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Rates of Mutant Structural Chromosome Rearrangements in Human Fetuses: Data from Prenatal Cytogenetic Studies and Associations with Maternal Age and Parental Mutagen Exposure

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SUMMARY

In 27,225 prenatal cytogenetic studies of amniotic fluid reported to the New York State Chromosome Registry and the United States Interregional Chromosome Register System, there were 61 cases with a structural chromosomal abnormality not known inherited, a rate per 1,000 of 2.24. Of these 33, 1.21 per 1,000 were known de novo and nonmosaic; consequently, the rate of events resulting from germinal mutation is highly likely to be between these two limits. The rates per 1,000 of unbalanced abnormalities were 0.59–1.29; of balanced abnormalities, 0.62–0.96; of balanced Robertsonian translocations, 0.22–0.29; and of unbalanced Robertsonian translocations, 0.07–0.11. The rates of fetuses with supernumerary markers and fragments were unexpectedly high: 0.26–0.70 per 1,000. These abnormalities were associated with increased maternal age (38.0 ± 5.4 to 38.4 ± 3.6 compared to 35.6 ± 4.3 in controls), but even after adjustment for the bias to preferential study of older women, the observed rates of these supernumerary abnormalities were greater than would be expected from live-birth studies or rates estimated in all recognized conceptuses. There were trends to elevated maternal age for the group of all balanced rearrangements, and to diminished maternal age for the nonsupernumerary, non-Robertsonian unbalanced rearrangements. In 136 women studied primarily because of exposure to a putative mutagen, a de novo deletion and an inversion not known inherited were detected. The rate of abnormality in these 136, 1.47%, was significantly greater than the rate of abnormality in the remainder: 0.14%–0.22%.

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INTRODUCTION

Sufficient data have now been accumulated by two chromosome registries receiving reports on prenatal cytogenetic diagnoses so that order of magnitude calculations of the rates of fetuses with mutant structural cytogenetic abnormalities can be made. Moreover, the data gathered in these registries make possible a search for associations with maternal age. As prenatal cytogenetic diagnosis is usually done at 16–20 weeks of gestation, the resulting estimates apply, of course, only for fetuses that have survived to this gestational stage.

MATERIALS AND METHODS

The data sources were the New York State Prenatal Cytogenetic ("yellow") Registry [1] and the U.S. Interregional Chromosome Register System (I.C.R.S.) [2]. For the New York State Chromosome Registry, results of prenatal diagnostic cytogenetic diagnoses reported between January 1, 1977, and April 15, 1981, comprising essentially the experience for the four years 1977–1980, were included. For the I.C.R.S., results of prenatal cytogenetic diagnoses received by August 1980 were included. This comprises the entire experience of the participating laboratories up to about July 1980.

Two laboratories (Yale and Birth Defects Institute) belong to both the I.C.R.S. and the New York State Registry. Yale's data were analyzed as part of the I.C.R.S. experience only, and the Birth Defects Institute data as part of the New York State Chromosome Registry only. As the I.C.R.S. and New York State Chromosome Registry are separate systems using somewhat different methods, results from each were first analyzed separately. There were no differences between the two that could not be attributable to statistical variation, so data from both groups were pooled and are considered together here.

Cases were excluded from the analysis if maternal age was not stated (307 cases) or listed as 50 or over (seven cases). Cases reported by laboratories as presumptive in vitro artifacts were not scored as mutations. There were seven such cases from the I.C.R.S. and six from the New York State Chromosome Registry. All such cases were mosaics for normal and structurally abnormal lines. If abnormalities were not specifically noted by the laboratory to be presumptive artifacts, they are included in the analysis, although we separated nonmosaic and mosaic cases to determine what contribution the latter category, which may include some abnormalities which arose in vitro, makes to the estimation of the mutation rates.

Because of the possibility that mutations have an association with parental age, direct maternal-age standardized rates were calculated as well as crude rates. The reference population was Upstate New York live births for 1963–1974. Five age groups were used in this standardization: < 30, 30–34, 35–39, 40–44, and 45–49. This population has been used for maternal-age adjustments of rates in many other studies. The derived standardized rate is thus the rate that would be observed in a population of live births if it had the same maternal-age specific rates as those studied at amniocentesis. This issue is discussed further below.

The proportions of the population in our study in the five age groups discussed above were, respectively, 9.8%, 13.3%, 63.7%, 12.7%, and 0.4%. The proportions in the reference population were, respectively: 74.8%, 15.6%, 7.5%, 2.0%, and 0.1%.

