marked contrast to the large stature commonly seen in XYY males, where, there is a duplication of each active factor carried on the Y chromosome.

We wish to thank Dr Byron Evans, Consultant Physician, University Hospital of Wales (Cardiff) H.M.C. for referring this patient to us.

HELEN LANGMAID and K. M. LAURENCE
Cytogenetics Unit, Child Health Laboratories, Department of Child Health, University Hospital of Wales, Heath Park, Cardiff

REFERENCES

Altman, P. L. and Dittmer, D. S. (1972). *Biology Data Book*, 2nd edition, vol. 1, p. 204. Federation of American Societies for Experimental Biology, Bethesda, Maryland.

Lo, M. T. and Kobernick, S. T. (1965). X"y"/XO mosaicism in a phenotypic intersex. *American Journal of Clinical Pathology*, **43**, 251–255.

McIlree, M. E., Price, W. H., Court Brown, W. M., Tulloch, W. S., Newsam, J. E., and Maclean, N. (1966). Chromosome studies on testicular cells from 50 subfertile men. *Lancet*, **2**, 69–71.

Meisner, L. F. and Inhorn, S. L. (1972). Normal male development with a Y chromosome long arm deletion (Yq −). *Journal of Medical Genetics*, **9**, 373–377.

Muldal, S. and Ockey, C. H. (1962). Deletion of a Y chromosome in a family with muscular dystrophy and hypospadias. *British Medical Journal*, **1**, 291–294.

Nakagome, Y., Sasaki, M., Matsui, I., Kawazura, M., and Fukuyama, Y. (1965). A mentally retarded boy with a minute Y chromosome. *Journal of Pediatrics*, **67**, 1163–1167.

Seabright, M. (1971). A rapid banding technique for human chromosomes. *Lancet*, **2**, 971–972.

Telfer, M., Baker, D., and Rollin, I. (1973). Probable long-arm deletion of Y chromosome in a boy of short stature. *Lancet*, **1**, 608.

Vaharu, T., Patton, R. G., Voorhess, M. L., and Gardner, L. I. (1961). Gonadal dysplasia and enlarged phallus in a girl with 45 chromosomes plus 'fragment'. *Lancet*, **1**, 1351.

A 48,XXXX female

Summary. A four-year-old mildly retarded girl with a 48,XXXX karyotype is described. Her phenotype is compared to previously reported cases.

The first tetra-X female was described by Carr, Barr, and Plunkett (1961). Since then only 16 other cases have been reported. The present paper reports a further case and the phenotype and origin of this abnormality are discussed.

Received 1 October 1973.

Case Report

The proposita was a Caucasian female born in August 1969 as the 2550 g product of an uneventful pregnancy and term delivery to a 25-year-old mother. Her mother, father, and the two older sisters were healthy and had normal intelligence and stature. During the first 6 months of life she had feeding difficulties, with frequent regurgitation and vomiting. Her growth and development were slow and at 32 months she was admitted to the Children's Centre in Winnipeg for investigation. Physical examination at that time showed a height of 85 cm, weight of 9·2 kg, and a head circumference of 43·5 cm, all of which were below the third percentile for her age. Facial features included prominent eyebrows growing together in the midline (synophrys), small epicanthic folds, and a small mandible (Fig. 1). She had a high arched palate. Her hands

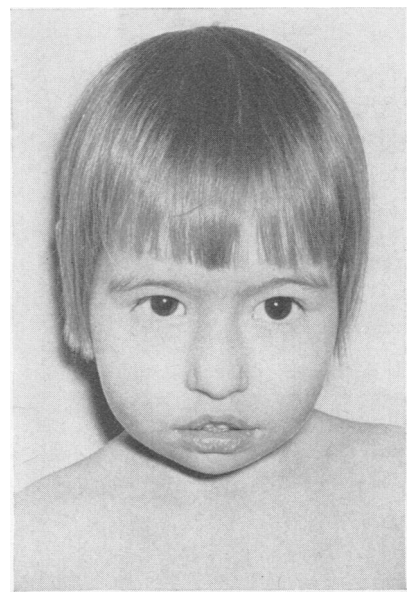

FIG. 1. The patient demonstrating prominent eyebrows growing together in midline (synophrys), small epicanthal folds, and micrognathia.

showed bilateral simian creases. Her gait was unsteady and she was mildly hypotonic. The remainder of her physical examination fell within normal limits. Laboratory tests showed her to have normal levels of calcium, phosphorus, alkaline phosphatase, BUN, glucose, and thyroxine. Radiology showed a bone age of 12 months and a reduced craniofacial ratio. Re-examination at 44 months did not reveal any other abnormalities and her measurements were still below the third percentile.

