Effects of Maternal Age and Birth Order on the Risk of Mongolism and Leukemia [1]

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SUMMARY—The maternal-age and birth-order effects on the risk of mongolism and leukemia were determined for children born in Michigan during 1950–64. There was a striking association between maternal age and mongolism, but birth order did not independently affect the risk of mongolism. On the other hand, both maternal age and birth order independently affected the risk of death from leukemia. Risk of death from leukemia decreased with advancing birth order and increased with advancing maternal age. Except for the older maternal age groups, these trends for leukemia are in contrast to the effects of maternal age and birth order on death due to all causes. This contrast suggests maternal age and birth order may be closely associated with the etiological agents of childhood leukemia.—J Nat Cancer Inst 37: 687–698, 1966.

MATERNAL AGE and birth order both seem to affect the probability of death due to childhood leukemia. Stewart *et al.* (*1*) observed a higher than expected proportion of first births among children with leukemia. The same authors and Manning and Carroll (*2*) noted an excess of older mothers among the parents of leukemic children. These observations were extended by MacMahon and Newill (*3*) who demonstrated independent maternal-age and birth-order effects.

As in childhood leukemia, advancing maternal age is also associated with an increasing probability of birth of a mongoloid child. During the past 50 years the striking maternal-age effect on the risk of mongolism has been confirmed by numerous studies (*4–16*). However, studies of the birth-order effect on the risk of mongolism have been inconclusive for one or more of the following reasons: 1) selection of an inappropriate study group, 2) use of a small study group, or 3) failure to separate birth-order from maternal-age effects (*4, 5, 7–9, 12, 14, 17–19*).

The present study determines the independent maternal-age and birth-order effects for both leukemia and mongolism in one population during the same time period. A large group of mongo-

[1] Received April 26, 1966.

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[3] We wholeheartedly thank all of the Michigan people who assisted us in gathering data. This study would not have been possible without the kind, competent, and effective help of the superintendents and staff of the State Homes and Training Schools and numerous people in the Michigan State Health Department, the Michigan Department of Mental Health, and the public schools of Michigan.

[4] National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

loid children born in the State of Michigan during 1950–64 was compared with the general population of Michigan to determine the independent effect of birth order, if any, on the risk of mongolism. In addition, the independent effects of birth order and maternal age on the risk of childhood leukemia in Michigan during the same time period were studied.

METHODS

Mongoloids born during a 15-year period, 1950–64, in the lower peninsula of Michigan were ascertained from the following sources: 1) birth certificates, 2) State institutions for the care of mentally handicapped persons, 3) private hospital records, and 4) school programs for the education of mentally handicapped persons.

In a study of this nature it was, of course, impossible to classify mongoloids by karyotype. A recent review by Edgren *et al.* (*20*) indicates that, among the 1,113 mongoloid karyotypes thus far reported, only 5.4% had other than regular G-trisomy. By extrapolation from these data, the present study population would include about 100 mongoloids with other than regular G-trisomy. In all probability this number of cases would not have affected the results obtained here, and would not be sufficient for the determination of independent maternal-age and birth-order effects.

Leukemia deaths among children born 1950–64 in Michigan were ascertained from the 1950–64 death records for the entire State of Michigan.

Information derived from birth certificates was used to classify all mongoloids and leukemics into 1 of 6 levels of maternal age (<20, 20–24, 25–29, 30–34, 35–39, 40+) and 1 of 5 birth positions (1–4, and 5+). A parallel distribution of all Michigan live births during 1950–64 was obtained from publications of the National Office of Vital Statistics (*21*), the National Center for Health Statistics (*22*), and the Michigan State Department of Health (*23*). These maternal-age by birth-order distributions were used to calculate mongolism occurrence rates and leukemia mortality rates.

In addition, an extension of the Mantel-Haenszel chi-square procedure (*24*) was used to analyze the data. This method of analysis permitted a determination of statistical significance for independent maternal-age and birth-order effects. Each mongoloid, leukemic, and normal liveborn child was assigned a birth-order score on the basis of his birth-order position: Firstborn children were scored "1"; secondborn children were scored "2", etc.; fifthborn children and those in higher ordinal positions were scored "5." Each child was also assigned a maternal-age score ("1" for mothers <20, "2" for mothers 20–24, etc., and "6" for mothers 40+). Also each child was identified by his year of birth. The distributions of birth order and maternal age by year of birth in mongoloids or leukemics were compared with the analogous distributions for all live births. Chi-square values derived from the procedure indicated whether the average or total scores for each variable—the other two held constant—differed significantly when mongoloids or leukemics were compared with the general population of births. Independent birth-order or maternal-age effects were thus isolated from confounding variation due to the other variable and from time-associated variation due to changing birth rates, differing periods of ascertainment for mongoloids, and differing periods of follow-up for leukemics.