For a significant proportion of structural rearrangements, parental carrier status for the rearrangement detected in the fetus could not be excluded, usually because the father could not be studied, but occasionally because neither parent was available after the fetal diagnosis had been made. Therefore, results on presumptive mutations are presented as ranges. The lower limits are the rates derived including only cases with abnormalities whose parents had been studied and found normal (the "de novo group"), and the upper limits are rates derived from data on all cases with aberrations not known to be inherited irrespective of whether or not both parents had been studied.

With regard to mosaic cases, there is great difficulty in excluding the possibility of in vitro artifacts. To our knowledge, all participating laboratories currently require the presence of a structural abnormality in more than one culture flask before regarding the detected abnormality as other than an artifact. We are less certain of the exact criteria, however, in the earlier years of reporting to the Registries. We took each laboratory's own assessment in the analysis but it is possible that some reported mosaic cases, particularly in the earlier years, are the result of in vitro events (see below).

To our knowledge, all laboratories reporting to the Registry had used "banding" methods in reaching the diagnoses reported. The list of all abnormalities and their classification appears in the APPENDIX. The diagnoses given are those reached by the reporting laboratory, although in some instances we edited them to accord with the "Paris" nomenclature [3].

The classification of abnormalities by subcategory is in some cases somewhat arbitrary. We included only markers and fragments in the "supernumerary" category, thus, for example, including a 47,+21q− with the deletions, as our primary interest was the structural abnormality observed. Similarly, it was occasionally difficult to determine if reported "other" rearrangements listed were "balanced" or "unbalanced." We classified, for instance, the 45,XX,−2,−22,+tdic(2;22) as "balanced," although it may well have been "unbalanced."

Data on maternal age were available on the 46 known de novo cases and 15 cases of unknown origin. Data on both paternal and maternal ages, however, were available on 37 cases of known de novo (30 from the New York State Registry) and nine cases of unknown origin (six from the New York State Registry), a considerably smaller proportion. (Control data on paternal age were available only from the New York State Registry experience and on only 13,040 normal cases studied.) A search for paternal-age effect in cases in the New York State Registry data was undertaken by comparing the differences between controls and abnormalities in this source with regard to maternal age, paternal age, and the difference of these two variables.

RESULTS

Data were available on 27,225 fetuses: 22,033 fetuses reported to the New York State Chromosome Registry and 5,192 to the I.C.R.S.

There were 61 fetuses with structural abnormalities in this analysis, and the rate of those affected was 2.24 per 1,000. There were 46 fetuses (13 mosaic and 33 nonmosaic) with abnormalities that were de novo and 15 (seven mosaic and eight nonmosaic) whose parents had not been studied. Crude and direct age-standardized rates for various categories of structural abnormalities appear in table 1.

The crude rate per 1,000 fetuses of those with nonmosaic unbalanced rearrangements was between 0.59 ± 0.15 and 0.70 ± 0.16, roughly the same as that for all those with nonmosaic balanced rearrangements: between $0.62 \pm .15$ and 0.81 ± 0.17. For both groups combined, the rate was between 1.21 ± 0.21 and 1.51 ± 0.24. Including mosaics, the rate was between 1.69 ± 0.25 and 2.24 ± 0.29.

With regard to the Robertsonian translocations, all of which were nonmosaic, the rate of fetuses with balanced translocations was 0.22 ± 0.09 to 0.29 ± 0.10. This was higher than the rate of those with unbalanced rearrangements: 0.07 ± 0.05 to 0.11 ± 0.06. The balanced de novo translocations were: 13q14q (four cases), 14q15q, and 13q15q. Among those in whom parental inheritance could not be excluded, there was one 13q14q and one 14q15q. Among unbalanced translocations, there was one de novo 13q13q, one de novo 13q14q, and one 21q21q of

TABLE 1

NO., CRUDE AND STANDARDIZED RATES OF STRUCTURAL CHROMOSOME REARRANGEMENTS THAT ARE DE NOVO OR NOT KNOWN FAMILIAL PER 1,000 FETUSES STUDIED AT AMNIOCENTESIS