Developmental Assessment (E.L.). Evaluation at 45 months showed her to be functioning for the most

TABLE I

DERMATOGLYPHIC STUDIES*

Digits

	Left					L	Total	R	Right				
	5	4	3	2	1				1	2	3	4	5
Patterns	L^u	W^s	W^s	W^d	W^s				W^s	L^r	L^u	W^o	L^u
Ridge counts	7	12/*13*	*10*/9	6/*7*	12/*14*	51	104	53	13/*13*	12	9	12/*13*	6

Palms

	D	C	B	A	Axial Triradius		HT	T–l_1	l_2	l_3	l_4
					Height	*atd* Angle					
Left	11	Not present	Not present	5″	30% (t′)	41°	0	0	0	0	0
Right	11	Not present	Not present	5″	27·6% (t′)	47°	0	0	0	0	0

* Simian creases were present on both the left and right palms.

part between 2 and 2½ years. Her developmental quotient (DQ) was estimated to be 60. Speech production and comprehension were in keeping with her overall development, and after assessment in a sound field setting her hearing was considered to be grossly normal. Her gross motor skills showed the greatest delay, being at the 18 month level (less than 50% of normal).

Dermatoglyphics

Table I shows bilateral simian creases. The fingerprints showed six whorls and the total ridge was 104. Both axial triradii were distally placed but the *atd* angles were in the normal range. The b and c triradii were absent in both hands.

TABLE II

CHROMOSOME COUNTS

		No. of Chromosomes					Total No. of Cells	Karyotype
		45	46	47	48	49		
Proposita	B (1)	—	1*	7*	42	—	50	48,XXXX
	B (2)	—	—	2*	48	—	50	
	S	—	—	1*	48	1†	50	
Mother	B	—	10	—	—	—	10	46,XX
Father	B	1*	9	—	—	—	10	46,XY
Brother	B	—	10	—	—	—	10	46,XY
Sister	B	—	10	—	—	—	10	46,XX

B = Blood culture.
S = Fibroblast culture.
* Random loss of chromosomes; broken cells.
† Additional C-group chromosome; not identified

Chromosome Studies

Buccal smears showed 6% of the nuclei to have three, 18% two, and 23% one X-chromatin body. Chromosome preparations from short-term peripheral blood leucocyte cultures were stained conventionally with orcein and by Q-, G-, and C-banding. Orcein preparations showed a chromosome number of 48 with 18 chromosomes in the C group (Table II). Q- and G-banding showed the presence of four X-chromosomes (Fig. 2). A 16h+ chromosome was shown to be present by C-banding (Fig. 2). Cells with less than 48 chromosomes showed random chromosome loss and were interpreted as technical artefacts. One conventionally stained cell with 49 chromosomes was observed with an additional chromosome in the C group which could not be identified. In our view this was most likely a technical artefact but the possibility of a 49,XXXXX cell could not be excluded. The karyotype was interpreted as 48,XXXX with no evidence of mosaicism. The karyotypes of the parents and sibs were all normal (Table II).

Discussion

Clinical data on 19 cases are presented in Table III. The mean total dermal ridge count determined from data on 10 patients is 84 ± 38* which is significantly lower than the mean for the general population of 127 ± 52 for females ($t = 3{\cdot}2$, $P < 0{\cdot}01$)

* Standard deviations follow the means in all cases.

