

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.

We thank Dr B. Bower for permission to report his case, Drs M. d'A. Crawford and Ruth Simpson for their great help with the *Dreissensia* tests, Drs Dick Hoefnagel and Kurt Benirschke for their kindness in sending slides and plasma from two of their D trisomies, and the many general practitioners in the Channel Islands who obtained blood specimens from members of this family. Also, thanks go to Drs Martin Bobrow and Peter Pearson for much advice and helpful criticism.

R. H. LINDENBAUM, N. L. BLACKWELL,
and D. J. DE SA'

Medical Research Council, Population Genetics
Unit, Oxford and The Radcliffe Infirmary, Oxford

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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

Received 14 September 1971.



FIG. 1. The patient.

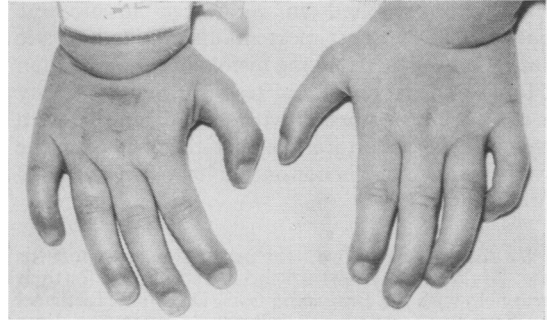


FIG. 2. Hands showing incurved little fingers and straight left thumb.

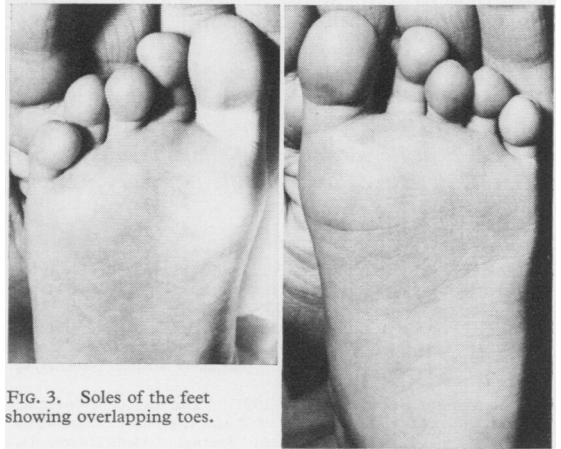


FIG. 3. Soles of the feet showing overlapping toes.

systolic murmur was noted which was thought to be due to a ventricular septal defect. Cytogenetic studies were performed at this time.

She was seen again at the age of 2 years 11 months to review her progress. At this time her height was 86 cm (between 3rd and 10th centile), her weight was 10.6 kg (less than 3rd centile), the upper to lower segment ratio was 1.27 (normal=1.30), and her head circumference was 49 cm (approximately 25th centile). Her IQ was estimated by A. Kaufmann using the Stanford-Binet criteria to be about 60. Her general condition had improved considerably and she was now a happy sociable child who was able to make simple requests and utter short sentences. She was unable to walk unaided but could do so with support. The heart murmur previously heard was no longer audible and it was thought that a small ventricular septal defect had closed spontaneously.

The main physical features are shown in Figs. 1, 2, and 3. She showed slight hypertelorism and epicanthus, a small mouth and jaw with a high arched palate and had a narrow, flat, nasal bridge. She had 2 supernumerary auricles on the left side. She had incurved 5th fingers, an inability to flex the interphalangeal joint of the left thumb and an inability to oppose this thumb. There

was marked hypotonia and hyperextensibility of all the joints and there was a mobile valgus deformity of both feet, the 2nd and 4th toes overlapping the 3rd.

Dermatoglyphs. (Dr D. C. B. Colver.) The hands showed a distal crease absent on left thumb, loop opens 3-4 on right. Triradius t was placed a little distally and to the ulnar side on right. Details of digital patterns are given in Table I. Total ridge count was 45 (mean for 46,XX females is 127).

TABLE I

	Hands		Feet	
	R	L	R	L
1	RL	W	FL	TL
2	A	A	A	A
3	A	A	FL	A
4	A	A	A	A
5	W	UL	FL	TL

Cytogenetic Studies

Methods. Samples of blood and buccal mucosal tissue were taken from the patient on each of 2 occasions.

A skin sample was also taken. Chromosome preparations were made by the separated leucocyte method. On the second occasion the cultures were labelled with tritiated thymidine (0.5 $\mu\text{C}/\text{ml}$ added 4 hours before harvesting) to examine the behaviour of the X chromosomes. The buccal smears were stained and counted by the method described in Curtis (1969). Primary cultures of fibroblasts grown from clots were trypsinised into carrel flasks and harvested at the 4th passage.

Chromosome analysis. Table II gives the results of chromosome counts on cells from 2 blood cultures and a skin culture. Approximately equal numbers of cells with 48 chromosomes (18 in the C group) and 49 chromosomes (19 in the C group) were found in the 3 preparations. From an analysis of labelled preparations (Table III) it was found that the majority of cells with 48 chromosomes showed 3 late-labelling chromosomes (48,XXXX) while the majority of cells with 49 chromosomes showed 4 late-labelling chromosomes (49,XXXXX). A degree of asynchrony was present, however, as had been demonstrated by Ricci *et al* (1968).