	KNOWN DE NOVO						ALL NOT KNOWN FAMILIAL					
	NONMOSAIC			MOSAIC AND NONMOSAIC			NONMOSAIC			MOSAIC AND NONMOSAIC		
		RATE/1,000			RATE/1,000			RATE/1,000			RATE/1,000	
	No.	Crude	Stand.*	No.	Crude	Stand.*	No.	Crude	Stand.*	No.	Crude	Stand.*
Unbalanced:												
Robertsonian	2	0.07	0.01	2	0.07	0.01	3	0.11	0.01	3	0.11	0.01
Rings	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.04	0.28
Supernumerary	7	0.26	0.31	14	0.51	0.34	7	0.26	0.31	19	0.70	0.36
Fragments	2	0.07	0.01	3	0.07	0.01	2	0.07	0.01	4	0.11	0.02
Markers	5	0.18	0.30	11	0.44	0.33	5	0.18	0.30	15	0.59	0.35
Deletions and other unbalanced	7	0.26	0.86	10	0.37	0.87	9	0.33	0.87	12	0.44	0.88
Deletions	5	0.18	0.58	7	0.26	0.59	6	0.22	0.58	8	0.29	0.59
Other	2	0.07	0.28	3	0.11	0.29	3	0.11	0.29	4	0.15	0.29
Balanced:												
Robertsonian	6	0.22	0.07	6	0.22	0.07	8	0.29	0.08	8	0.29	0.08
Inversions	2	0.07	0.01	2	0.07	0.01	3	0.11	0.05	4	0.15	0.06
Other reciprocals	9	0.33	0.12	12	0.44	0.13	11	0.40	0.17	14	0.51	0.18
All unbalanced	16	0.59	1.18	26	0.96	1.22	19	0.70	1.19	35	1.29	1.54
All balanced	17	0.62	0.20	20	0.74	0.21	22	0.81	0.30	26	0.96	0.32
All Robertsonian	8	0.29	0.08	8	0.29	0.08	11	0.40	0.09	11	0.40	0.09
Unbalanced (non-Robertsonian and nonsupernumerary)	7	0.26	0.86	10	0.37	0.87	9	0.33	0.87	13	0.48	1.16
Balanced and unbalanced (non-Robertsonian and nonsupernumerary)	18	0.66	0.99	24	0.88	1.01	23	0.84	1.09	31	1.14	1.40
All balanced and all unbalanced	33	1.21	1.37	46	1.69	1.43	41	1.51	1.49	61	2.24	1.85

* Stand. = Direct age standardized rate (see text).

unknown origin but highly likely to be a mutant [4]. It is striking that of 11 known or possible mutations resulting in Robertsonian translocations, all but one involved a D/D translocation.

In table 2 we present data on the mean and standard deviations of maternal age. Differences significant at the $P = .10$ level or lower (two-tailed) are noted by asterisks. The most striking finding is the association of the supernumerary markers with older age.

In analysis of cases for whom both paternal and maternal ages were reported, there were no significant associations of any abnormality with paternal age. The association of supernumerary markers with elevated maternal age remained, however. For the 12 with supernumerary markers in the New York State Registry on which data on both variables were available, mean maternal age was 38.8 ($\pm$ 2.6), mean paternal age was 38.3 ($\pm$ 4.7), and the mean difference was -0.5 ($\pm$ 3.0). In the 13,040 with normal genotypes in the New York Registry with data on both variables, these values were 35.8 ($\pm$ 4.0), 37.6 ($\pm$ 6.6), and 1.8 ($\pm$ 5.7), respectively.

In table 3, we compare the crude rates (and their standard errors) observed in this series with crude rates (and their standard errors) derived from data summarized by Jacobs [5] on abnormalities in all recognized conceptuses and in live births. As Jacobs presented data only on nonmosaics, we limit comparisons to this group only. Her study also excluded data on sex-chromosome abnormalities, and we therefore also exclude such cases from our data in this analysis only. In our series, there was one (nonmosaic) case involving a sex chromosome that involved an "other" reciprocal translocation.

The predominant interest in this analysis was calculation of rates of events resulting from germinal mutation. This raised some questions as to classification of the 20 reported mosaic cases. These could, in principle, be the result of at least five separate processes: (1) a germinal structural mutation producing a rearrangement that was lost in some but not all somatic tissues during development (for tissues to remain viable, almost all of such cases would involve supernumerary fragments, and markers, or structural abnormalities of sex chromosomes); (2) somatic mutation resulting in one normal line and one structurally abnormal line; (3) artifacts resulting from mutation in vitro or maternal cell contamination of amniotic fluid from an XX fetus with structural abnormality; (4) germinal mutation resulting in a euploid zygote with structural abnormality followed by somatic back mutation resulting in a mosaic normal line, a process that appears so unlikely it is not considered further; (5) chimerism resulting from dispermy involving a mutant and normal sperm, another unlikely outcome not considered further. In some, but not all, of the mosaic cases, it is possible to state whether germinal or somatic mosaicism is relatively more likely. For example, there were six cases with two different lines with 46 chromosomes, one of which was normal and one of which had a structurally abnormal chromosome or chromosomes. In one case, the abnormality involved a ring; in three, a translocation; in one, an inversion; and in one, a deletion. If not the consequence of in vitro events, these six mosaic cases are almost certainly the result of somatic mutation. But with regard to a mosaic case with a de novo abnormal deleted Y in a 46 line and a 45 line missing this Y

