Frequency and Occurrence of Chromosomal Syndromes. I. D-Trisomy

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ACCURATE ESTIMATES OF frequency of autosomal abnormalities other than mongolism have not yet been made because of their relative rarity. With increasing awareness of the patterns of multiple anomalies of the D and E syndromes (Smith, 1964), the diagnoses may be suspected more often, strengthened by finding characteristic dermatoglyphics (Uchida, Patau, and Smith, 1962) and confirmed by chromosome analyses.

The Hospital for Sick Children (Toronto) serves a large population, and nine cases of D syndrome and 17 cases of E syndrome have been verified by chromosome studies at this center. Some of these cases were the basis for frequency estimates, and observations from all the cases were used to investigate parental age, sex ratio, and survival times of patients with these syndromes. Cases with mosaicism or suspected partial trisomy have not been included in this series.

MATERIALS AND METHODS

The cases to be reported were located during the period 1962 through 1965 during the course of karyotype analysis of patients with developmental anomalies and of their relatives. Clinical details were obtained from case records at this and neighboring hospitals. Vital statistics for York County were obtained from the *Vital Statistics of the Province of Ontario* (1960 through 1963), and further information was gained directly from the Medical Statistics Branch of the Department of Health, Government of Ontario.

Chromosomal analyses were made by standard methods on blood, skin, marrow, muscle, lung, kidney, and spleen by a modification of the blood method (Conen and Erkman, 1964). Full descriptions of some of the cases have been reported (Conen, Phillips, and Mautner, 1962; Erkman, Basrur, and Conen, 1965; Conen, Erkman, and Metaxotou, 1966).

Frequency estimates were based on chromosomally proven cases from York County, Ontario, an area chosen for the survey because it included most of Toronto and records of Vital Statistics were available. Results of studies on the E syndrome are reported separately (Conen and Erkman, 1966).

The characteristic pattern of anomalies of D syndrome made it possible to search the records of this hospital and examine certain vital statistics for York County to estimate the number of cases not referred to our hospital for chromosome studies and therefore "missed" from this survey.

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Criteria for Presumptive Diagnosis

The criteria used during the survey of medical records were the presence of the majority of the following:

Group A. Microcephaly, eye anomalies (corneal opacities, colobomata, microphthalmia, anophthalmia), cleft lip, cleft palate, brain anomalies (particularly arrhinencephaly).

Group B. Supernumerary digits, renal anomalies (especially cortical microcysts), and heart anomalies. Cases with the presence of some of these features were selected from York County records for further review.

Patients with anomalies suggestive of D syndrome, restricted to head and brain (Group A) with no abnormalities elsewhere, were reported by De Meyers, Zeman, and Palmer (1963) to have normal chromosomes, and similar findings have been made at this laboratory (unpublished data).

Smith *et al.* (1963) used similar criteria in a review of cases described in older literature to detect "probable D syndrome" patients. Using these criteria, our cases could readily be detected from clinical and autopsy descriptions. Similarly, descriptions of D syndrome patients in the literature enabled a presumptive diagnosis to be made readily. Only one apparent exception has been reported—a patient with normal leukocyte karyotype and the pattern of anomalies characteristic of the D syndrome (Marshall *et al.*, 1964). It was possible that this case was a mosaic and only chromosomally normal cells were represented in blood cultures.

Loss Estimates

Direct assessment of loss by nontransfer. Through the courtesy of the Medical Statistics Branch of the Ontario Department of Health, notices of live births and stillbirths (Form I) for 1963 were examined. The completion of this notice by the attending physician was compulsory and included a question about the presence and type of anomalies. Data on these forms were checked with death certificates in fatal cases. The 1963 forms included details of 489 infants born alive with one or more anomalies in York County. The first three anomalies listed on forms were routinely coded, using the International Classification of Diseases system, and punchcards were prepared. Cleft lip or cleft palate, in combination with other anomalies, was found in 13 cases from York County, including the three D syndrome cases in 1963 with chromosomal studies.

Indirect assessment of loss by nontransfer. Records of live births in 1963 at six delivery hospitals of Metropolitan Toronto were searched, with the help of the pediatrician-in-charge of the newborn nursery of each hospital and the staff of each medical records department, for possible cases of D syndrome.