RESULTS

Mongolism

A total of 2,432 mongoloids born 1950–64 in the lower peninsula of Michigan was found. The distribution of these children, leukemia deaths, and all Michigan live births by maternal age, birth order, and 5-year birth cohorts is shown in table 1. Table 2 shows the contribution of each ascertainment source to the sample. The percentages contributed by each source indicate that the sample was at least 39% larger than it would have been if only the best single source had been used. Also, the small, unique contributions from each of the sources indicate that for about 80% of the cases the diagnosis of mongolism was made at more than one source. The use of multiple ascertainment sources thus resulted in a more complete sample than any single source could have provided, and the high redundancy in ascertainment suggests a high degree of validity in the diagnoses of mongolism.

Despite intensive ascertainment efforts, the observed occurrence rate for mongolism in Michigan was somewhat lower than had been previously reported in England and Australia. After adjustment by the direct method to the maternal-age distribution of all U.S. births for 1960, the mongolism occurrence rate in Michigan was 1 in 1,120 live births. After adjustment to the same standard population, the data of Collmann and Stoller yielded an occurrence rate of 1 in 842 live births, and Carter and McCarthy's data yielded a rate of 1 in 922 live births. Apparently, many mongoloids born in Michigan were not known to the ascertainment sources used in this study. Possible explanations for this include death, delay in registration at the sources, and migration out of State.

When all mongoloids were arranged in a maternal-age by birth-order table and a rate (total number of cases/total number of live births) calculated for each cell (table 3), there was no consistent effect of birth order on the probability of a mongoloid birth. Although the rates at the 30–34 maternal-age level appeared to show a general downward trend with increasing birth order, no similar consistent pattern was evident at any of the other maternal-age levels. The total crude rates indicated a sharply increasing risk with increasing birth order, but this apparent effect vanished after adjustment (direct method) for maternal age. Apparently, the greater risk of mongolism at higher birth orders was due to a strong, independent maternal-age effect and the correlation of maternal age and birth order.

Although no independent birth-order effect is discernible in table 3, the well-known maternal-age effect on the risk of mongolism is clearly demonstrated. Almost without exception the probability of a mongoloid birth increased at each successive maternal-age level in each birth-order category. The total crude rates indicated a striking rise in risk with advancing maternal age, and this pattern remained after adjustment for birth order.

Because the rates in table 3 could have been confounded by annual birth-rate variations and differing periods for ascertainment of mongoloids born during the 15-year study, an extension of the Mantel-Haenszel chi-square procedure (*24*) was used for further analysis of the data in table 1. In this procedure both maternal age and time of birth were held fixed when the birth-order effect was determined, and birth order and time of birth were held fixed when the maternal-age effect was determined.

For each 5-year time interval (birth cohort) and maternal-age combination, the upper portion of table 4 shows the average birth-order score for mongoloid children and for all children, as well as an individual chi square (with one degree of freedom) associated with the difference between these 2 average birth-order scores. In the Mantel-Haenszel procedure any tendency for the various differences to be in the same direction is reinforced, and this is reflected in summary chi squares (each with one degree of freedom) for each birth cohort and each maternal-age group, as well as in an overall summary chi square. Except for the summary chi square for the 50–54 birth cohort, the individual chi squares, summary chi squares, and the overall chi square were nonsignificant. This indicates that mongoloid children have the same average birth-order score as all children when birth cohort and maternal age are taken into account.

In contrast, the lower portion of table 4 shows highly significant individual and summary chi squares and an overall chi square of 1,840. These reflect a consistent pattern in which the average maternal-age score for mongoloid children exceeds that for all children in the general population.

When the data in table 1 were analyzed in the same manner as indicated in table 4, but with single-year birth cohorts, the same pattern of significant maternal-age effects and nonsignificant birth-order differences emerged.