TABLE 2

MEAN MATERNAL AGE, SD, AND *P*-VALUE FOR STRUCTURAL CHROMOSOME REARRANGEMENTS THAT ARE DE NOVO OR NOT KNOWN FAMILIAL FOR FETUSES STUDIED AT AMNIOCENTESIS

	KNOWN DE NOVO				ALL NOT KNOWN FAMILIAL			
	NONMOSAIC		MOSAIC AND NONMOSAIC		NONMOSAIC		MOSAIC AND NONMOSAIC	
	Mean maternal age	SD	Mean maternal age	SD	Mean maternal age	SD	Mean maternal age	SD
Unbalanced:								
Robertsonian	36.5	2.1	36.5	2.1	36.0	1.7	36.0	1.7
Rings	...	...	...	...	...	...	22.0	0.0
Supernumerary	38.0	5.4	37.7	3.8*	38.0	5.4	38.4	3.6†
Fragments	36.0	0.0	36.0	0.0	36.0	0.0	38.3	4.0
Markers	38.8	6.4	38.0	4.0*	38.8	6.4	38.4	3.7†
Deletions and other unbalanced	32.1	8.8	33.6	7.6	33.0	7.8	34.0	6.9
Deletions	32.6	9.9	33.7	8.3	33.3	9.0	34.1	7.8
Other	31.0	8.5	33.3	7.2	32.3	6.4	33.8	6.0
Balanced:								
Robertsonian	37.7	4.3	37.7	4.3	37.9	3.9	37.9	3.9
Inversions	36.5	0.7	36.5	0.7	34.7	3.2	35.3	2.9
Other reciprocals	36.3	2.5	36.8	2.5	35.7	2.8	36.2	2.8
All unbalanced	35.3	7.2	36.0	5.7	35.3	6.5	36.2	5.7
All balanced	36.8	3.1	37.0	2.9‡	36.4	3.4	36.6	3.2
All Robertsonian	37.4	3.8	37.4	3.8	37.4	3.5	37.4	3.5
Unbalanced (non-Robertsonian and nonsupernumerary)	32.1	8.8	33.6	7.6	33.0	7.8	31.3	8.1
Balanced and unbalanced (non-Robertsonian and nonsupernumerary)	34.7	5.9	35.4	5.3	34.5	5.3	34.8	5.3
All balanced and all unbalanced	36.1	5.4	36.5	4.7	35.9	5.0	36.4	4.8
(Comparison population: 26,558 prenatal diagnoses with normal findings)	(35.6	4.3)	(35.6	4.3)	(35.6	4.3)	(35.6	4.3)

* $P < .1$, two-tailed t test.
† $P < .01$, two-tailed t test.
‡ $P < .05$, two-tailed t test.

TABLE 3

CRUDE RATES OF STRUCTURAL CHROMOSOME REARRANGEMENTS THAT ARE DE NOVO OR NOT KNOWN FAMILIAL PER 1,000 FETUSES STUDIED AT AMNIOCENTESIS COMPARED WITH PREVALENCE RATES IN LIVE BIRTHS AND IN RECOGNIZED CONCEPTUSES

	RECOGNIZED CONCEPTUSES (NONMOSAIC)*		FETUSES AT AMNIOCENTESES (NONMOSAIC)		LIVE BIRTHS (NONMOSAIC)*	
	De novo	Not known familial	De novo	Not known familial	De novo	Not known familial
Unbalanced:						
Robertsonian	0.55	0.83	0.07	0.11	0.03	0.05
	(0.12)	(0.15)	(0.05)	(0.06)	(0.02)	(0.03)
Rings	0.03	0.08	0	0	0	0
	(0.03)	(0.05)	...	...	...	...
Supernumerary	0.03	0.07	0.26	0.26	0.03	0.08
	(0.02)	(0.03)	(0.10)	(0.10)	(0.02)	(0.04)
Fragments	...	...	0.07	0.07	...	...
	...	...	(0.05)	(0.05)	...	...
Markers	...	...	0.18	0.18	...	...
	...	...	(0.08)	(0.08)	...	...
Deletions and other unbalanced	0.44	0.73	0.26	0.33	0.05	0.08
	(0.10)	(0.13)	(0.10)	(0.11)	(0.03)	(0.04)
Deletions	...	...	0.18	0.22	...	...
	...	...	(0.08)	(0.09)	...	...
Others	...	...	0.07	0.11	...	...
	...	...	(0.05)	(0.06)	...	...
Balanced:						
Robertsonian	0.06	0.26	0.22	0.29	0.07	0.27
	(0.03)	(0.06)	(0.09)	(0.10)	(0.03)	(0.07)
Inversions	0.01	0.05	0.07	0.11	0.02	0.03
	(0.01)	(0.03)	(0.05)	(0.06)	(0.02)	(0.02)
Other reciprocals	0.29	0.42	0.33	0.37†	0.22	0.37
	(0.07)	(0.09)	(0.11)	(0.12)	(0.06)	(0.08)
All unbalanced	1.04	1.71	0.59	0.70	0.12	0.22
	(0.16)	(0.21)	(0.15)	(0.16)	(0.04)	(0.06)
All balanced	0.36	0.73	0.62	0.77†	0.30	0.67
	(0.08)	(0.11)	(0.15)	(0.17)	(0.07)	(0.11)
All Robertsonian	0.61	1.08	0.29	0.40	0.10	0.32
	(0.12)	(0.16)	(0.10)	(0.12)	(0.04)	(0.07)
All balanced and all unbalanced	1.41	2.43	1.21	1.47†	0.42	0.89
	(0.18)	(0.23)	(0.21)	(0.23)	(0.08)	(0.12)

