Review article

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Reciprocal translocations in man

3:1 Meiotic disjunction resulting in 47- or 45-chromosome offspring*

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Summary. Five cases of chromosome imbalance resulting from 3:1 disjunction of reciprocal translocations are described. A review of the literature suggests this phenomenon is more common than has previously been recognized.

Reciprocal translocations are a well-known source of heritable chromosome imbalance in man. Abnormal offspring usually have 46 chromosomes, including only one of the translocation products, and are therefore partially trisomic for one chromosome and partially monosomic for the other. The subject has been reviewed by Ford and Clegg (1969), Lejeune, Dutrillaux, and de Grouchy (1970), and Hamerton (1971).

Less often, imbalance results from a numerically unequal meiotic disjunction of the translocated chromosomes and their normal homologues. We have identified 47- and 45- chromosome individuals presumptively due to 3:1 disjunction in balanced translocation heterozygotes. More extreme degrees of aneuploidy have not been described in man, and may be inviable.

This paper describes five new cases of 3:1 disjunction from reciprocal translocations, and summarizes information on 51 cases from the literature.

Case reports

Case 1 (MB/531). See Figs. 1a and 1b. Parent: 46,XX,t(2;4)(q31;q12). Abortus: 47,XX,+der(4),t(2;4)(q31;q12)mat (tertiary trisomy).‡

A couple (II.1 and II.2) presented for counselling having had six spontaneous abortions and an infant with Down's syndrome. The Down's child showed trisomy 21, but also carried a balanced reciprocal translocation

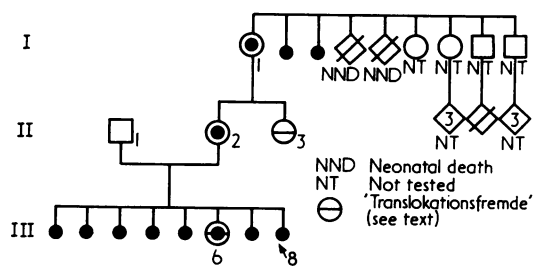

FIG. 1a. Pedigree of case 1. I.1 and II.2: 46,XX,t(2;4)(q31;q12). II.1: 46,XY. II.3: 46,XX/47,XXX. III.6: 47,XX,+21,t(2;4)(q31;q12)mat (Down's syndrome). III.8: 47,XX,+der(4),t(2;4)(q31;q12)mat (abortus-tertiary trisomy).

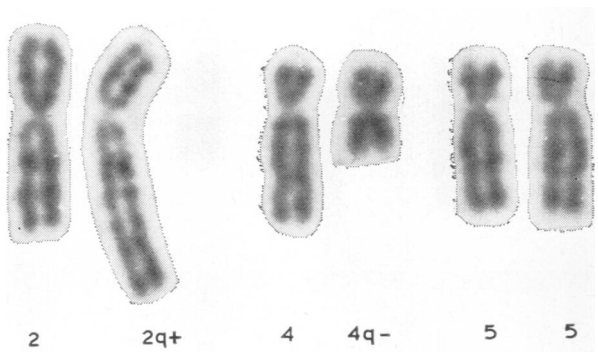

FIG. 1b. Partial karyotype (Giemsa) of balanced carrier (mother of case 1): 46,XX,t(2;4)(q31;q12).

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‡ See Table II and p. 33

involving 2q and 4q, inherited from the mother. Subsequently an eighth pregnancy ended spontaneously at 8 weeks; the fetus was found to be 47,XX,+der(4).

The mother's mother also carried the translocation; the only sib of the mother had a 46,XX/47,XXX constitution (50 cells with 46 chromosomes and four with 47), but did not carry the translocation.

Two members of this family (II.3 and III.6), both born to balanced carriers of the translocation, showed non-disjunction for a chromosome not itself involved in the translocation: in one instance non-disjunction for an X chromosome, in the other non-disjunction for a 21 chromosome. These would appear to be instances of 'Translokationsfremde', or 'Non-disjunktion eines Chromosoms Z' (Stalder, Bühler, and Bühler, 1965).

Case 2 (RL/197). See Fig. 2. Parent: 46,XX, t(4;9)(q35;q12). Child: 47,XX,+der(9),t(4;9)(q35;q12) mat (tertiary trisomy).

After eight years of parental infertility, a child was born with the following features: birth weight 3225 g, severe talipes, neonatal hyperpyrexia, respiratory problems, strabismus, and frequent screaming attacks. She sat alone at 13 months, walked at 4 years and at 6½ years her DQ (Denver) approximated to 30. Height was then below the 10th centile, weight on the 25th, and head circumference on the 50th. She had widely spaced teeth with notched incisors. The fifth fingers showed single flexion creases and extreme clinodactyly, the *c* and *d* triradii were replaced by a *z*, and a large whorl occupied the left thenar area. The hand anomalies resemble those described in cases of presumptive 9p trisomy (Edwards *et al*, 1962/1963; Butler, Eades, and France, 1969; Rethoré *et al*, 1970; 1973).

Chromosome analysis, with quinacrine and trypsin-banding, identified a balanced translocation t(4;9) in the mother, and a 47,XX,+der(9) state in the proposita. The mother's only sib had normal chromosomes; her parents were deceased, and no other family members were tested.

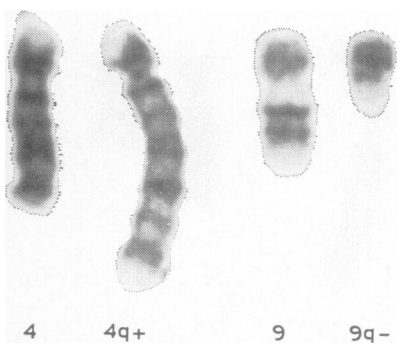

FIG. 2. Partial karyotype (trypsin) of blanced carrier (mother of case 2): 46,XX,t(4;9)(q35;q12).

Case 3 (MB/351). See Figs. 3a and 3b. Parent: 46,XX,t(7;21)(q31;q22).* Child: 47,XY,−7,+der(7), +der (21),t(7;21)(q31:q22)mat (interchange trisomy).†

The brother of a man with Down's syndrome requested amniocentesis for his wife's first pregnancy. He, another brother, and his mother were found to carry a balanced translocation t(7;21) whilst the abnormal sib had a 47,XY,−7,+der(7),+der(21) constitution. Amniocentesis was technically unsuccessful, termination was requested, and the fetus found to be a balanced heterozygote.