Attempted estimate of stillborn D syndrome frequency. The Ontario Vital Statistics for 1963 listed 500 stillbirths of 28 weeks gestation or more delivered in York County (Table 1). Study of these stillbirth notification forms for presumptive identification of D syndrome was not possible, since few details of abnormalities were given for the 71 cases with one or more malformations.

Assessment of loss by nonrecognition at this hospital. D syndrome patients

TABLE 1. BIRTH STATISTICS FOR YORK COUNTY, ONTARIO

Year	Livebirths	Stillbirths (>28 weeks gestation)	Population
1960	45,331	492	1,660,370*
1961	44,804	493	1,733,108†
1962‡	44,293	465	1,776,100*
1963‡	45,016	500	1,820,000*
1964‡	(45,016)§	(500)§	(1,820,000)§

*Estimated.
†Figures from census.
‡Survey period.
§Approximate figures; information for 1964 is not available yet.

transferred here would be indexed in the medical records department files under any or all of the following classifications: multiple anomalies, microcephaly, microphthalmia, cleft lip, cleft palate, and polydactyly. This syndrome is lethal, and most cases would also be found in autopsy files. Autopsy rate was 77% during the period 1962–1964.

Medical records department cross-index files for 1962 through 1964 were searched for histories of cases with any of the previously described abnormalities found in the D syndrome to find any cases not brought to our attention and "lost" from our chromosome files. Protocols of 1,238 autopsies performed here during this period were also carefully searched.

Calculations for Estimates

Identification estimates at this hospital from York County were obtained from the product of the proportion of cases transferred and the proportion of cases recognized. Frequency estimates of patients with the D syndrome in York County were obtained from the number of cases observed divided by the product of the identification estimates and the number of live births during the period. Corrected frequency estimates were also calculated using the Poisson 90% confidence interval (Pearson and Hartley, 1962) to make statistical allowance for the small number of cases observed.

RESULTS

Estimates of Frequency

York County includes Metropolitan Toronto, and the majority of serious pediatric problems in the area are referred to this hospital. The population, live births and stillbirths over 28 weeks gestation, per year from 1960 through 1964 are shown in Table 1. D syndrome estimates were based on 134,325 live births from 1962 through 1964 (Table 2).

During this period, seven cases of D syndrome were verified at this hospital (Table 3). Five were born in York County, but only three were examined in this hospital. Other Toronto delivery hospitals notified us of the two patients who were not transferred here. One survived half an hour, the other 28 hours. Two additional cases were born in 1965.

The five cases of D syndrome observed during the three-year period when

TABLE 2. FREQUENCY ESTIMATES FOR THE D SYNDROME

Period surveyed		1962–1964
Live births in period		134,325
Number of observed cases		5
90% Poisson confidence interval		1.97–10.51
Estimate of proportion of cases transferred to the Hospital for Sick Children*		0.5–0.75
Estimate of proportion of cases recognized at the Hospital for Sick Children*		0.75–0.95
Estimate of proportion of cases from York County recognized at the Hospital for Sick Children	Maximum	(0.75) (0.95)
	Minimum	(0.5) (0.75)
Frequency estimate without 90% confidence interval	Maximum	$5/(0.5)(0.75)(134{,}325) = 9.9 \times 10^{-5}$
	Minimum	$5/(0.75)(0.95)(134{,}325) = 5.2 \times 10^{-5}$
Frequency estimate using 90% confidence interval	Maximum	$10.51/(0.5)(0.75)(134{,}325) = 2.1 \times 10^{-4}$
	Minimum	$1.97/(0.75)(0.95)(134{,}325) = 2.1 \times 10^{-5}$
Most probable value using intermediate identification estimate		$5/\frac{1}{2}[(0.5)(0.75) + (0.75)(0.95)]$ $(134{,}325) = 6.8 \times 10^{-5}$

*See text for basis for these estimates

TABLE 3. FEATURES OF FIVE D-TRISOMY (ONE STILLBORN) AND FOUR D/D TRANSLOCATION D SYNDROME CASES

	Trisomy D					Translocation D/D			
Reference	a	b	b	b	b	b	c	c	c
Maternal age	38	36	43	19	23	27	19	23	27
Paternal age	45	38		22	29	28	21	25	35
Month and year of birth	1/62	5/63	2/64	2/65	4/65	10/64	1/63	5/63	5/64
Birth order	16	9	4	2	1	2	1	1	4
Sex	♀	♀	♀	♂	♂	♀	♂	♂	♂
Age at death (days)	2	199	2	3	SB*	61	0.02†	2	216

[a]Conen *et al.* (1962).
[b]Conen *et al.* (1966).
[c]Erkman *et al.* (1965).
*Stillborn.
†Half an hour.

there were 134,325 live births provided a frequency of 3.7×10^{-5} for York County. The Poisson 90% confidence interval for an estimate of five cases was 1.97–10.51 cases (Table 2).