* Derived from data presented in [5].

† One observed case with sex chromosome abnormality is excluded from this list for purposes of comparison with data of [5].

chromosome, mosaicism almost certainly resulted from anaphase loss of the abnormal Y after a presumptive germinal mutation. With regard to the 13 cases involving supernumerary fragments and markers that also have a normal 46 line, there are, at present, no strong grounds of which we are aware for regarding germinal mutation or somatic mutation as relatively more likely. Thus the rates of abnormalities in the categories of supernumerary abnormalities resulting from germinal mutation are somewhere between the rates of the nonmosaic cases and the rates of both nonmosaic and mosaic cases. (See also below.) With regard to all the other categories with the exception of the deletions, the rates of the nonmosaics are likely the best approximation to the rate of cases in this series resulting from germinal mutation. For deletions, because of the case with abnormal Y and 45 line cited above, the rate of cases resulting from germinal mutation is best estimated as the midpoint between the rate of nonmosaics and of mosaics plus nonmosaics. This is 0.22 per 1,000 for the de novo cases and about 0.26 per 1,000 for all not known familial.

There were in these series a total of about 24,500 fetuses for which there was no risk factor for a cytogenetic abnormality other than advanced maternal age. (Cytogenetic study was often done of amniotic fluid obtained from younger women because of such reasons as alpha-fetoprotein determination, diagnosis of recessive disorders, etc.) Among structural abnormalities of known origin, the proportions that were mutant or inherited may be determined in this group of 24,500 fetuses without bias to inclusion of cases born to carrier parents. Among the unbalanced rearrangements, there were no inherited unbalanced Robertsonian translocations or rings. Of the supernumerary markers, nine of 16 cases (56%) were de novo; of the deletions, five of six (83%) were de novo; and for the other "unbalanced" rearrangements, three of five (60%) were de novo. Among the balanced rearrangements, the proportion de novo were: Robertsonian—5/13 (38%); reciprocal—12/41 (29%); and inversions—2/26 (8%). (Note that polymorphisms have been excluded.) All of these proportions refer only to cases of known origin.

DISCUSSION

The proportions presented here are derived from a relatively small number of studies, so that great precision in the rates is not possible. The data provide, however, useful order of magnitude estimates of rates of mutant structural aberrations (detectable with currently available techniques) in the population studied and leads as to some factors to be taken into consideration in their evaluation such as parental age.

The data suggest an association of advanced maternal age with supernumerary markers independent of paternal age. Other trends of interest, albeit not significant, are the associations of Robertsonian rearrangements, especially those that are balanced, with advanced maternal age, and of unbalanced non-Robertsonian, nonsupernumerary rearrangements with younger maternal age. These trends, irrespective of their formal statistical significance, must be investigated in further data sources.

This study illustrates the difficulty in comparing the results in observations from midtrimester amniocentesis with those in live births or estimated in all conceptuses. Most of the women in this study were studied because of advanced maternal age. Therefore, if age is positively associated with the rate of structural chromosome mutations, then the observed rates of those affected will be elevated compared to the rates in the general population (i.e., rates in fetuses of 16–20-weeks gestation of women of all ages), and diminished if age is negatively associated. One way of adjusting for age differences in comparisons between populations is through direct age standardization. Our standardization approach used the maternal-age distribution of a group of live births for reference. This will *tend* to result in standardized rates that are lower than the crude rates for conditions associated with elevated maternal age, and this tendency will occur even if the maternal-age association is due to chance only. Similarly, the standardized rates will tend to be higher than the crude rates for conditions associated with lower maternal age. When the observed numbers are small, however, as in some of the categories studied here, some distortion may be introduced. There may be a paradoxical change in opposite direction to that expected, as with the nonmosaic de novo supernumerary group in this data set for which, despite a higher mean maternal age, the standardized rate is 0.31 per 1,000 compared to a crude rate of 0.26 per 1,000. Similarly, the magnitude of the differences between crude and standardized rates may be greater or less than that expected from the observed maternal-age trends if small numbers are observed. (Indirect age standardization will avoid the problem when there are sparse observations of affected, but this approach requires a reference maternal-age-specific rate schedule, which is not available for the structural abnormalities.)