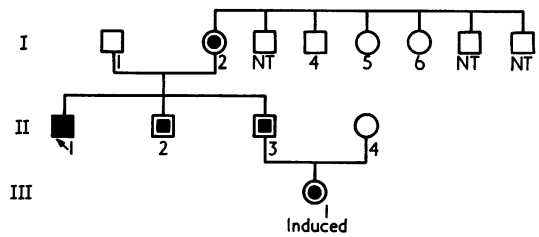

FIG. 3a. Pedigree of case 3. I.1 and I.4: 46,XY. I.5, I.6, and II.4: 46,XX. II.2 and II.3: 46,XY,t(7;21)(q31;q22). I.2 and III.1: 46,XX,t(7;21)(q31;q22). II.1: 47,XY,−7,+der(7),+der(21) t(7;21)(q31;q22)mat (Down's syndrome—interchange trisomy).

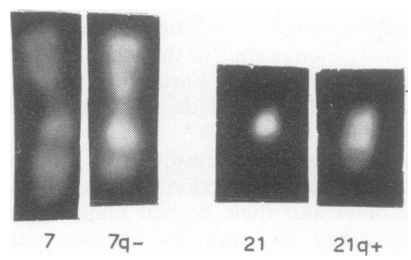

FIG. 3b. Partial karyotype (quinacrine fluorescence) of consultand (II.3): 46,XY,t(7;21)(q31;q22).

Case 4 (CD/309). See Figs. 4a and 4b. Parent: 46,XX,t(7;21)(p22;q22). Children: 46,XY/47,XY, +der(21),t(7;21)(p22;q22)mat and 47,XY,+der(21), t(7;21)(p22;q22)mat (both tertiary trisomy).

Two mentally retarded brothers presented with the clinical features shown in Table I.

Analysis of G-banded chromosomes (Seabright, 1971) showed that the younger brother had a small extra acrocentric in all cells, which resembled a 21q−. The older brother was a mosaic 46,XY/47,XY,+der(21). Sixteen out of 128 lymphocytes contained 47 chromosomes, as did 21 out of 29 skin fibroblasts; remaining cells counted 46. R-banding with acridine orange (Bobrow and Madan, 1973) showed that the sister and mother of the

* This translocation appears identical with that described by Bass, Crandall, and Marcy (1973); unbalanced 2:2 segregants appeared in their family.

† See Table II and p. 33.

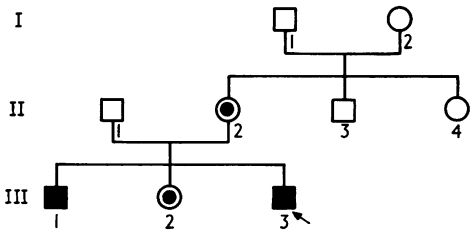

FIG. 4a. Pedigree of case 4. I.1, II.1, and II.3: 46,XY. I.2 and II.4: 46,XX. II.2 and III.2: 46,XX,t(7;21)(p22;q22). III.1: 46,XY/47,XY,+der(21),t(7;21)(p22;q22)mat (tertiary trisomy mosaic). III.3: 47,XY,+der(21),t(7;21)(p22;q22)mat (tertiary trisomy).

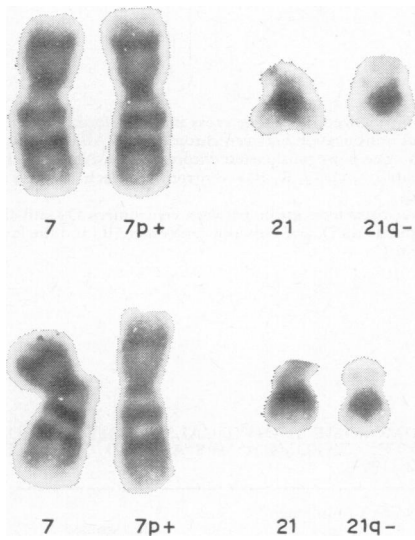

FIG. 4b. Partial karyotype (trypsin) of balanced carrier (mother of case 4): 46,XX,t(7;21)(p22;q22).

propositi carried a balanced translocat involving 7pion and 21q. Parents and sibs of the mother had normal chromosomes.

The chromosomally unbalanced brothers did not resemble any cases of 'partial mongolism' hitherto reported (see references to numerous examples in Finley *et al*, 1965; Lenz, 1967; Niebuhr, 1974).

Case 5 (PLF/353). See Fig. 5. Parent: 46,XX, t(2;21)(p16;q22). Child: 47,XY,−2,+der(2),+der(21), t(2;21)(p16;q22)mat (interchange trisomy).

A child with Down's syndrome was found to have a 47,XY,−2,+2p−,+21q+ constitution. His mother carried a balanced translocation involving 2p and 21q. Her other four pregnancies resulted in a balanced translocation heterozygote, a stillborn infant (no further information), and two abortuses. No other family members have yet been tested.

Markers

Thirty polymorphic markers (blood groups and enzyme types) were studied in the families of cases 2 and 4; no examples of anomalous segregation were found.

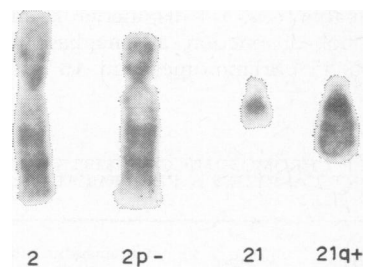

FIG. 5. Partial karyotype (trypsin) of balanced carrier (mother of case 5): 46,XX,t(2;21)(p16;q22).

TABLE I

CLINICAL FINDINGS IN MENTALLY RETARDED BROTHERS WITH 47,+der(21) (Case 4, III.3, and III.1)

	Older Sib	Younger Sib
Gestation, birth weight	Term, 2600 g	38 weeks, 3400 g
First sat	11 months	18 months
First walked	21 months	3½ years
Remained incontinent at	9 years	4½ years
Behaviour	Hyperkinetic	Retiring
Degree of mental retardation	Both severely subnormal	
Facies	Both unremarkable	
Height (centile)	50th	3rd
Weight (centile)	50th	50th
Head circumference (centile)	85th	85th
Ears	Small	Normal
Eyes	A few Brushfield's spots in both brothers	
Other anomalies		Umbilical hernia; R inguinal hernia; R testis undescended?
Dermatoglyphic probability of Down's (Penrose and Loesch, 1971)	$0.03 < P < 0.50$	$0.00125 < P < 0.03$

Meiotic derivation of aneuploid gametes from reciprocal translocations

Meiotic segregation of the chromosomes involved in a reciprocal translocation and their normal homologues can lead to a considerable variety of unbalanced gametes (Ford and Clegg, 1969; Hamerton, 1971; Paris Conference, 1971). The cases considered in this paper are best explained by 3:1 disjunction of the four chromosomes at pachytene in a translocation heterozygote, leading to 45- or 47-chromosome offspring.

The situation at pachytene is given schematically in Fig. 6. 3:1 Disjunction of centromeres at anaphase I (eg, Q_1, R_1, and R_2 going to one pole, Q_2 to the other), when followed by normal symmetrical disjunction at anaphase II, results in some gametes carrying 24 chromosomes while others carry only 22. 2:2 Disjunction at anaphase I, of whatever type (alternate, adjacent-1, or adjacent-2), followed by non-disjunction of one chromatid pair at anaphase II, has a similar effect on gametic chromosome number; crossing-over within the interstitial segments can allow non-disjunction at anaphase II to mimic 3:1 disjunction at anaphase I.