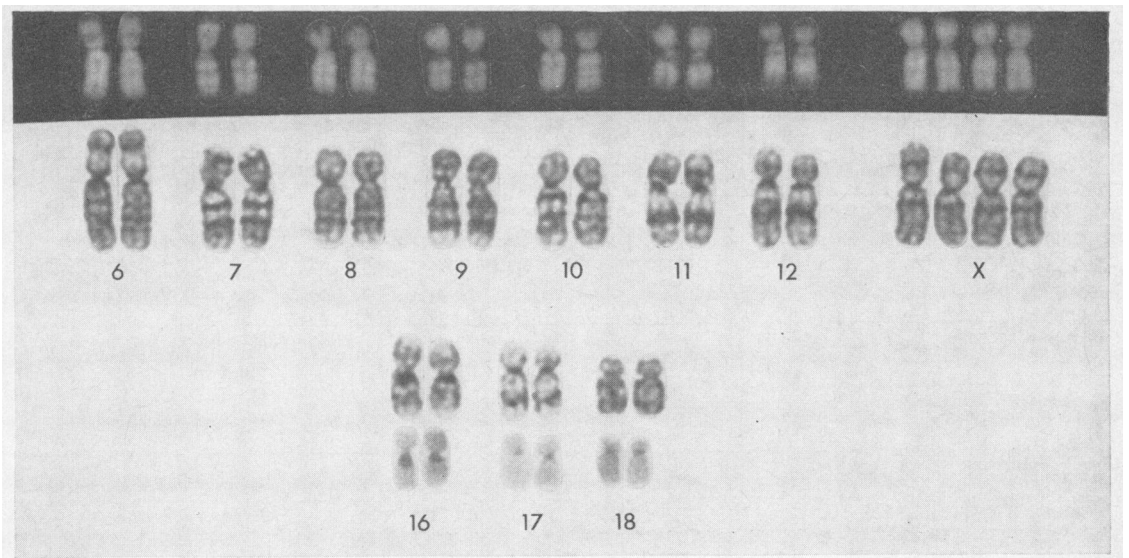

FIG. 2. Top: Partial karyotype of the C group showing four X-chromosomes (Q- and G-banding). Bottom: Partial karyotype of the E group showing a 16h + chromosome (G- and C-banding).

(Holt, 1955/1956). This supports Penrose's concept (1967) that extra heterochromatic X-chromosomes lead to a reduction in the total ridge count. The mean maternal age at birth of 15 patients is $28{\cdot}0 \pm 6{\cdot}6$ years; this is not significantly elevated over the population mean (27·0 years) for Canada (Vital Statistics Canada, 1969). Successive non-disjunction at both meiotic divisions in oogenesis is the most likely origin for this chromosome abnormality and has been shown by Xg groups to be operating in at least one patient with tetra-X chromosomes (De Grouchy *et al*, 1968) and in three patients with a 49,XXXXY chromosome complement (Race and Sanger, 1969); these findings therefore suggest that a maternal age effect may not account for the occurrence of non-disjunction in the majority of tetra-X females. Von Bergemann (1962) reported a 48,XXXX woman who gave birth to a 47,XX,+G child. She also reported a family in which a 47,XXX/48,XXXX woman gave birth to a child with the same chromosome complement and to another child with a 47,XX,+G karyotype; her mother also had a 47,XXX/48,XXXX karyotype and her sister was a 46,XX/47,XXX/48,XXXX mixoploid. These data on the 48,XXXX state may be compared to data on the 47,XXX condition, in which the mean maternal age is elevated over the mean for the population (Hamerton, 1971) and in which aneuploid states are rare among the offspring of affected patients (Barr *et al*, 1969) and may suggest the possibility of familial non-disjunction in the aetiology of the 48,XXXX state.

The clinical data (Table III) indicate the absence of a definite 48,XXXX phenotype. Mental retardation was noted in 16 patients; of the remaining three subjects one had normal intelligence (Blackston and Chen, 1972) while the IQ of two others fell into the sub-normal range (Di Cagno and Franceschini, 1968; Hanicka *et al*, 1969). The patient reported by Duncan, Nicholl, and Downes (1970) had an IQ of 94 in a nonverbal test; however, her verbal IQ was only 59. Since most of the patients were ascertained because of mental retardation, an association between the tetra-X state and mental retardation is at least questionable. A speech disorder has been reported in seven patients; in three instances the development of speech was more retarded than expected for the DQ (Carr *et al*, 1961; De Grouchy *et al*, 1968; Duncan *et al*, 1970). In four cases an articulation defect was reported (Di Cagno and Franceschini, 1968; Hanicka *et al*, 1969; Telfer *et al*, 1970; Blackston and Chen,