For this reason, interpretation of differences between either the crude or standardized rates in this study and those observed in live births or estimated in all conceptuses as presented in table 3 must be done with caution. Some inferences do appear plausible, however, from the available data.

Whether crude or standardized rates are used, there is clearly a higher rate of supernumerary markers and fragments detected in amniocentesis than in the studies of live births or estimated in all conceptuses from studies of embryonic and fetal deaths. The reasons for this are not clear. Perhaps such aberrations are less likely to survive in tissues studied in aborted embryos and fetuses or in blood of newborns than in tissues that shed cells into amniotic fluid. The relatively low rate of the supernumerary aberrations in abortuses suggests that these aberrations are not associated with a very high risk of embryonic or early fetal death. Results on fetuses with markers and fragments whose mothers declined abortion indicate no associated high rate of fetal death after the usual time of amniocentesis [6, 7].

It is possible that many of the apparent de novo instances of these supernumerary markers and fragments are not the result of germinal mutation but (1) are inherited from a parent in whom the line is present but has been missed because of parental mosaicism, or (2) resulted from somatic mutations that occurred preferentially in precursors of amniotic fluid cells. On the other hand, instances of mosaicism for supernumerary markers in fetuses may well have resulted from germinal mutation with subsequent somatic development of a normal line. War-

burton reported, for instance, that of 10 fetuses with markers in whom the chromosome is known to have been in the original zygote because it was familial, seven had mosaicism [8]. Thus, there is clearly a tendency for somatic loss of markers originally in the zygote line and no firm grounds for concluding that the observed rates of supernumerary aberrations in fetuses, whether including or excluding mosaics, are necessarily serious overestimates of the rates of fetuses with such aberrations that resulted from germinal mutation.

Another trend of interest that may be noted in table 3 is that the crude rates of all categories of the balanced rearrangements are higher at amniocentesis than in the other series. This may be attributable in part to an association with maternal age. The standardized rates (see table 1) for these categories are all much lower than the observed crude rates and are not incompatible with the rates in live births or those estimated in all recognized conceptuses.

A factor complicating comparison with the results from the live-birth series is that almost all of these studies were done without use of banding, whereas the studies at amniocentesis and in embryonic and fetal deaths analyzed here used banding methods. The rates in live births may, therefore, be slightly lower than they would be with use of more modern techniques. Nevertheless, it is likely that most of the differences between the crude rates at amniocentesis and in live births for the unbalanced Robertsonian translocations and the "deletions plus other unbalanced" group is spontaneous death of affected fetuses between the usual time of amniocentesis and the time of live birth [6, 7].

Our results may also be compared with observations of Warburton, who, in an investigation of prognosis of structural abnormalities diagnosed prenatally, collected some data incidentally that are pertinent [8]. She surveyed 200 prenatal cytogenetic centers in the United States and received responses from about 80 on an estimated total of about 77,000 amniocenteses. We note below in each category of abnormality, first, the rates per 1,000 fetuses of those with structural mutations in her study and, second, for comparison, the (crude) rates in our own. The rates are for known de novo cases and, except where noted, on nonmosaics only: balanced Robertsonian, 0.12 vs. 0.22; inversions, 0.05 vs. 0.07; other balanced non-Robertsonian, 0.39 vs. 0.33; unbalanced Robertsonian, 0.05 vs. 0.07; supernumerary, 0.16 or 0.19 (depending on whether data in table 3 or table 7 of [8] are used) vs. 0.26; supernumerary including mosaics, 0.30 vs. 0.51; and other unbalanced, 0.18 vs. 0.26. In general, there is relatively good agreement, except on the supernumerary group including mosaics, which is higher in this series ($\chi^2 = 2.8$, $P \sim .09$), and the balanced Robertsonian translocations ($\chi^2 = 1.5, P \sim .20$). Three problems, however, enter into the comparison. First, as she notes, there may have been a bias in response to her study in that centers may have been more likely to report the total amniocentesis experience to her if they had observed a mutant. Our own data sources do not have such a bias, and as the rates are higher for most categories in our analysis than they are in her survey, it suggests that such a problem did not contribute significantly to the results of her study. Second, at least 16 individuals out of 73 listed by Warburton as responding to her survey are members of laboratories affiliated with one of the two Registries considered here, so the results of these two studies are not entirely independent. Third, many of

those responding to her survey are likely to have depended upon memory to relocate records of abnormal cases, and many cases, especially ones with clinically nonsignificant diagnoses, may have been overlooked selectively. This may account for the fact that not only are the rates for all but one category in our study greater than those she observed but that the greatest differences between her survey and our own results are for the balanced Robertsonian translocations and supernumerary markers and fragments.