Table II shows the types of chromosome complement derivable from 3:1 disjunction at anaphase I, or from non-disjunction at anaphase II. Four types with 45 chromosomes and 16 with 47 are

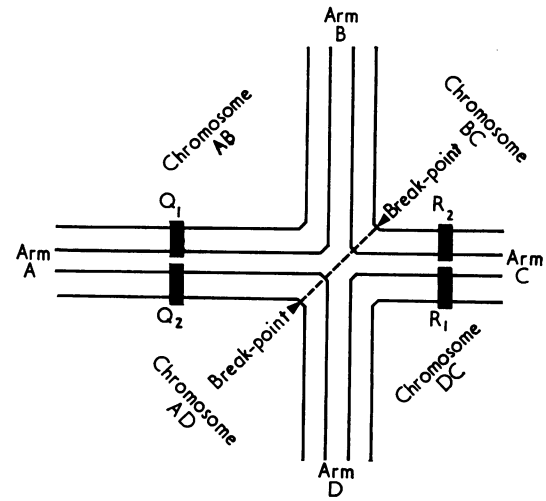

FIG. 6. Formalized pachytene cross in a translocation heterozygote (reciprocal translocation between chromosomes AB and CD).

AB,CD = the non-translocated chromosomes; AD,BC = the translocation carriers; Q_1,Q_2,R_1,R_2 = centromeres, each carrying a pair of chromatids.

The *interstitial segments* lie between centromere Q_2 and the junction of arms A and D, and between centromere R_2 and the junction of arms B and C.

TABLE II

POSSIBLE CHROMOSOME CONSTITUTIONS OF 45- OR 47-CHROMOSOME INDIVIDUALS, DERIVED FROM A PARENT CARRYING A RECIPROCAL TRANSLOCATION BETWEEN CHROMOSOMES AB AND CD (AS IN FIG. 6). SEE ALSO FORD (1969)

Type No.	Number of Chromosomes	Chromatids/Chromosomes Derived from Heterozygote Parent			Chromosome Complement			Recognized Nomenclature
					Monosomy for	Trisomy for	Tetrasomy for	
1	45	AB			CD	—	—	—
2	45	CD			AB	—	—	—
3	45	AD			BC	—	—	Tertiary monosomy
4	45	BC			AD	—	—	Tertiary monosomy
5	47	AB	CD	AD	—	AD	—	Tertiary trisomy
6	47	AB	CD	BC	—	BC	—	Tertiary trisomy
7	47	AB	AD	BC	—	AB	—	Interchange trisomy
8	47	CD	AD	BC	—	CD	—	Interchange trisomy
9	47	AD	AD	BC	—	AD	—	—
10	47	AD	BC	BC	—	BC	—	—
11	47	AB	AB	CD	—	AB	—	—
12	47	AB	CD	CD	—	CD	—	—
13	47	AB	AB	BC	D	A	B	—
14	47	AB	BC	BC	D	C	B	—
15	47	CD	CD	AD	B	C	D	—
16	47	CD	AD	AD	B	A	D	—
17	47	AB	AB	AD	C	B	A	—
18	47	AB	AD	AD	C	D	A	—
19	47	CD	CD	BC	A	D	C	—
20	47	CD	BC	BC	A	B	C	—

Types 5–8 are effectively trisomic for the same chromosome segments as types 9–12, ie, the 20 chromosome arrangements correspond with 16 different chromosome complements.

Types 1–16 are derivable by 3:1 disjunction at anaphase I, or by non-disjunction at anaphase II. Types 17–20 are only derivable by non-disjunction at anaphase II. It is necessary to postulate crossing-over in the interstitial segments if types 5–8 are to be derived by anaphase II non-disjunction, and likewise if types 9–16 are to be derived by 3:1 disjunction at anaphase I.

derivable. In addition to partial monosomies and trisomies, the last eight types in the table would produce tetrasomy of some chromosome regions. These 20 derivable chromosome types result in 16 different chromosome complements, since four 'equivalent pairs' can be found among the 47-chromosome offspring (see footnote to Table II).

Terminology

First described in the trisomics of Datura (Belling and Blakeslee, 1924; Blakeslee, 1924; Belling and Blakeslee, 1926; Belling, 1927; Blakeslee, 1930; 1934), 3:1 disjunction has been observed in maize, barley, rye, pea, tomato, Nicotiana, Oenothera, Crepis, and Campanula (see references in Burnham, 1956; also Ramage, 1960; Sybenga, 1966a; 1966b; Khush and Rick, 1967); and in Drosophila, the mouse, and man (Dobzhansky, 1933; Glass, 1935; Lyon and Meredith, 1966; Hamerton, 1969; 1971).

Belling and Blakeslee established the various types of chromosome constitution present in varieties of Datura carrying $2n+1$ chromosomes. The third type to be identified consisted of a normal complement plus a translocation derivative originating from a balanced translocation carrier parent, and was called 'tertiary trisomy'.

Offspring of translocation heterozygotes may carry other types of $2n+1$ chromosome complement. When the two complementary translocation chromosomes are pesent together with one of the non-translocated pairs (types 7 and 8, Table II) the term 'interchange trisomy' has been used (Burnham, 1956; 1962). This is confusing, as 'interchange' regularly has a wider meaning, but we have retained the term to distinguish this phenomenon from 'tertiary trisomy'.

$2n-1$ Offspring of translocation heterozygotes, carrying a single translocation derivative and neither of the non-translocated pair (types 3 and 4, Table II) were recognized by Rick (1943); they later acquired the name 'tertiary monosomy' (Rieger, Michaelis, and Green, 1968).

Other types of aneuploid constitution (1 and 2 and 9 to 20, Table II) are seldom recognized in offspring of translocation carriers.

Incidence of 3:1 disjunction

The true incidence of a rare phenomenon such as 3:1 disjunction could only be ascertained by a large prospective population survey. Estimates from published data suffer from bias in the discovery and reporting of individual cases. Many of these ascertainment biases apply equally to data on other forms of chromosome imbalance arising from reciprocal translocations, and it seems justifiable to estimate the incidence of 3:1 disjunction relative to these.

Our own Unit has identified 24 reciprocal translocations, 20 of these in chromosomally unbalanced propositi; in five propositi the imbalance arose by 3:1 disjunction in a carrier parent. In a similar consecutive series of 20, Leisti (1971) found two cases of 3:1 disjunction from a parental carrier. Brøgger (1967) collected reports of 50 reciprocal translocations, and Hamerton (1971) reports 76; at least three in the former series and 11 in the latter were identified after 3:1 disjunction in a parent. Data on ascertainment of abnormal offspring thus suggest that 6–25% of chromosomally unbalanced offspring of reciprocal translocation carriers result from 3:1 disjunction. Ascertainment is so biased that this must represent a maximum incidence estimate.