Cases who died too rapidly after birth or were too ill to be transferred and patients on whom plastic surgery and other special treatment was not thought feasible or worthwhile were classified as lost due to nontransfer. After discussions with pediatricians at other hospitals and consideration of age-at-death figures, we estimated that 25–50% of cases might be lost from this series by nontransfer. Therefore, the proportion of cases reaching this hospital was 0.5–0.75 (Table 2).

No additional cases of D syndrome for 1963 were found in a search of Ontario Department of Health notices of live births or from records of six large delivery hospitals in Toronto.

TABLE 4. SURVIVAL TIME (DAYS), D SYNDROME

Source	Category	Cases	Arithmetic mean	Geometric mean	Observed survival
This report	Trisomic	4	51.5	6.9	2, 2, 3, 199
	Translocation	4	69.8	15.2	0.02, 2, 61, 216
This report	♂	4	55.3	2.3	0.02, 2, 3, 216
	♀	4	66.0	14.8	2, 2, 61, 199
	Total	8*	60.6	5.8	
From the literature	♂	12	154.3	51.7	
	♀	16	150.3	44.0	
	Total	28	150.7	41.5	
Combined cases	♂	16	129.6	23.6	
	♀	20	133.5	35.4	
	Total	36	131.7	29.6	

*Stillborn case not included.

It was estimated from discussions with pediatricians that 5–25% of cases of D syndrome might not be recognized. Therefore, the proportion recognized was 0.75–0.95. Survey of clinical records and autopsy protocols for the 1962–1964 period did not reveal any cases suggestive of D syndrome other than the five cases examined and autopsied at this hospital.

Correcting for these losses gave estimates of D syndrome live births of 9.9×10^{-5} to 5.2×10^{-5}. Addition of the previously calculated Poisson 90% confidence interval gave a maximum estimate of 2.1×10^{-4} live births and a minimum of 2.1×10^{-5}. However, this range was too broad for a 90% confidence interval because each extreme assumed three factors varying in a specified manner. The most probable value, using 54.5% as an intermediate between the 37.5% and 71.25% identification estimates, is 6.8×10^{-5} (1 in 14,500 live births).

Clinical Features

Comparison of D trisomy and D/D translocation cases. Five of our nine cases had 47 chromosomes with D-trisomy, and the other four had 46 chromosomes with a D/D translocation. No significant clinical differences were found apart from the greater severity of cardiovascular anomalies in the trisomic patients. Four of nine patients were female (44%), but only one of the four patients with a D/D translocation was female (Table 3).

Survival period in days was recorded for trisomic and translocation patients and separately for males and females (Table 4). Little difference was noted between survival periods of trisomic and translocation patients or between male and female patients, even when survivals were expressed as log days (Fig. 1). Probit curves plotted from log days survival times suggested there were two populations of survivors (Fig. 2).

Maternal age. There was an apparent significant difference (t test, $0.005 > P > 0.001$) between the young age (mean 22.2 years) of mothers of five male patients compared with the older age (mean 36 years) of mothers of four

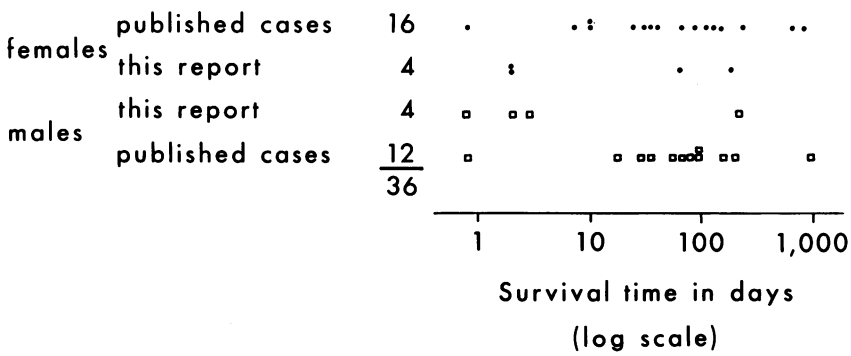

FIG. 1. Log day survival times of reported cases and cases forming this report.

