disorder with normal intelligence is presented.

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A Case of Double Aneuploidy, 47,XXY,14-t(13q14q)+, also Probably Homozygous for the Cystic Fibrosis Gene

Case History

The proband was born weighing 3405 g after an uneventful 42-week pregnancy; at birth his mother was

aged 26 and his father 27. Multiple congenital abnormalities were evident—a central scalp defect, microphthalmia, cleft soft palate, and prominent heels suggested the trisomy 13 syndrome (Patau *et al*, 1960). In addition, there was widening of cranial vault sutures, a unilateral accessory auricle, cardiomegaly, a small penis, and partially-descended testes, ulnar deviation at the wrists, low-set thumbs, and normal palmar creases, whilst the finer dermatoglyphs were not distinguished. The right ankle was subluxated; the right hallux showed camptodactyly. He died from pneumonia, uraemia, and generalized sepsis at 8 days.

Necropsy

At necropsy there was severe bilateral otitis media and a complicating basal meningitis; swabs of these exudates grew *Pseudomonas aeruginosa*. Focal lesions of coagulative necrosis with colonies of Gram-negative bacilli were identified in adrenals, liver, and kidney; the lungs showed extensive bronchopneumonia, with foci of vasculitis and necrosis. The heart contained a large defect of the membranous portion of the interventricular septum, and there was moderate preductal coarctation. There was excessive notching of the spleen and several splenunculi were present. The kidneys were of normal size, but on the cut surface small pale nodules diffusely scattered through the parenchyma obliterated much of the corticomedullary differentiation. These nodules were made up of microcystic areas and tangles of tubules and were not clearly differentiated. The testis appeared normal on gross and microscopic examination with conventional staining procedures.

The pancreas appeared firmer than normal; histological examination showed a general increase in interstitial fibrous tissue, scantily infiltrated with mononuclear cells, and an atrophy of acinar tissue. Inspissated secretions were seen in each acinus, with attenuation of the epithelial cells. Islet tissue was unaffected. Many larger ducts contained inspissated secretions, with small areas of microcyst formation. A reassessment of sections of the trachea and gut showed, in both, a widening of the mouths of the mucous glands, with the acinar elements distended by inspissated secretions. A pathological diagnosis of mucoviscidosis was made.

Cytology and Tests for Cystic Fibrosis

Chromosome analysis in PHA-stimulated lymphocytes showed a modal count of 47; there was a missing D, an extra 3, and an extra C. Quinacrine fluorescence (Bobrow and Pearson, 1971; Caspersson, Lomakka, and Zech, 1971) showed the sex-chromosome constitution to be XXY, and the autosomal constitution 14-t(13q14q)+. Further examination of the translocation chromosome showed an area of intense fluorescence adjacent to, but on the 14q side of the centromere; such bright fluorescence is characteristic of the proximal part of the 13 short arm, suggesting that within the translocation chromosome the whole of the 13 was represented, excepting the most distal parts of the short arm (Fig. 1).

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FIG. 1. Metaphase plate, mother of propositus, quinacrine fluorescence. The 2 short arrows point to the number 3 chromosomes, the large arrow to the translocation chromosome. The long arm of the 14 is on the left, the 13 on the right, and the bright spot (13p) appears to be just to the 14 side of the centromere.

The paternal chromosomes were normal. The translocation was found, in balanced form, in the mother and several members of her family.

The diagnosis of cystic fibrosis was made only after the death of the propositus. Other family members were tested for carrier activity, observing the effect of their plasma on the ciliary activity of the fresh-water mussel *Dreissensia* (Besley, Patrick, and Norman, 1969)—these tests were kindly undertaken by Dr M. d'A. Crawford of Leeds. Both parents of the propositus and his sister appeared to be carriers; results of testing other relatives are shown in Figure 2. The mother and sister of the propositus had normal sweat chloride levels (51 and 16 mEq/l, respectively).

Discussion

Ford reported the first case of double aneuploidy, a male with features of both Down's and Klinefelter's syndromes; his constitution was 48,XXY, 21+ (Ford *et al*, 1959). Double aneuploids of this constitution have been found frequently since; an incidence at birth as high as one per 11,614 males has been estimated by Taylor and Moores (1967); it has been suggested that strong selection against such double aneuploids operates in early life (Hecht *et al*, 1969).