Published chromosome surveys of consecutive newborn, covering 46 058 infants (Friedrich and Nielsen, 1973; Jacobs *et al*, 1973/1974; Bochkov *et al*, 1974) contain no definite instance of 3:1 disjunction; 38 reciprocal translocations, of which four were unbalanced, were found in euploid infants. Carr (1971) found no clear evidence of 3:1 disjunction amongst 936 'unselected' abortuses. Kajii (1974) reports a sibship with five spontaneous abortions, two of the three karyotyped abortuses representing 3:1 disjunction from a paternal carrier. Among liveborn 'handicapped' populations, Jacobs, Frackiewicz, and Law (1971/1972) reported seven of 3816 individuals as carrying a supernumerary 'rearranged' chromosome; at least one of these (Newton *et al*, 1972) was derived by 3:1 disjunction from a carrier parent. In a similar 'handicapped' population of 800 Leisti (1971) found two instances of 3:1 disjunction from a balanced carrier.

Chromosomes involved in 3:1 disjunction

Table III includes 56 families showing 3:1 disjunction in a balanced translocation heterozygote. In 50 families both translocation products were clearly identified; in six only one of the products was identified, the presence of a balanced translocation being inferred in a parent of normal phenotype.

The representation of the various chromosome groups among these translocations is not proportional to the total length of chromosomes within the groups, nor to the number of chromosomes present within each group. Comparison on a length basis shows an over-representation of groups D, E, and G (Table IV). Comparison on a chromosome

TABLE III

FAMILIES IN WHICH 47- OR 45-CHROMOSOME OFFSPRING WERE DERIVED FROM HETEROZYGOTES FOR A RECIPROCAL TRANSLOCATION

	Reference	Translocation	Recognizable Phenotype of Unbalanced Offspring
With 45 chromosomes. Types 3 and 4 (Table II); tertiary monosomy			
1	Fredga and Rayner (1967); Fredga (1968)	15p+;18q− (or 15q−;18p+)	
2	Leisti (1971; case 16)	9q+;14 or 15q−	
3	Pfeiffer *et al* (1967a)	14p+;21q−	
With 47 chromosomes. Types 5 and 6; tertiary trisomy			
4	Present case 1	2q+;4q−	Abortus
5	Present case 2	4q+;9q−	Trisomy 9p
6	Present case 4	7p+;21q−	
7	Bloom and Gerald (1968; case 1)	Cp+;13q−	
8	Butler *et al* (1969)	9p+;15q−	Trisomy 9p
9	Francke (1972; case 8)	9p+;18q−*	
10	Gleissner *et al* (1970)	Dq+;18q−	Partial trisomy 18
11	Guanti *et al* (1971)	9p+;12q− (or 9q−;12p+)	
12	Hamerton (1971)	Dp+;16q	Abortus
13	Insley *et al* (1968); Hirschhorn *et al* (1972/1973)	10q−;15q+	'Intersex'
14	Lejeune *et al* (1970a)	18q−;Fq+	
15	Lejeune *et al* (1972)	8q;22q†	
16	Macintyre *et al* (1964)	D−;F+	Partial trisomy 13
17	Macintyre *et al* (1971)	17p+;Gq−	
18	Mason (1973)	1p+;9q−	Trisomy 9p
19	Newton *et al* (1972; case 178/69)	9q−;22p+	Trisomy 9p
20	Orye and van Nevel (1968)	14q−;17q+	
21	Pfeiffer *et al* (1966)	4q+;14q−	
22	Pitt *et al* (1967)	6 or 8p+;14q−	
23	Rethoré *et al* (1970; case 1)	6p+;9q−	Trisomy 9p
24	Rethoré *et al* (1970; case 2)	9q−;Gq+	Trisomy 9p
25	Revazov and Russkikh (1966)	9 or 11q−;Dp+	
26	Rott *et al* (1971)	4p+;9q−	
27	M. Seabright and N. M. Gregson (personal communication)	9q−;Xp+	Trisomy 9p
28	M. Seabright and N. M. Gregson (personal communication)	13p+;17q−	
29	Short *et al* (1972)	9p+;14q−	
30	Smith *et al* (1967)	17 or 18q−;Gp+	
31	Smith *et al* (1969)	3q+;7 or 8q−	
32	Vislie *et al* (1962); Brøgger (1967; case 3497)	Dq−;17q+	
With 47 chromosomes. Types 7 and 8; interchange trisomy			
33	Present case 3	7q−;21q+	Down's
34	Present case 5	2p−;21q+	Down's
35	Brodie and Dallaire (1962)	Dq+;18q−	Trisomy 18
36	France and Butler (1969)	Bq−;18q+	Trisomy 18
37	Hall (1963a; first case)	?+;21q−‡	Down's
38	Hall (1963a; second case)	?+;21q−‡	Down's
39	Kontras *et al* (1966)	1q−;21q+	Down's
40	Laurent and Robert (1968)	2q−;21q+	Down's
41	Miller *et al* (1970)	2p−;21q+	Down's
42	Pfeiffer *et al* (1967b)	6q−;21q+	Down's
43	Soukup *et al* (1969; case 1)	3−;21+	Down's
44	Soukup *et al* (1969; case 2)	3−;21+	Down's
45	Vogel and Löning (1973)	19p or q−;21q+	Down's
With 47 chromosomes. Types 9 and 10			
46	Monteleone *et al* (1969)	Bq+;Dq−	
47	Opitz *et al* (1973)	14q+;Xq−	Klinefelter's
48	Reiss *et al* (1972)	2q+;14q−**	
With 45, 46, or 47 chromosomes. More than one type of unbalanced disjunction in a single pedigree			
49	Bühler *et al* (1972)	?+;22q−	TT or IT or both ? (cat-eye syndrome)
50	Day and Miles (1965)	?+;21q− (or Dq−;21q+)	TT; IT; UB2:2 (Down's)
51	Hall (1963b)	?−;21p+††	TT; IT (Down's)
52	Hauschtek *et al* (1966)	13q−;17 or 18p+	TT; UB2:2 (partial 13 and 18 trisomies)
53	Jacobsen *et al* (1963; 1965/1966)	13q+;14q−	TT; TM (includes 1 abortus)
54	Kajii (1974)	13q−;18q+	TT; IT, UB2:2 (3 abortuses)
55	Leisti (1971; case 15)	Bp+;14q−	TT; TM
56	Schmidt *et al* (1972)	?+;21q−	TM; UB2:2 (includes a partial Down's)

?− or ?+—denotes translocation derivative of unidentified chromosome; TT = tertiary trisomy; IT = interchange trisomy; TM = tertiary monosomy; UB2:2 = unbalanced offspring resulting from 2:2 disjunction (adjacent-1 or -2, or alternate with cross-over in interstitial segment).