TABLE III
FINDINGS IN PATIENTS WITH 48,XXXX CHROMOSOME COMPLEMENT

Reference	Age at Examination (yr)	Maternal Age	Paternal Age	Height (cm)	Weight (Kg)	Total Ridge Count	IQ/DQ	Somatic Malformations
Carr *et al* (1961)	12·5	21	19	158·8	50·8	—	30	Strabismus
Carr *et al* (1961)	32	41	39	163·2	48·1	—	50	Enlarged thyroid
Von Bergemann (1962)	33	—	—	—	—	—	—	Enlarged thyroid
Davies (1963)	5	—	—	—	—	—	40	Bilateral congenital dislocated hip; large naevus left thigh and leg
Anderson *et al* (1968)	13	—	—	Tall	—	—	47–54	Tall stature; short fingers; enlarged end of radius and ulna
Di Cagno and Franceschini (1968)	4·6	25	31	103·5	16·6	125	80	Abnormal facies reminding Down's syndrome
Lejeune and Abony (1968)	14	31	38	156	60·0	—	Retarded	Hypertelorism; abnormal face
De Grouchy *et al* (1968)	6·5	26	27	125	25	139	50	'Impression of Down's syndrome'
Konishi and Yanagisawa (1968)	29	—	—	—	—	—	51	Slight deafness; cataracts; myopia; irregular menses
Hanicka *et al* (1969)	6	Young	Young	—	—	110	83	Hypertelorism; iridoschisis; webbed neck; clinodactyly of fifth digits
Halikowski *et al* (1969)	12	22	27	—	—	30	65	Myopia; strabismus; patent ductus arteriosus (?); infantile genitalia
Telfer *et al* (1970)	28	23	30	158·6	72·4	26	75	Esotropia; nystagmus; abnormal EEG; radio-ulnar synosteosis; underdeveloped breasts
Telfer *et al* (1970)	3·5	28	25	98·75	15·3	70	55	Microcephaly; abnormal ears; esotropia; abnormal EEG
Duncan *et al* (1970)	10·5	43	60	—	—	95	59/94	Clinodactyly of fifth digit; mandibular prognathism; slight kyphosis and lordosis
Berkeley and Faed (1970)	33	31	26	—	—	87	Severely retarded	Kyphosis; abnormal EEG; short terminal phalanges
Park *et al* (1970)	16	23	27	180	79	—	70	None
Blackston and Chen (1972)	3·75	25	28	88	13·7	60	101	Epicanthal folds; clinodactyly of fifth digit; widely spaced nipples; external tibial torsion
Larget-Piet *et al* (1972)	5	28	30	103	15	132	69	Mongoloid slant of the eyes; epicanthus; flat bridge of the nose; low hair line
Present report	3·5	25	28	93	11·1	104	60–65	Low stature; microcephaly; synophrys; small epicanthal folds; high arched palate; small mandible; bilateral simian creases; mild hypotonia

1972). In four other patients in whom speech development was recorded the level was found to be consistent with the reported DQ (Berkeley and Faed, 1970; Telfer *et al*, 1970; Larget-Piet *et al*, 1972; and the present report). In one patient surprising verbosity was reported (Carr *et al*, 1961). Further studies will be necessary to determine whether speech disorder forms part of the 48,XXXX phenotype or is merely secondary to mental retardation.

Addendum

Since submission of our manuscript for publication two additional cases of 48,XXXX have been published. Gardner, Veale, and Sands (1973) reported a 14-year-old girl ascertained by speech problems and epilepsy. Maternal and paternal ages were 31 and 28 years, respectively. Total ridge count was 132. Her full scale IQ was 58–68. Malformations noted were hypertelorism epicanthal folds, bilateral radioulnar synostosis, clinodactyly, and camptodactyly of the fifth finger. Walbaum *et al* (1973) have reported a 21-month-old infant ascertained by features suggestive of Down's syndrome. Maternal and paternal ages were 20 and 21 years, respectively. Total ridge count was 54. DQ was 85 with more marked retardation in speech development. Malformations reported were epicanthal folds, depressed nasal bridge and a right cataract.

These two case reports give further evidence suggestive that a speech impairment might represent a phenotypical manifestation of the 48,XXXX state.

We are grateful to Dr J. N. Briggs for allowing us to study his patient. The expert technical assistance of Mr F. Bauder, Miss V. Niewczas-Late, and Mrs M. Riffell is gratefully acknowledged. This work was supported by MRC operating grant No. 4458 and The Children's Hospital Research Foundation, Winnipeg. G.R.D. acknowledges an MRC Postdoctoral Fellowship.

S. D. J. PEÑA, M. RAY, G. DOUGLAS, E. LOADMAN, and J. L. HAMERTON
Division of Medical Genetics, Health Sciences Children's Centre, Winnipeg, Manitoba, Canada

REFERENCES

Anderton, L. G., McLendon, W. M., Ford, E. L. and Hall, L. O. (1968). Two extra X-chromosomes found in a teenage girl. *Hospital Tribune*, **2**, 30.