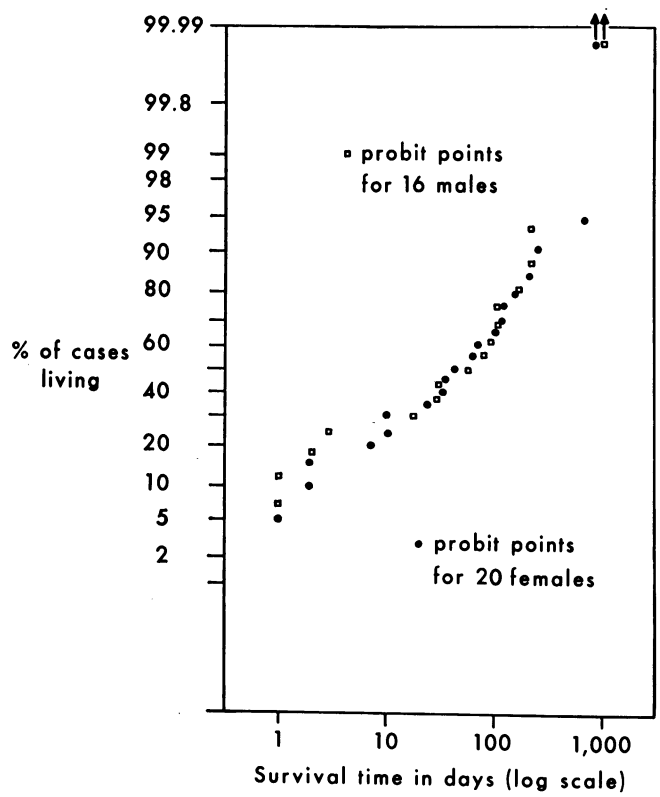

FIG. 2. Probit curves of the percentage of survivors and log day survival of males and females from the literature and this report.

female patients (Table 5, section A). This may be due in part to the presence of three translocation patients (with younger mothers) among the five males. Maternal age (mean 31.8 years) of five trisomic infants was higher than the maternal age (mean 24 years) of four translocation patients, but the difference was not significant ($0.4 > P > 0.2$). Birth orders of the patients were related to maternal ages (Table 3). Most cases in this series were born in the first half

TABLE 5. AGE OF MOTHERS OF D SYNDROME CASES

Source	Karyotype	♂ Infant		♀ Infant		Mean ages ♂ and ♀
		Maternal ages	Mean	Maternal ages	Mean	
A. Present study	Trisomy D	19, 23*	21	36, 38, 43	39.0	31.8
	D/D translocation	19, 23, 27	23	27		24.0
	Combined		22.2		36.0	28.3
B. From the literature	Trisomy D	21, 23, 25, 26, 28, 35, 42, 42, 43, 43, 47	34.1	24, 25, 25, 26, 27, 29, 30, 32, 32, 33, 34, 34, 35, 38, 39, 41	31.5	32.6
	D/D translocation	23, (21, 32)†	25.3			
	Combined		32.3		31.5	31.8
Pooled data	Trisomy D		32.1		32.7	32.4
	D/D translocation		24.2		(27)	24.6
	Combined		29.6		32.4	39.0

*Mother of stillbirth.
†Unpublished cases.

of the year: January, 2 cases; February, 2 cases; March, 1 case; May, 3 cases; and October, 1 case.

DISCUSSION

Case reports of D syndrome have described very similar patterns of developmental anomalies which suggests that the chromosome abnormality is causally related to the anomalies. Further case reports are needed to determine frequency of certain clinical features of possible diagnostic help. Additional reports may answer problems outlined in this presentation involving differences between types of chromosomal aberration and observations on maternal age.

An accurate incidence of D syndrome will best be made from detailed examination of consecutive newborns at many large delivery hospitals or from fully documented death certificate records from large populations. The true incidence of this syndrome at conception will not be known until cases lost in early pregnancy can be estimated. Carr (1965), in a study of 200 spontaneous abortions, found six abortuses with D-trisomy among 44 with chromosome abnormalities. The phenotype was not compared to D syndrome in infants because of the early stage of fetal development and because the amniotic sac frequently was empty. The general incidence of chromosome abnormalities in abortuses was more than fifty times the incidence at birth.