* Or 3:2 segregation from mosaic mother.

† Equal lengths of translocated segments.

‡ Or familial very short Y.

** Mosaic.

†† Perhaps 21p+;22q− (see Mikkelsen, 1973).

TABLE IV

FIFTY-SIX RECIPROCAL TRANSLOCATIONS, RESULTING IN OFFSPRING WITH 47 OR 45 CHROMOSOMES. (DISTRIBUTION OF BREAK POINTS BETWEEN CHROMOSOME GROUPS—COMPARISON BY LENGTH)

Chromosome Group	Total Relative *Length* of Chromosomes in Group*	No. of Breaks		*Contribution to* χ^2_{6DF}
		Observed	Expected	
A	49.18	10	24.86	8.883
B	25.36	7	12.83	2.649
C†	78.06	25	39.46	5.299
D	21.10	25	10.66	19.291
E	18.28	14	9.24	3.591
F	9.70	3	4.91	0.743
G‡	8.00	22	4.05	79.555
Total	209.68	106	106.01	χ^2_{6DF} = 120.011 (P < 0.00001)

* Derived from Penrose (1964/1965), as in Ford and Clegg (1969).
† Includes one and a half X chromosomes.
‡ Includes half a Y chromosome.

number basis still shows a significant over-representation of groups D and G ($\chi^2_{6DF} = 31.092$, $P < 0.001$). Comparison of the 3:1 series with the series of reciprocal translocations reviewed by Ford and Clegg (1969) shows an over-representation of group G and under-representation of group B in the 3:1 series (Table V). The relatively high intra-uterine viability of trisomies 13, 18, and 21 might in part explain the high frequency of D-, E-, and G-group chromosomes in the 3:1 series. However, 13 out of the 25 D-group chromosomes in this series were identified as No. 14 or 15. Twelve of the 25 C-group chromosomes involved were identified as a No. 9, and two were X-autosome translocations.

TABLE V

FIFTY-SIX RECIPROCAL TRANSLOCATIONS RESULTING IN OFFSPRING WITH 47 OR 45 CHROMOSOMES. (COMPARISON WITH 129 RECIPROCAL TRANSLOCATIONS REPORTED IN FORD AND CLEGG, 1969)

Chromosome Groups Involved	Translocations, Resulting in 47- or 45-Chromosome Offspring	Series of Ford and Clegg (1969)
A	10	32
B	7	46
C (includes X)	25	52
D	25	52
E	14	32
F	3	4
G (includes Y)	22	25
Total	106	243

$\chi^2_{5DF} = 15.04$, $P \approx 0.01$ (amalgamating groups F and G).

Disjunctional types

Tertiary trisomics are partially trisomic for both chromosomes involved in the reciprocal translocation (Table II). This situation was found in 35 families, and included seven cases of trisomy for 9p (with a fairly consistent phenotype; Rethoré *et al*, 1973), some cases of partial trisomy 13, 18, or 21, and three cases with trisomy for the proximal third of 14q. Tertiary monosomics are partially monosomic for both chromosomes involved in the translocation (Table II). Interchange trisomics are trisomic for one complete chromosome (Table II); 14 families have a propositus with Down's syndrome and two with trisomy 18.

The tertiary monosomics always carried the longer of the translocated chromosomes, never the shorter. In the tertiary trisomics the extra chromosome was always the shorter of the two derivative chromosomes, while in the interchange trisomics the supernumerary chromosome was always the shorter of the non-translocated homologues. These abnormal karyotypes are always those with the least possible gain or loss of chromosomal material, suggesting that they may represent a selected group sufficiently normal to survive intra-uterine life. A similar observation was made by Lyon and Meredith (1966) in respect of two mouse translocations disjoining 3:1.

The parents of 3:1 segregants

In six families the translocation was identified through four generations, in 13 families through three, and in seven it appeared *de novo* in a parent. Other pedigrees were incompletely recorded.

Sixty-one of the 68 chromosomally unbalanced individuals (90%) resulting from 3:1 disjunction were born to female heterozygotes. For comparison, chromosomally unbalanced euploid offspring of translocation heterozygotes arose from maternal carriers in 68 of 87 cases (Hamerton, 1971) or 65 of 93 cases (Ford and Clegg, 1969).

The mean age of 50 female carriers, at the birth of 3:1 offspring, was 28.32 years (Table VI). This differs little from the mean maternal age at birth of normal infants (Blank, 1959/1960; Lurie, 1972), or at the birth of infants with other structural chromosomal abnormalities (Jacobs *et al*, 1971/1972). In our series, there was a progression in mean age of maternal carriers, from 26.37 years at birth of chromosomally balanced infants, to 27.10 years at birth of unbalanced 46-chromosome infants, to 28.32 years at birth of 3:1 offspring. The difference in mean maternal age, between the chromosomally balanced and 3:1 groups, does not attain statistical

TABLE VI
PARENTAL AGES

	Mean Maternal Age (±1SD)		Mean Paternal Age (±1SD)		Mean Paternal–Maternal Age Difference (±1SD)	
General population (Blank, 1959/1960)*	27.65±5.84		31.69±6.47			
Controls (Lurie, 1972)†	26.44±5.22	(n=225)	30.00±5.96	(n=176)		
At birth of infants with segregant chromosome rearrangements (Jacobs *et al*, 1971/1972)†	28.74	(n=46)	30.59	(n=46)		
3:1 series—segregants‡						
At birth of balanced carriers, or normal non-carrier infants, derived from maternal carriers	26.37±5.61	(n=38)				
At birth of unbalanced 2:2 infants derived from maternal carrier	27.10	(n=5)				
At birth of 3:1 infants derived from maternal carrier	28.32±6.17	(n=50)	30.87±6.88	(n=47)	+2.40±3.22	(n=40)
At birth of 3:1 infants derived from paternal carriers	25.87	(n=3)	29.17	(n=3)	+3.33	(n=3)
3:1 series—de novo *cases*‡						
At birth of *de novo* tertiary monosomics	33.15±7.18	(n=20)	36.45±7.09	(n=19)	+2.84±2.23	(n=19)
At birth of *de novo* reciprocal translocations (Lurie, 1972)†	30.35±6.3	(n=40)	32.36±6.6	(n=41)		

* Age last birthday.
† Not mentioned whether 'age last birthday' was corrected or not.
‡ Correction of 0.5 years added to 'age last birthday'.

significance ($d=1.55$, $P<0.10$), but may reflect a tendency to family limitation after the birth of an abnormal child. In those few cases where 3:1 infants were born to paternal carriers, the mean paternal age at birth (29.2 years) was not above the general population mean. The increase in mean parental age at the birth of *de novo* 3:1 infants (Table VI) is discussed later.