Double aneuploidy involving the D-group seems

Fig. 2. Pedigree of the proband.

rather less common. Cases of 48,XY,D+21+, or 48,XXY,D+ have been described by Becker, Burke, and Albert (1963) and Gustavson (1964). Double aneuploids with balanced D/D translocation—46,XXY,D-D-t(DqDq)+ have been described by Lejeune, Turpin, and Decourt (1960) and Tiepolo *et al* (1967); 44,X,D-D-t(DqDq)+ by Stahl *et al* (1966); and 46,XY,21+,D-D-t(DqDq)+ by Hamerton, Gianelli, and Carter (1963), as well as by various authors since. No report of a double aneuploid with an *unbalanced* D/D translocation has been found; hitherto, the only case of D-trisomy with XXY had the constitution 48,XXY,D+, and was an early abortus (Pergament and Kadotani, 1965).

Coincidence of D-trisomy and cystic fibrosis would be expected once in 15,000,000 live births, given the respective incidences in European neonates as 1 in 7600 (Taylor, 1968) and 1 in 2000 (Hall and Simpkins, 1968). Such coincidence has not been reported previously, though cystic fibrosis has been found in Down's syndrome (Milunsky, 1968; Vetrella, Barthelma, and Matsuda, 1969), and in the sib of a non-disjunction D-trisomy (Campbell, 1969). In two neonates dying with D-trisomy, Marin-Padilla, Hoefnagel, and Benirschke (1964) noted pancreatic abnormalities somewhat resembling those of fibrocystics—dilatation and irregularity of ductules and acini, intraductal mucoid and inspissated materials, etc. We have not been able to discover similar reports elsewhere in the literature of

trisomy D (reviews in Warkany, Passarge, and Smith, 1966; Bocquet, 1968; Taylor, 1968); nor in individual case reports. Dr Hoefnagel kindly offered slides of lung and pancreas from the neonates described in the 1964 paper, and on comparison with slides from our proband we were satisfied that considerable differences were detectable between them, of such sort that we would adhere to our diagnosis of cystic fibrosis in our proband, whilst unprepared to diagnose this in the other cases. *Dreissensia* testing of plasma from the 4 parents of Dr Hoefnagel's cases gave negative results for each.

The present case received a single cystic fibrosis gene from each parent. If the locus for the cystic fibrosis gene is on the trisomic (13) chromosome, then two cystic fibrosis genes working with a normal allele produced the full histological phenotype of cystic fibrosis. Nothing is known of the phenotypic expression of recessive genes in trisomic humans, when in such 'duplex' state; but in polyploid plants the phenotype is either totally determined by the dominant allele, or an intermediate phenotype appears (Dawson, 1962). Arguing from this botanical analogy, it seems probable that the cystic fibrosis locus does not lie on the 13 chromosome.

Summary

A new case of double aneuploidy is described. Trisomy for the 13 chromosome arose from a balanced 13/14 translocation in the mother, and the

infant also exhibited an XXY sex-chromosome constitution. A post-mortem diagnosis of cystic fibrosis was made following histological examination of lungs and pancreas, and tests for heterozygosity in the parents accorded with this diagnosis. An attempt was made to argue that the locus for the cystic fibrosis gene is not on the long arm of the 13 chromosome.

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Comparative Clinical Studies and X Chromosome Behaviour in a Case of XXXX/XXXXX Mosaicism

The XXXX sex chromosome complement was first described by Carr, Barr, and Plunkett (1961) in 2 institutionalized, mentally retarded females. Since that time 7 other cases have been reported in detail with a multiple X complement of either XXXX (de Grouchy *et al*, 1968; Lejeune and Abonyi, 1968; Berkley and Faed, 1970), XXXXX (Kesaree and Woolley, 1963; Brody, Fitzgerald, and Spiers, 1967), or mosaic form (Ricci *et al*, 1968). Four other cases of XXXX have been reported without clinical details in surveys of mental subnormality hospitals (Davies, 1963; Day, Larson, and Wright, 1964; Yanagisawa and Shuto, 1970). This paper describes the 2nd case of XXXX/XXXXX mosaicism and examines the behaviour of the X chromosomes.

Case Report

Clinical Features. The patient was the 2nd child of a 33-year-old mother and 33-year-old father; birth weight was 2.5 kg. She was born at term by breech delivery and there was a delay in the onset of respiration. She was originally referred to the Centre for Human Genetics at the age of 3 months because of mental retardation and minor physical malformations. At this time she was a pale and unresponsive child. A loud

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