Frequency estimates of D syndrome (Table 6) based on examination of consecutive live born infants have been reported. Marden, Smith and McDonald (1964) found two cases in a two-year survey of 4,412 newborns, which gave a frequency of 4.5×10^{-4}, but when this survey was extended to four years (Smith, 1964) there were still only two cases among the 10,345 newborns examined, which gave a revised frequency of 2×10^{-4}. Prader (1962), in a

TABLE 6. PUBLISHED FREQUENCY ESTIMATES FOR D SYNDROME

Source	Population	Frequency
Therman *et al.* (1961)	One case compared with 250–300 mongols	1:10,000–1:200,000
Marden, Smith, and McDonald (1964)	Two cases from 4,412 newborns	4.5×10^{-4} (1:2,222)
Smith (1964)	Two cases from 10,345 newborns	2.0×10^{-4} (1:5,000)
Prader (1962)	Source of figures not stated	2.5×10^{-4} (1:4,000)
This report	Five cases from 224,460 live births	6.8×10^{-5} (1:14,500*)

*Calculations include estimates for "missed cases."

general review of chromosome abnormalities, quoted a frequency of one in 4,000 live births, although the source of his figure was not stated.

Therman *et al.* (1961) made the first estimates of the frequency of D syndrome when few cases had been reported and suggested a rough figure of one in 200,000 and rarer than one in 10,000. These figures were based on comparison of the incidence of one case of D syndrome with 250–300 mongoloids in a survey, although most patients with D syndrome die in early infancy and would not be expected in the population she studied. The Madison group have since reported details of seven cases and clinically screened 3,638 patients from three state mental institutions in Wisconsin for further cases (Smith *et al.*, 1963).

An attempt was made in the present study to correct for cases born in the population under study but untested because of nontransfer to this hospital or nonrecognition here. However, without chromosome studies, even indirect confirmation of the D syndrome, such as examination of leukocytes from autopsy material, is unlikely, since nuclear projections described by Huehns, Lutzner, and Hecht (1964) were not seen in tissue sections and were not pathognomonic of the syndrome (Powars, Rohde, and Graves, 1964; Erkman, Basrur, and Conen, 1965).

The significance of frequency estimates of D syndrome from this survey is limited because the number of cases is small, the accuracy of estimates for untested cases is uncertain, and there appears to be some clustering in time, also noted by K. M. Laurence (personal communication). Clustering of cases with chromosomal abnormalities has been discussed by Day (1966), but in our series the effect of variation in clinical interest is difficult to assess. The allowances made for "losses" were probably overestimated since no actual "missed" cases were identified by searching either the Ontario statistics for nontransferred cases or the records of this hospital for cases "lost" by nonrecognition. The probable frequency from this series was 6.8×10^{-5} with a range from 9.9×10^{-5} to 5.2×10^{-5}. This was less than one-third of that found for the E syndrome (Conen and Erkman, 1966), whereas other reports (Table 6) of D syndrome frequency—4.5×10^{-4} (Marden, Smith, and McDonald, 1964), 2×10^{-4} (Smith, 1964), and 2.5×10^{-4} (Prader, 1962)—are approximately the same as for E syndrome.

In our series, the incidence of D/D translocation in D syndrome was unusually high, four of nine cases compared with one (Jongbloet *et al.*, 1964) of 28 cases reported in the literature (Table 7). Although four other D/D translocation cases (K. Hirschhorn; J. R. Miller; P. S. Gerald, personal communications)