Recurrence risks in families showing 3:1 disjunction

Reproductive risks to translocation carriers after an episode of 3:1 disjunction can be divided into (1) risk of abortion, (2) risk of a chromosomally unbalanced offspring following 2:2 disjunction, and (3) risk of a further episode of 3:1 disjunction. We may also ask whether certain translocations are particularly liable to undergo 3:1 disjunction, or whether this is equally likely to occur in carriers of any reciprocal translocation. Accurate answers to these questions can clearly not be derived from a retrospective survey of a small number of families published in the literature. We have only attempted rough estimates of the relevant risks: the data seem too heterogeneous to warrant complex analysis (Stene, 1969/1970a and b; 1970/1971).

Information is available for 69 sibships derived from female carriers, and 14 derived from male carriers (Table VII). In this table probands are defined as 'the first case of 3:1 disjunction found among those family members referred for chromosome analysis'. The proband sibships were corrected by Weinberg's method; the anterior sibships, parental and grandparental, each contain a 'necessary' carrier through which they are ascertained (Lejeune *et al*, 1970b), and correction is by subtraction of this 'necessary' carrier. The collateral sibships require no correction.

The total corrected data relating to female carriers show a combined recurrence risk of 9.1±1.2% for 3:1 and unbalanced 2:2 infants; about three-quarters (14/19) of this is due to further 3:1 offspring. For livebirths only, the combined recurrence risk is 14.0±3.2%. The incidence of spontaneous abortion (all pregnancies) is 38.0±3.4%.

Data for offspring of male carriers is less extensive, but a combined recurrence risk of 7.7±5.2% for 3:1 and unbalanced 2:2 infants (one of each) was found; for liveborn only, the recurrence risk was zero (0/17). The abortion rate was 34.6±9.3%.

An alternative definition of proband—'any referred child with unbalanced chromosome constitution resulting from a parental translocation, in a 3:1 disjoining family'—was applied to the proband sibships born to female carriers. Only livebirths were included; the multiple selection methods of Lejeune *et al* (1970b) and of Cavalli-Sforza and Bodmer (1971), yielded estimates of 21.7±5.0%, and 35.0±7.0% malsegregants, respectively. There were not sufficient offspring of male carriers for such analysis.

Lejeune *et al* (1970b) collected data on 80 reciprocal translocation families (74 of which had shown only 2:2 malsegregation), and estimated a 10–20% malsegregation risk for carrier females, and a 5-10% risk for carrier males. Their estimates are roughly similar to our own derived from the 3:1 disjunction series.

TABLE VII

RECURRENCE RISKS IN FAMILIES SHOWING 3:1 DISJUNCTION

	No. of Sibships	Offspring with Normal Chromosomes	Translocation Heterozygotes; 'Balanced Carriers'	Normal Phenotype, Not Tested	3:1 Segregant*	Unbalanced 2:2 Segregant*	Spontaneous Abortus‡	Stillbirth/Neonatal Death, Not Tested	Total	Combined Incidence of 3:1 and 2:2 Unbalanced, Livebirths Only	Combined Incidence of 3:1 and 2:2 Unbalanced, Including Abortuses	Incidence of Spontaneous Abortion
Offspring of female carriers												
Proband sibships (PS)	46	26	29†	2	56 (3)	5	52**	1	168			
Corrected PS		26	29	2	10 (1)	5	50	1	122	0.194 (14/72)	0.123 (15/122)	0.410 (50/122)
Anterior sibships (AS)	13	10	31	5	2	0	15	0	63			
Corrected AS		10	18	5	2	0	15	0	50	0.057 (2/35)	0.040 (2/50)	0.300 (15/50)
Collateral sibships	10	5	6	9	2	0	14	0	36	0.091 (2/22)	0.056 (2/36)	0.389 (14/36)
Total crude data	69	41	66	16	60 (3)	5	81	1	267			
Total corrected data		41	53	16	14 (1)	5	79	1	208	0.140 (18/129)	0.091 (19/208)	0.380 (79/208)
Offspring of male carriers												
Proband sibships	6	3	2	0	7 (2)	1 (1)	8	0	18			
Corrected PS		3	2	0	1 (1)	1 (1)	7	0	12	(0/5)	(2/12)	(7/12)
Anterior sibships	5	5	7	1	0	0	1	1	15			
Corrected AS		5	2	1	0	0	1	1	10	(0/9)	(0/10)	(1/10)
Collateral sibships	3	0	2	1	0	0	1	0	4	(0/3)	(0/4)	(1/4)
Total crude data	14	8	11	2	7 (2)	1 (1)	10	1	37			
Total corrected data		8	6	2	1 (1)	1 (1)	9	1	26	0.000 (0/17)	0.077 (2/26)	0.346 (9/26)

* The numbers in parentheses denote the number of 3:1 or 2:2, unbalanced, segregants that are also included in the list of spontaneous abortuses.
† May include one 'aneusomie de recombinaison'.
‡ Very few of these were analysed chromosomally, so that estimates of incidence of 3:1 disjunction (penultimate column) are minimal.
** Includes two induced abortions.

Abortion rates are higher (38% and 35%) in the 3:1 series, than in the offspring of reciprocal translocation carriers in general. For the latter, Hamerton (1971) quotes an incidence of 25.6% (male and female carriers combined), and Ford and Clegg (1969) quote figures which, when corrected by Weinberg's method, give abortion rates of 27.6% for female carriers and 22.2% for male carriers.

In offspring of female mice with a 3:1 disjoining translocation (T 194 H—Lyon and Meredith, 1966), 15% had tertiary trisomy and 4–5% tertiary monosomy: but male carriers were sterile. There is no general evidence of male sterility in the human families reviewed here, although at least one male carrier was oligospermic (Butler *et al*, 1969). Among the 3:1 pedigrees, childless carriers were as likely to be female as male (19/19) and most of these had not yet attained adulthood. The mean family size for female carriers who did reproduce was 3.86 (251/65) pregnancies, compared to 3.14 (44/14) pregnancies for male carriers. Considering livebirths only, the figures are: female carriers—2.94 pregnancies (191/65) and male carriers—2.62 pregnancies (34/13). This suggests that the larger number of pregnancies in carrier females is mainly due to compensatory replacement of abortuses.

Factors predisposing to 3:1 disjunction

Hamerton (1971) suggests that reciprocal translocations showing 3:1 disjunction are characterized by extreme asymmetry, extremely short interstitial segments, involvement of an acrocentric chromosome, and a III + I, or chain IV configuration at meiosis.

We compared the series of translocations disjoining 3:1 with a 'control' group ascertained through unbalanced 2:2 offspring collected from our recent experience and the literature. Approximate break points were located in 37 of the translocations showing 3:1 disjunction—in 15 by banding, in the remainder by autoradiography or on morphological grounds; and by banding in all 23 'control' translocations.