Barr, M. L., Sergovch, F. R., Carr, D. H., and Shaver, E. L. (1969). The triplo-X female: An appraisal based on a study of 12 cases and a review of the literature. *Canadian Medical Association Journal*, **101**, 247–258.

Bergemann, E. Von (1962). Die Häufigheit des Abweichens vom normalen Geschlechtschromatin und eine Familienuntersuchung bei Triplo-X. *Helvetica Medica Acta*, **29**, 420–422.

Berkeley, M. I. K. and Faed, M. H. W. (1970). A female with the 48,XXXX karyotype. *Journal of Medical Genetics*, **7**, 83–85.

Blackston, R. D. and Chen, A. T. L. (1972). A case of 48,XXXX female with normal intelligence. *Journal of Medical Genetics*, **9**, 230–232.

Carr, D. H., Barr, M. L., and Plunkett, E. R. (1961). An XXXX chromosome complex in two mentally defective females. *Canadian Medical Association Journal*, **84**, 131–137.

Davies, T. S. (1963). Buccal smear surveys for sex chromatin. *British Medical Journal*, **1**, 1541–1542.

De Grouchy, J., Brissaud, H. E., Richardet, J. M., Représsé, G., Sanger, R., Race, R. R., Salmon, C., and Salmon, D. (1968). Syndrome 48,XXXX chez une enfant de six ans. Transmission anormale du group Xg. *Annales de Génétique*, **11**, 120–124.

Di Cagno, L. and Franceschini, P. (1968). Feeblemindness and XXXX karyotype. *Journal of Mental Deficiency Research*, **12**, 226–236.

Duncan, B. P., Nicholl, J. O., and Downes, R. (1970). An XXXX sex chromosome complement in a female with mild mental retardation. *Canadian Medical Association Journal*, **102**, 969–970.

Gardner, R. I. M., Veale, A. M. O., and Sands, V. E. (1973). XXXX syndrome: case report and a note on genetic counselling and fertility. *Humangenetic*, **17**, 323–330.

Halikowski, B., Kleczkowska, A., Gościnka, Z., and Knaus, A. (1969). Zespol 'superfemale' u 12-letniej dziewczynki. *Pediatria Polska*, **44**, 1147–1154.

Hamerton, J. L. (1971). *Human Cytogenetics*, vol. 2. Academic Press, New York.

Hanicka, M., Kleczkowska, A., Makowska, J., Sokolowski, J., and Jarczyk, K. (1969). Rozszczep teczowki u dziewczynki z kariotypem 48,XXXX. *Polski Tygodnik Lekarski*, **24**, 1164–1166.

Holt, S. B. (1955/1956). Genetics of dermal ridges: parent-child correlations for total finger ridge count. *Annals of Human Genetics*, **20**, 270–281.

Konishi, S. and Yanagisawa, S. (1968). A case of an XXXX sex chromosome complex. *Congenital Anomalies*, **8**, 211–218.

Larget-Piet, L., Pignier, J., Berthelot, J., Ayache, P., Bourdon, P., and Larget-Piet, A. (1972). Syndrome 48,XXXX chez une enfant de 5 ans. *Pédiatrie*, **27**, 433–443.

Lejeune, J. and Abonyi, D. (1968). Syndrome 48,XXXX chez une fille de quatorze ans. *Annales de Génétique*. **11**, 116–119.

Park, I. J., Tyson, J. E., and Jones, H. W. (1970). A 48,XXXX female with mental retardation. *Obstetrics and Gynecology*, **35**, 248–252.

Penrose, L. S. (1967). Finger-print pattern and sex chromosomes. *Lancet*, **1**, 298–300.

Race, R. R. and Sanger, R. (1969). Xg and sex-chromosome abnormalities. *British Medical Bulletin*, **25**, 99–103.

Telfer, M. A., Richardson, C. E., Helmken, J., and Smith, G. F. (1970). Divergent phenotypes among 48,XXXX and 47,XXX females. *American Journal of Human Genetics*, **22**, 326–335.

Vital Statistics Canada (1969). Information Canada, Ottawa.

Walbaum, R., Vandevelde-Staquet, H. F., Lefebvre, C., Gnamey, D. K., DeLattre, B., and Leconte, D. (1973). Syndrome 48,XXXX chez un nourisson. *Journal de Génétique Humaine*, **21**, 43–56.