With regard to environmental factors that may predispose to structural chromosome abnormality, it is of interest to compare the rates observed in those studied at amniocentesis primarily because of suspected exposure to a mutagen with those studied for some other reason. Of 71 studied primarily because of exposure to radiation, 58 were under 35. A de novo deletion, 46,XY,del(18)(q12.05q21), was found in a fetus carried by a woman aged 23. There were also 65 studied primarily because of exposure to a drug or other chemical, of whom 61 were under age 35. There was one inversion, 46,inv(3)(p12;p27), not known familial in a fetus of a mother age 31. The rate of structural abnormalities not known familial in those exposed either to radiation, drugs, or chemicals is 2/136 = 1.47% (95% confidence interval 0.2%–5.2%). This is significant at the .04 level (Fisher's exact test, two-tailed) when compared with the rate of structural abnormalities not known familial (59/27,089 = 0.22%) in the remainder, and is significant at the .02 level (Fisher's exact test, two-tailed) when comparison is limited to the nonmosaic group only, in which the rate is 39/27,089 = 0.14%. (Note that the observed rate in the exposed group is based on sparse data and we do not recommend its uncritical use in genetic counseling.)

The women in whose fetus the inversion was found was studied because her husband had taken multiple drugs, both licit and illicit, including lysergic acid (LSD). Unfortunately, he was not available for further study. The mother of the fetus with the deletion was studied because her husband had been exposed to therapeutic irradiation for Hodgkin disease (W. R. Breg, personal communication, 1982). These examples suggest that further systematic investigation of chromosome abnormalities diagnosed prenatally is likely to be useful for characterization of human environmental mutagens.

Lastly, we emphasize that the rates presented here are on the proportions of fetuses with putative mutant aberrations, not on actual mutation rates "per gamete." Because of the possibility of prezygotic selection against mutant gametes or post-zygote selection against mutant embryos, or fetuses before the age of ascertainment, no inferences are possible concerning the "true" mutation rates per gamete for cytogenetic abnormalities. It may appear plausible that such selection is not significant for some (but not all) specific locus mutations whose rates are usually denoted as "per gamete." But such an assumption appears highly unlikely to hold for many, if not most, unbalanced chromosome mutations given what is already known about the very high rate of cytogenetic aberrations in aborted embryos.

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Appendix follows on next page

APPENDIX

LIST OF STRUCTURAL CHROMOSOMAL REARRANGEMENTS, DE NOVO OR NOT KNOWN INHERITED

Classification	Registry no.	R. F. S.*	Maternal age	Paternal age	Origin	Diagnosis
Unbalanced:						
Robertsonian	BDI 40438	a	35	...	Unknown	46,XX,−21,+t(21;21)
	BDI 40715	a	38	41	De novo	46,XY,−13,+t(13;13)
	ICRS 4210/1	a	35	35	De novo	46,XX,−14,+t(13;14)den,inv(3)mat
Rings	BDI 40254	e	22	...	Unknown	mos 46,XX/46,XX,r(13)
Supernumerary fragments	BDI 40361	a	36	33	De novo	45,X,+f
	BDI 40455	a	36	43	De novo	45,X,+f
	ICRS 5335/1	a	43	41	Unknown	mos 46,XX/47,XX,+f
Markers	BDI 40607	d	38	36	De novo	47,XX,+mar
	BDI 40641	a	43	44	De novo	47,XY,+mar
	BDI 40131	a	43	45	De novo	47,XX,+mar
	BDI 40135	a	42	45	De novo	47,XX,+mar
	BDI 40351	e	28	...	De novo	47,XY,+mar?r
	BDI 40688	a	39	...	Unknown	mos 46,XY/47,XY,+mar
	BDI 40716	a	39	40	De novo	mos 46,XX/47,XX,+mar
	BDI 40083	a	38	39	De novo	47,XY,+marI/48,XY,+marI, +marI/49,XY,+marI,+marI, +marI
	BDI 40658	b	36	32	De novo	mos 46,XX/47,XX,+mar
	BDI 40072	f	36	40	De novo	mos 46,XX/47,XX,+mar?
	BDI 40596	a	38	35	De novo	mos 46,XY/47,XY,+mar
	BDI 40638	d	36	32	De novo	mos 46,XX/47,XX,+mar
	BDI 40309	a	39	34	De novo	mos 46,XX/47,XX,+mar
	BDI 40588	a	38	38	Unknown	mos 46,XY/47,XY,+mar
	ICRS 23668/1	a	43	...	Unknown	mos 46,XX/47,XX,+mar
	ICRS 25836/1	a	38	44	Unknown	mos 46,XX/47,XX,+mar
Deletions	BDI 40520	a	36	...	De novo	47,XX,+21q−
	BDI 40140	d	22	...	De novo	46,XY,5p−
	BDI 40728	a	37	59	Unknown	46,XX,del(18)(p11)
	BDI 40462	a	37	37	De novo	46,XY,del(8)(p21)
	ICRS 24796/1	a	45	39	De novo	46,XX,del(4)(p16)
	ICRS 25384/1	i	23	25	De novo	46,XY,del(18)(q12.05q21)
	BDI 40466	a	37	...	De novo	mos 45,X/46,X,del dic(Y)?
	BDI 40283	a	36	46	De novo	mos 46,XX/46,X,del(X)(qter→ p11:)