It is not clear from Hamerton's text (1971) whether 'extreme asymmetry' refers to unequal length of exchanged segments, asymmetry at pachytene, or gross disparity in length of the two chromosomes involved. If asymmetry is defined as a situation where the longer translocated segment was more than twice the length of the shorter, 34/37 of the exchanges in the 3:1 group, and 23/23 of those in the control group, were of this nature. Asymmetry at pachytene implies a subterminal break,

giving one very short arm to the pachytene cross. Thirty-three of 36 of the translocations in the 3:1 group, and all 23 of those in the control group, had such a break, and one arm of the resulting pachytene cross is likely to be shorter than 1/200 of the haploid autosome set length. Extreme disparity in total length of chromosomes involved seems to characterize interchange trisomy. The ratio of the length of the longer to that of the shorter chromosome averaged 3.69 (n = 12, including one *de novo*) in this group. By comparison, the ratio in the control group averaged 2.80 (n = 23), in the tertiary trisomy group 1.58 (n = 29), and in the tertiary monosomy group 1.83 (n = 34, including *de novo* cases). Comparing the interchange group with all other groups combined, $t_{12DF} = 4.75$, $P < 0.001$.

A 'short interstitial segment' implies one of the break-points is close to the centromere. We defined 'extremely short' as less than 1/200 of the length of the haploid autosome set, and on this criterion 23/24 of the translocations in the 3:1 group, but only 7/22 of those in the control group, possessed extremely short interstitial segments ($\chi^2 = 5.53$, $P < 0.025$). Preferential localization of break-points near centromeres or telomeres has been described in both spontaneously occurring reciprocal translocations and radiation-induced damage (Buckton, 1974; San Roman and Bobrow, 1973; Seabright, 1973).

Comparison of the 3:1 series with the series of Ford and Clegg (1969) in respect of chromosomes involved (Table V), shows significant excess of G-group chromosomes and a slight increase in D-group representation. Because of the shortness of the Gp, Gq, and Dp arms these translocations were usually scored as having 'extremely short' interstitial segments, so that the higher incidence of short interstitial segments in the 3:1 series may merely reflect the greater frequency of D- and G-group involvement. Exclusion of translocations containing D- or G-group chromosomes leaves only five in the 3:1 series (of which two have very short interstitial segments), and 13 in the control series (two with very short interstitial segments).

There is evidence (Dobzhansky, 1933; Burnham, 1956; 1962; Sybenga, 1966a; but see also Cook *et al*, 1973/1974) that chiasma formation is inhibited in the vicinity of a break-point. Involvement of a short chromosome, such as a human G-group, may therefore predispose to one chromosome forming no chiasmata. Such a III + I pachytene configuration would clearly increase the possibility of 3:1 disjunction occurring. A III + I meiotic configuration has often been observed in plant translocations that disjoin 3:1 (Burnham, 1962). It was also observed in mouse translocations frequently disjoining 3:1 (43%, and 80%, in two different translocations) more frequently than in other translocations (mean frequency 16% in nine translocations—Lyon and Meredith, 1966). However, there is evidence from several species that III + I configurations are not an absolute prerequisite for 3:1 disjunction. Both chain quadrivalents (Brink and Cooper, 1932) and ring quadrivalents may disjoin 3:1 (Glass, 1935; Hagberg, 1954; Burnham, 1962). Although III + I configurations have occasionally been observed in human translocation heterozygotes (Butler *et al*, 1969) we know of no adequate data on the frequency of this phenomenon in different translocations.

In summary, it seems that reciprocal translocations involving an acrocentric chromosome, and particularly a short acrocentric, are especially likely to show 3:1 disjunction. Such translocations are more likely to have short interstitial segments. Unequal size of exchanged segments, and asymmetry at pachytene, are not found more frequently in the 3:1 series. Extreme disparity in total length of chromosomes involved characterizes the interchange trisomy type of 3:1 disjunction.

There is as yet no evidence that 3:1 disjunction is ever due to disturbances of anaphase II, but every instance of 3:1 disjunction reported in this paper could in theory as well result from non-disjunction at the second meiotic division as from 3:1 disjunction at anaphase I.

3:1 Disjunction arising *de novo*

There are many instances of individuals with karyotype identical to those produced by 3:1 disjunction, but with chromosomally normal parents (Table VIII). We suggest that this represents the occurrence of both a chromosomal rearrangement and 3:1 disjunction of the resultant products within the germ line of one of the parents, analogous to the sporadic appearance of the unbalanced state of centric fusion translocations (Hamerton, Gianelli, and Polani, 1965; Mikkelsen, 1971; Ying, 1973), and we refer to it as 3:1 disjunction *de novo*.

Table VIII lists one *de novo* interchange trisomy (with Down's phenotype), 25 *de novo* cases of tertiary monosomy and six possible *de novo* monosomies. Tertiary monosomy is more often identified arising *de novo* (25 reports) than from a balanced carrier (six reports). Of the 61 chromosomes identified in the monosomy translocations (Table VIII), 45 were from groups D, E, and G. The 31 monosomics included six children with the 18p− phenotype and four with the 5p− syndrome. Among the recorded sibs (families with both parents karyotyped) were 49