TABLE II
CHROMOSOME COUNTS

Tissue	Number of Chromosomes				Total No. of Cells
	46	47	48	49	
Blood sample 1	1	0	15	14	30
Blood sample 2	0	1	13	15	30
Skin	0	0	12	20	32

TABLE III

OBSERVED NUMBERS OF CELLS WITH 0.5 'HOT' X CHROMOSOMES IN CELLS WITH 48 AND 49 CHROMOSOMES

No. of Chromosomes	Number of Heavily Late-labelling C Group Chromosomes						Total
	5	4	3	2	1	0	
48	—	—	58	7	1	0	66
49	1	30	8	1	0	0	40

Analysis of buccal smears. Four counts of 30 cells were made on 4 slides taken on 2 separate occasions (240 cells in all). The results of the analysis are given in Table IV. The results from the 2 sets of analysis were homogeneous ($\chi^2_4=0.51$, not significant) so they were pooled. Following the method given by Curtis (1970) the expected number of cells with 0-4 bodies were calculated for model 1 and model 2 situations. By interpolation, the expectations for a case of approximately 50:50 mosaicism for XXXX and XXXXX cell lines were calculated. The observations fitted model 1 better than model 2 but neither differed significantly. It must be concluded that, at least in this individual, the supernumerary X chromosomes were behaving independently in respect of their interphase condensation.

Discussion

Chromosome analysis, autoradiographic analysis, and buccal smear analysis showed the patient to have an approximately 50:50 mosaicism between a 48 chromosome cell line with 3 supernumerary X chromosomes and a 49 chromosome cell line with 4 supernumerary X chromosomes. The supernumerary X chromosomes in both cell lines were shown to be behaving independently of each other in respect of interphase condensation and late-labelling behaviour.

In comparing the clinical descriptions of the 9 other cases of XXXX or XXXX/XXXXX with the present case it is difficult to define any specific clinical features or characteristic facial appearance. With one exception (di Cagno and Franceschini, 1968) all the individuals were either severely subnormal (IQ < 50%) or subnormal (50-70%). Epicanthic folds were noted in 3 cases including our own; in 2 other cases the appearance was said to be that of Down's syndrome (de Grouchy *et al*, 1968; Lejeune and Abonyi, 1968).

The head circumference in our case was at the 25th centile but in all the other cases (where given) the head circumference was at or below the

TABLE IV

OBSERVED SEX CHROMATIN COUNTS (EXPRESSED AS PERCENTAGES) FOR TWO SEPARATE BUCCAL SMEAR SAMPLES TOGETHER WITH THE EXPECTED FREQUENCIES AS CALCULATED FROM THE MODEL 1 AND MODEL 2 HYPOTHESES

	No. of Sex Chromatin Bodies					χ^2 against Observed Values
	0	1	2	3	4	
<i>Observed</i> (%)						
Sample 1	18	37	31	13	1	
Sample 2	20	38	31	10	1	
Pooled values	38	75	62	23	2	
Mean	19	37	31	12	1	
Expected model I	17	38	32	12	1	Het $\chi^2_1 = 0.19$, NS Het $\chi^2_1 = 5.30$, NS
Expected model II	25	26	31	16	2	

3rd centile. In our case height lay between the 3rd and 10th centiles and weight was below the 3rd centile. In previous cases height has usually been between the 25th and 50th centiles with 3 exceptions: the cases of Ricci *et al* (1968) and Kesaree and Woolley (1963) being less than the 3rd centile for height while the patient of de Grouchy *et al* (1968) was above average height. The weights showed no consistent features. In every case (where given) except our own (in which the ratio was of a child aged 3½ years) and that of Ricci *et al* (1968), the ratios of upper to lower segment were less than 1.00 showing that the legs were abnormally long.

The skin creases on the palms and soles were not markedly abnormal in our case, but in Kesaree and Woolley's case (1963) there was a simian crease, which is not necessarily of much significance. In view of the findings of a murmur in the present case it is of interest that a patent ductus arteriosus was found by Brody *et al* (1967) and Kesaree and Woolley (1963).

In conclusion, it would appear that no characteristic clinical picture can be defined, but mental subnormality and dwarfism are to be expected, together with a few abnormalities of the feet and hands; a congenital cardiac abnormality may be present in about a third of the cases.

Summary

A child is described with approximately 50:50 mosaicism 48,XXXX/49,XXXXX. The clinical features are compared with those of previously published cases with multiple X complements.

Examination of the frequency distribution of sex chromatin bodies and 'hot' Xs shows that each supernumerary X appears to be acting independently in respect of interphase condensation and DNA synthesis.

We are grateful to Drs J. Diggle and I. Cullum at Boston for allowing our studies of the patient.

PATRICIA COOKE,* J. A. BLACK,
and DIANA J. CURTIS

*United Sheffield Hospitals, Centre for Human
Genetics and Department of Child Health,
University of Sheffield*

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* Present address and address for reprint requests: The Department of Zoology, The University, Highfield, Southampton SO9 5NH.

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Triple X Female and a Down's Syndrome Offspring

The triple X female has been characterized by the variability of her physical findings (Harnden and Jacobs, 1961; Telfer *et al*, 1970). Less attention has been given to the variability of her mental abilities (Day, Larson, and Wright, 1964). Most of these females have been purported to have reduced mental abilities. The following report deals with a triple X female who has normal intelligence and who is functioning as a quite adequate housewife and mother. She came under our observation after she produced a child with Down's syndrome (mongolism).

Case Report

Physical Findings. The patient is 30 years of age. She is a housewife who completed 2 years of college. Her height is 157.6 cm and weight is 69 kg. There was nothing unusual about her physical features that would have called attention to her abnormal chromosomal pattern. She has had 4 pregnancies. The first 2 re-