TABLE 7. D SYNDROME CASES REPORTED

Authors	Case	Maternal age ♂	Maternal age ♀	Survival Time quoted	Survival Days ♂	Survival Days ♀
Atkins and Rosenthal (1961)			27	5M		150
Blanck *et al.* (1964)		21		105D	105	
Bühler *et al.* (1962)			41	4H		0.16
Ellis and Marwood (1961)			30	68D		68
Jongbloet *et al.* (1964)	F.N. (D/D)	23		3½M	105	
Koenig *et al.* (1962) and Lubs *et al.* (1961), same case	3 B.S.		33	63D+7W		112
Marin-Padilla *et al.* (1964)	1		26	10D		10
	2		29	10D		10
Miller, J. Q., *et al.*, (1963)	M.B.		38	7D		7
Miller, M., *et al.* (1963)			34	116D		116
Northcutt (1962)			25	32D		32
Powars *et al.* (1964)		42		32M	960	
Rosenfield *et al.* (1962)		26		7M	210	
Sergovich *et al.* (1963)		42		3¾H	0.15	
Shärer *et al.* (1962)		47		18D	18	
Shaw and Nishimura (1961)			32	3M*		90
Smith *et al.* (1963)	5		25	22M		660
	20		35	27M*		810
	46	43		2M 3W	81	
	163		34	3½W		25
	286	43		5½M*	165	
	288		24	5W		
	408	25		2M	60	
Taylor and Polani (1964)	8	35		1M	30	
Teller and Pfeiffer (1964)	1	28		28D	28	
Townes *et al.* (1962)		23		3M	90	
Warburg and Mikkelsen (1963)			39	238D		238
Yunis *et al.* (1964)	1		32	6W		42
Hirschhorn, K., unpublished	(D/D)	21		4M	120	
Miller, J. R., unpublished	(D/D)	32				

*Alive at time of report.

have been brought to our attention, these should not be added to the comparative survey because details of most unpublished D trisomy patients are unknown to us. It may be assumed that the rarer D/D translocation cases would be reported more readily than D trisomies, particularly since familial carriers have been detected (K. Hirschhorn; J. R. Miller, personal communications).

Major clinical differences were not found between the trisomic and translocation types apart from greater severity of cardiovascular defects in trisomic

patients (unpublished data). Parents of the four translocation cases had normal karyotypes, which was important because two families with a D syndrome patient and phenotypically normal D/D translocation carriers have been found (K. Hirschhorn; J. R. Miller, personal communications).

Three of five trisomic cases were female, which was in accord with the slight excess of female cases reported in the literature (Smith, 1964). In contrast, three of our four D/D translocation patients and three cases from other centers were male (Jongbloet *et al.*, 1964; also K. Hirschhorn; J. R. Miller, personal communications). Studies of two female D/D translocation D syndrome patients (P. Gerald, personal communication) have been brought to our attention.

The mean age of mothers of five D-trisomy cases in this report was 31.8 years, which was not significantly different (t test, $0.4 > P > 0.2$) from the lower mean age of 24.0 years for mothers of four D/D translocation cases. The mean maternal age of one reported case (Jongbloet *et al.*, 1964) and two of the unpublished cases with D/D translocation from other centers was 25.3 years, which agrees closely with the figure from this center. The combined maternal age figures from this report and cases from other centers (Table 5) yielded a mean age of 32.4 years for 32 mothers of trisomic D syndrome cases and 24.6 years for seven mothers of D/D translocation cases, which was a significant difference (t test, $0.025 > P > 0.01$).

Although an apparently significant difference was found in our series between the ages of mothers of five male patients (mean 22.2 years) compared with the older ages of mothers of four female patients (mean 36 years), this was not found in a study of published D syndrome cases. Three of the five male patients in our series were translocation type, who tend to have younger mothers, as judged by a combination of published reports and our own figures. From the literature and two unpublished cases, the mean age of mothers of 14 male patients was 32.2 years compared with mean maternal age for 16 female patients of 31.6 years. The pooled figures from the literature and the present series provided a mean maternal age of 29.6 years for 19 male patients compared with a mean maternal age of 32.4 years for 20 female patients, which was not a significant difference.

The majority of patients with D syndrome die in early infancy (Table 4), but survivals beyond one year of age have been reported: 22 months (Smith *et al.*, 1963), 32 months (Powars, Rohde, and Graves, 1964), and two patients were alive at 2½ and 5 years (Smith, 1964). In our series, the longest survival time was 6½ months. Little difference was found between the mean survival period of male and female patients with D syndrome, survival being similar to that of males with E syndrome.

SUMMARY

Nine cases of D syndrome from this center were used to estimate the frequency of the syndrome, effect of chromosomal variants, sex ratios, survival periods, and maternal ages. Five of the patients were born in York County, Ontario, and provided maximum and minimum estimates of D syndrome fre-

quency of 2.1×10^{-4} and 2.1×10^{-5} live births, with a probable frequency of 6.8×10^{-5} (1 in 14,500).