TABLE VIII

De novo CASES OF 3:1 DISJUNCTION

Reference	Chromosome Constitution of Propositus	Recognizable Phenotype (if any)
A. *Interchange trisomy* de novo (*both parents tested and found normal*)		
Aarskog (1966)	47,XY, − 5, + der(5), + der(21),t(5;21)(p;p)	Down's
B. *Tertiary monosomy* de novo (*both parents tested and found normal*)		
Breibart *et al* (1964)*	45,XY, − D, − 18, + der(18),t(D;18)(q;q)	
Brøgger (1967; case 812)	45,XX, − C, − D, + der(D),t(C;D)(?;q)	
De Capoa *et al* (1969)	45,XX, − C, − 15, + der (C) or der(15),t(C;15)	
Capotorti and Ferrante (1966)	45,XY, − B, − D, + der(B),t(B;D)(p;q)	Cri du chat
Cohen and Putnam (1972)	45,XX, − 18, − 21, + der(18) or der(21),t(18;21)	18p −
Fraccaro *et al* (1972; first case)	45,XY, − 18, − G, + der(18) or der(G),t(18;G)	18p −
Fraccaro *et al* (1972; second case)	45,XY, − 18, − 22, + der(18) or der(22),t(18;22)	18p −
Gilgenkrantz *et al* (1972)	45,XX, − 18, − 22, + der(18) or der(22),t(18;22)	18p −
Hoefnagel *et al* (1963)	45,XX, − 6, − G, + der(6),t(6;G)(p;q)	
Ikeuchi *et al* (1967)	45,XX, − 5, − G, + der(5),t(5;G)(p;q)	Cri du chat
Jackson and Barr (1970)	45,XY, − 5, − 15, + der(5) or der(15),t(5;15)	Cri du chat
Kroll and Mostafawy (1969)	45,XY, − D, − 16, + der(16),t(D;16)(q;q)	
Leisti (1971); Leisti *et al* (1973)	45,XY, − 13, − 18, + der(13) or der(18),t(13;18)	18p −
Malpuech *et al* (1971)	45,XX, − 18, − G, + der(18) or der(G),t(18;G)	18p −
Moore and Engel (1970; case 10)	45,XX, − F, − G, + der(F),t(F;G)(?;q)	
Nakagome *et al* (1973)	45,XX, − 17, − 22, + der(17),t(17;22)(p12 or 13;q11)	
Pasquali *et al* (1973)	45,XY, − 13, − 15, + der(15),t(13;15)(q;q)	
Pfeiffer (1964)	45,XX, − D, − D, + der(D),t(D;D)(q;q)	
Pfeiffer (1969)	45,XX, − 14, − 18, + der(14) or der(18),t(14;18)	
Püschel *et al* (1965)	45,XX(?), − C, − F, + der(C),t(C;F)(q;?)	
Reinwein and Wolf (1965); Wolf *et al* (1966)	45,XX, − 5, − 14, + der(5),t(5;14)(p;q)	Cri du chat
Soudek *et al* (1969)	45,XY, − 1, − D, + der(1),t(1;D)(p;q)	
Valdmanis *et al* (1967)	45,XX, − 4, − 14, + der(4),t(4;14)(p;q)	
Wyandt *et al* (1971)	45,XX, − 18, − 21, + der(18),t(18;21)(q;q)	
MRC Unit (CDM/245) (unpublished)	45,X, − 22, + der(X),t(X;22),(p22;q11)	
C. *Tertiary monosomy* (*one or both parents not tested*); *possibly* de novo, *possibly segregant 3:1*		
Dutrillaux *et al* (1973)	45,XX, − 4, − 21, + der(4),t(4;21)(q22;q33)	
Mercer and Darakjian (1962)	45,XY, − 2, − D, + der(2),t(2;D)(q;q)	
Townes and Ziegler (1965)	45,XY, − D, − 17 or 18, + der(D) or der(17) or der(18), t(D;17 or 18)	
Wallace and Anderson (1964)	45,XX, − 4, − 15, + der(4),t(4;15)(q;q)	
H. E. Wyandt *et al* (in press; see Wyandt *et al*, 1971)	45, − 1, − D, + der(1),t(1;D)	
Zellweger and Mikamo (1961; case 2)	45,XY, − 14, − 18, + der(14) or der(18),t(14;18)	

* Alternatively, represents 45,XY, − D, − 18, + i(18q).

with normal phenotype, four abortuses, and one neonatal death with multiple abnormalities.

Mean maternal age at birth of *de novo* tertiary monosomics is markedly raised at 33.15 years (see Table VI), and mean paternal age is 36.45 years. These are significantly higher than the parental ages at birth of 3:1 offspring from translocation carrier mothers (maternal age: $t_{31DF} = 2.64$, $P < 0.02$; paternal age: $t_{32DF} = 2.92$, $P < 0.01$). There is no significant increase in paternal–maternal age difference in the *de novo* group ($t = 0.61$). Lurie (1972) found an increase in parental ages (30.35 and 32.36 years) at birth of sporadic reciprocal translocations.

We have not attempted to analyse cases of tertiary trisomy *de novo*, as they are difficult to identify definitely without information on chromosome banding. There are many reports of extra morphologically abnormal chromosomes in offspring of chromosomally normal parents (Borgaonkar, Schimke, and Thomas, 1971; Leisti, 1971; Newton *et al*, 1972), some of which could be explained as sporadic tertiary trisomies. This could, for example, explain the diversity of phenotype in cases described as 'trisomy 22' before the advent of chromosome banding (Walbaum *et al*, 1970). Instances of two or more sibs with an extra abnormal chromosome (Biesele, Schmid, and Lawlis, 1962; Gustavson *et al*, 1962; Wender *et al*, 1965) are particularly likely to arise from an unidentified translocation.

Conclusions

1. Chromosome imbalance in the offspring of reciprocal translocation heterozygotes may result from 3:1 disjunction, producing aneuploid individuals with 45 or 47 chromosomes. Of 24 reciprocal translocations identified in this Unit, five were ascertained through aneuploid offspring resulting from 3:1 disjunction in a carrier parent; 51 further examples have been found in the literature. As a maximum estimate, 6–25% of all chromosomally unbalanced offspring of translocation carriers

may arise in this way. Occasionally 3:1 disjunction and unbalanced 2:2 disjunction appear in the same family.

2. Sixteen different chromosome complements are theoretically derivable by 3:1 disjunction from any given reciprocal translocation. In practice nearly all observed individuals represent tertiary trisomy (normal complement plus one derived chromosome), interchange trisomy (translocation heterozygote plus one non-translocated homologue), or tertiary monosomy (presence of one derived chromosome, and absence of the two non-translocated homologues).

3. Translocations involving G- and D-group chromosomes are found more often in families presenting with 3:1 disjunction than in those identified mainly through unbalanced 46-chromosome propositi. Differential viability of the resulting aneuploid offspring may partly explain this over-representation.

4. Interchange trisomy has always been identified in association with a typical trisomy 18 or trisomy 21 phenotype. Trisomy for 9p has been identified seven times within the tertiary trisomy group. The abnormal karyotypes identified are practically always those with the least possible gain or loss of chromosome material, given the aneuploid situation.

5. Nearly all aneuploid individuals resulting from 3:1 disjunction are born to female heterozygotes. The mean age of maternal carriers, at birth of 3:1 individuals, is not significantly raised.

6. The recurrence risk following an episode of 3:1 disjunction is apparently similar to that for translocations identified through an unbalanced 2:2 proposita. The abortion rate is higher in families presenting with 3:1 disjunction.

7. Factors that may predispose to 3:1 disjunction include involvement of an acrocentric chromosome, short interstitial segments, and extreme disparity in length of chromosomes involved (especially predisposing to the interchange trisomy type of 3:1 disjunction).

8. Some sporadic cases of chromosome imbalance can be explained as 3:1 disjunction arising *de novo* in a parental germ cell. Mean parental age is much increased in *de novo* tertiary monosomy.

Addendum

Six cases of 3:1 disjunction are not included in the body of this paper; one is a referral to MRC Unit: 47,XX,+der(22),t(11;22)(q25;q13)mat. The others can be found in the following reports (Weiss and Wolf [possible 3:1]; Prieur *et al*, 1971; Borgaonkar, 1973 and Borgaonkar, McKusick, and Farber, 1973; de la Chapelle, Koivisto, and Schröder, 1973; Giraud *et al*, 1974).

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