Other	BDI 40278	a	37	35	De novo	46,XX,21q+
	BDI 40358	a	35	...	Unknown	46,XY,22p+
	BDI 40713	e	25	...	De novo	46,XY,dup(1)(q32q41)
	ICRS 5664/1	a	38	36	De novo	mos 46,XX/47,XX,+t(15p;15p)
Balanced:						
Robertsonian	BDI 40619	a	41	42	Unknown	46,XY,−13,−14,+t(13;14),+21
	BDI 40636	a	37	49	De novo	45,XX,−13,−14,+t(13;14)
	BDI 40699	a	35	32	De novo	45,XX,−13,−14,+t(13;14)
	BDI 40233	a	38	36	De novo	45,XY,−13,−14,+t(13;14)
	BDI 40441	c	34	35	De novo	45,XY,−14,−15,+t(14;15)
	BDI 40687	a	36	29	Unknown	45,XY,−14,−15,+t(14;15)
	ICRS 7642/1	a	46	58	De novo	45,XY,−13,−15,+t(13;15)
	ICRS 25219/1	a	36	45	De novo	45,XX,−13,−14,+t(13;14)
Inversions	BDI 40606	a	36	55	De novo	46,XX,inv(8)(p23q11)
	BDI 40406	h	31	...	Unknown	46,XY,inv(3)(p12p27)
	BDI 40311	a	37	31	De novo	46,XX,inv(1)(p36q21)
	BDI 40686	a	37	37	Unknown	mos 46,XY/46,XY,inv(6)(p22.07?q32.09?)
Other reciprocals	BDI 40573	f	35	40	Unknown	47,XY,t(1;11),+21
	BDI 40409	a	36	33	De novo	46,XY,t(3;17)(q21;q23)
	BDI 40171	a	42	35	De novo	46,XX,t(2q;17q)
	BDI 40694	a	37	37	De novo	46,XX,t(1;5)(q32;q11)
	BDI 40695	a	34	33	De novo	46,XX,t(5;11)
	BDI 40242	a	37	43	De novo	45,XX,−2,−22,+tdic(2;22)(p25;p11?)
	BDI 40574	a	33	33	De novo	46,XY,t(4;11)(q13;p15)
	BDI 40535	a	36	...	De novo	46,XX,t(1;8)(p32;q24)
	BDI 40629	a	37	...	De novo	46,XY,t(3;15)(q27;q22)
	ICRS 11863/1	g	31	34	Unknown	46,X,t(X;20)
	ICRS 5572/1	a	35	38	De novo	46,XX,t(9;12)(q34;q24.3)
	BDI 40326	a	40	43	De novo	mos 46,XX/46,XX,t(9;13)(q21;q34)
	BDI 40502	a	38	...	De novo	mos 46,XX/46,X,t(Xq;3q)
	BDI 40209	a	36	...	De novo	mos 46,XY/46,XY,t(1;3)(p21?;p27?)

* R.F.S. = Reason for study, coded as follows:
a = elevated maternal age
b = previous offspring with Down syndrome
c = family history of Down syndrome
d = previous offspring with chromosome abnormality other than Down syndrome
e = alpha-fetoprotein determination
f = previous child with neural tube defect
g = metabolic disorder
h = suspected chemical mutagen
i = radiation.