Of these nine patients, four (44%) had 46 chromosomes with D/D translocation, compared with one case in 28 patients (3.6%) reported in the literature. No significant clinical differences were found between trisomic and translocation cases in our series, apart from greater severity of cardiovascular lesions in the trisomic patients. The mean maternal ages of five trisomic and four D/D translocation cases were not significantly different, but, when pooled with figures from 27 reported trisomic cases and three D/D translocation cases (two unpublished), a significant difference was found.

Three of the five trisomic D syndrome cases were female, but, in D/D translocation cases, three of four from our series and the three cases reviewed from other centers were male. Although only 51% of all 39 cases reviewed were female, the sex ratio was different in the 32 D-trisomy (59% female) and seven D/D translocation (14% female) types, but the numbers are small. In our series, the mean age of mothers of five males appeared significantly different from that of mothers of four females, but this difference was not significant when pooled with figures for 14 male and 16 female cases from other centers. Little difference was found between survival of male and female patients with D syndrome.

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REFERENCES

ATKINS, L., AND ROSENTHAL, M. K. 1961. Multiple congenital abnormalities associated with chromosomal trisomy. *New England J. Med.* 265: 314–318.

BLANCK, C., JALLING, B., LINDSTEN, J., AND ZETTERQVIST, P. 1964. Trisomy 13–15. Report of a case with clinical, cytogenetic and pathologic findings. *Acta Pathol. Microbiol. Scand.* 60: 36–46.

BÜHLER, VON E., BODIS, I., ROSSIER, R., AND STALDER, G. 1962. Trisomie 13–15 mit cebocephalie. *Ann. Paediat.* 199: 198–205.

CARR, D. H. 1965. Chromosome studies in spontaneous abortions. *Obstet. Gynecol.* 26: 308–326.

CONEN, P. E., AND ERKMAN, B. 1964. Necropsy spleen samples for chromosome cultures. *Lancet* 1: 665–667.

CONEN, P. E., AND ERKMAN, B. 1966. Frequency and occurrence of chromosomal syndromes. II. E-Trisomy. *Amer. J. Hum. Genet.* 18: 387–398.

CONEN, P. E., ERKMAN, B., AND METAXOTOU, C. 1966. The "D" syndrome. Report of 4 trisomic and one D/D translocation case. *Amer. J. Dis. Child.* 111: 236–247.

CONEN, P. E., PHILLIPS, K. G., AND MAUTNER, L. S. 1962. Multiple developmental anomalies and trisomy of a 13–15 group chromosome ("D" syndrome). *Canadian Med. Assoc. J.* 87: 709–712.

DAY, R. W. 1966. The epidemiology of chromosome aberrations. *Amer. J. Hum. Genet.* 18: 70–80.

DEMEYERS, W., ZEMAN, W., AND PALMER, C. G. 1963. Familial alobar holoprosencephaly (arhinencephaly) with median cleft lip and palate: Report of patient with 46 chromosomes. *Neurology* 13: 913–918.

ELLIS, J. R., AND MARWOOD, J. C. 1961. Autosomal trisomy syndromes. *Lancet* 2: 263.

ERKMAN, B., BASRUR, V. R., AND CONEN, P. E. 1965. D/D translocation "D" syndrome: Report of 3 cases. *J. Pediat.* 66: 270–286.

HUEHNS, E. R., LUTZNER, M., AND HECHT, F. 1964. Nuclear abnormalities of the neutrophils in D_1 (13–15)-trisomy syndrome. *Lancet* 1: 589–590.

JONGBLOET, P., VAN WINCKEL, H., ADRIAENSSENS, K., AND HOOFT, C. 1964. Sporadic trisomy D_1 with translocation D/D. *Helv. Paed. Acta* 19: 121–126.

KOENIG, E. U., LUBS, H. A., JR., AND BRANDT, I. K. 1962. The relationship between congenital anomalies and autosomal chromosome abnormalities. *Yale J. Biol. Med.* 35: 189–205.

LUBS, H. A., KOENIG, E. U., AND BRANDT, I. K. 1961. Trisomy 13–15: A clinical syndrome. *Lancet* 2: 1001–1002.

MARDEN, P. M., SMITH, D. W., AND MCDONALD, M. J. 1964. Congenital anomalies in the newborn infant, including minor variations. A study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. *J. Pediat.* 64: 357–371.

MARIN-PADILLA, M., HOEFNAGEL, D., AND BENIRSCHKE, K. 1964. Anatomic and histopathologic study of two cases of D_1 (13–15) trisomy. *Cytogenetics* (Basel) 3: 258–284.

MARSHALL, R., NEWHAM, R. E., RAWSTRON, J. R., ELLIS, J. R., AND STEVENS, L. J. 1964. Features of 13–15 trisomy syndrome with normal karyotype. *Lancet* 1: 556.

MILLER, J. Q., PICARD, E. H., ALKAN, M. K., WARNER, S., AND GERALD, P. S. 1963. A specific congenital brain defect (arhinencephaly) in 13–15 trisomy. *New England J. Med.* 268: 120–124.

MILLER, M., ROBBINS, J., FISHMAN, R., MEDENIS, R., AND ROSENTHAL, I. 1963. Chromosomal anomaly with multiple ocular defects. *Amer. J. Ophthal.* 55: 901–910.

NORTHCUTT, R. 1962. Multiple congenital anomalies in a Negro infant with 13–15 trisomy. *Southern Med. J.* 55: 835–839.

PEARSON, E. S., AND HARTLEY, H. O., eds. 1962. *Biometrika Tables for Statisticians,* 2nd Ed. London: Cambridge University Press, p. 203, Table 40.

POWARS, D., ROHDE, R., AND GRAVES, D. 1964. Foetal hemoglobin and neutrophil anomaly in the D_1 trisomy syndrome. *Lancet* 1: 1363.

PRADER, V. A. 1962. Die Klinik der Häufigsten chromosomanomalen Störungen. *Helv. Med. Acta* 29: 403.

ROSENFIELD, R. L., BREIBART, S., ISAACS, H., JR., KLEVIT, H. D., AND MELLMAN, W. J. 1962. Trisomy of chromosomes 13–15 and 17–18: Its association with infantile arteriosclerosis. *Amer. J. Med. Sci.* 244: 763–779.

SERGOVICH, F., MADRONICH, J. S., BARR, M. L., CARR, D. H., AND LANGDON, W. A. 1963. The D trisomy syndrome: A case report with a description of ocular pathology. *Canadian Med. Assoc. J.* 89: 151–157.

SCHÄRER, D., HAUSCHTECK, E., AND MÜHLETHALER, J. P. 1962. Trisomiesyndrom D. *Helv. Med. Acta* 29: 423–424.

SHAW, M. W., AND NISHIMURA, F. 1961. Cited by Lubs, Koenig, and Brandt, 1961.

SMITH, D. W. 1964. Autosomal abnormalities. *Amer. J. Obstet. Gynecol.* 90: 1055–1077.

SMITH, D. W., PATAU, K., THERMAN, E., INHORN, S. L., AND DEMARS, R. I. 1963. The D_1 trisomy syndrome. *J. Pediat.* 62: 326–341.

TAYLOR, A. I., AND POLANI, P. E. 1964. Autosomal trisomy syndromes, excluding Down's. *Guy's Hosp. Rep.* 113: 231–249.

TELLER, W., AND PFEIFFER, R. A. 1964. Die Trisomie D_1 (13–15) als Ursache multipler Abartungen. *Z. Kinderheilk.* 89: 36–48.

THERMAN, E., PATAU, K., SMITH, D. W., AND DEMARS, R. I. 1961. The D trisomy syndrome and XO gonadal dysgenesis in two sisters. *Amer. J. Hum. Genet.* 13: 193–204.

TOWNES, P. L., DE HART, G. K., JR., HECHT, F., AND MANNING, J. A. 1962. Trisomy 13–15 in a male infant. *J. Pediat.* 60: 528–532.

UCHIDA, I. A., PATAU, K., AND SMITH, D. W. 1962. Dermal patterns of 18 and D_1 trisomies. *Amer. J. Hum. Genet.* 14: 345–352.

Vital Statistics of the Province of Ontario. 1960–1963. (Reports 91 through 94) Toronto, Ontario: Office of the Registrar General.

WARBURG, M., AND MIKKELSEN, M. 1963. A case of 13–15 trisomy or Bartholin-Patau's syndrome. *Acta Ophthalmol.* 41: 321–334.

YUNIS, J. J., HOOK, E. B., AND MAYER, M. 1964. Deoxyribonucleic-acid replication pattern of trisomy D_1. *Lancet* 2: 935–937.