Leukemia

A total of 706 leukemia deaths among children born in Michigan between 1950 and 1964 was found from the 1950–64 records for the entire State of Michigan. Ascertainment of leukemia deaths was probably more complete than that of mongoloid births because virtually all deaths due to leukemia are registered as such in Michigan (*23*). Emigration did not seriously reduce the number of leukemia deaths found. A review of 1950–59 leukemia deaths for the entire United States re-

TABLE 1.—Distribution of mongoloids born in lower Michigan, leukemics born and residing in Michigan, all lower Michigan live births, and all Michigan live births, by maternal age, birth order, and 5-year birth cohorts, 1950–64*

Maternal age group	Birth-order group														
	1			2			3			4			5		
	Number of mongoloids born			Number of mongoloids born			Number of mongoloids born			Number of mongoloids born			Number of mongoloids born		
	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64
<20...	26	42	36	5	13	7	1	0	2	0	0	1	0	0	0
20–24..	44	41	50	49	63	36	19	25	24	6	11	9	0	5	2
25–29..	22	29	8	44	39	20	37	40	26	12	33	17	7	26	28
30–34..	18	17	4	38	29	14	34	39	22	23	31	29	23	43	43
35–39..	17	12	8	32	26	24	36	41	28	36	58	39	48	94	105
40+...	7	10	8	5	20	14	20	27	25	27	42	20	57	107	118
Total..	134	151	114	173	190	115	147	172	127	104	175	115	135	275	296
	Number of leukemia deaths, 1950–64 among children born			Number of leukemia deaths, 1950–64 among children born			Number of leukemia deaths, 1950–64 among children born			Number of leukemia deaths, 1950–64 among children born			Number of leukemia deaths, 1950–64 among children born		
	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64
<20...	20	23	2	7	9	2	1	0	1	0	0	0	0	0	0
20–24..	53	34	9	41	17	11	13	12	5	7	6	0	3	2	1
25–29..	30	11	1	41	21	3	25	31	8	9	13	5	7	9	2
30–34..	8	6	0	19	7	1	29	11	0	11	10	5	12	14	5
35–39..	1	0	0	1	3	3	8	3	2	2	3	1	7	14	5
40+...	0	0	1	3	0	1	3	2	1	2	1	0	1	5	0
Total..	112	74	13	112	57	21	79	59	17	31	33	11	30	44	13

Maternal age group	Birth-order group														
	1			2			3			4			5+		
	Number of live births (lower Mich.)			Number of live births (lower Mich.)			Number of live births (lower Mich.)			Number of live births (lower Mich.)			Number of live births (lower Mich.)		
	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64
<20...	63, 927	77, 870	79, 725	19, 073	25, 607	24, 847	3, 709	5, 414	5, 370	555	835	818	86	119	110
20–24..	107, 047	107, 925	102, 214	99, 231	110, 497	104, 833	46, 954	60, 977	61, 256	16, 425	24, 453	25, 376	6, 328	11, 225	11, 983
25–29..	47, 768	37, 199	25, 657	82, 724	68, 836	49, 317	65, 016	73, 427	60, 948	33, 315	48, 270	45, 939	25, 784	44, 204	48, 890
30–34..	16, 701	13, 239	8, 073	34, 815	28, 399	16, 907	39, 933	43, 410	29, 601	26, 672	37, 042	30, 951	32, 655	52, 580	59, 177
35–39..	5, 707	4, 778	3, 193	10, 754	10, 143	6, 510	14, 645	16, 516	12, 194	12, 732	17, 060	14, 576	23, 392	36, 136	40, 797
40+...	1, 191	979	768	1, 787	1, 929	1, 459	2, 565	3, 150	2, 623	2, 543	3, 531	14, 609	8, 198	11, 507	13, 519
Total..	242, 340	241, 990	219, 629	248, 383	245, 410	203, 873	172, 824	202, 894	171, 993	92, 242	131, 190	132, 269	96, 443	155, 772	174, 476
	1			2			3			4			5+		
	Number of live births (all Mich.)			Number of live births (all Mich.)			Number of live births (all Mich.)			Number of live births (all Mich.)			Number of live births (all Mich.)		
	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64	1950–54	1955–59	1960–64
<20...	66, 531	80, 690	82, 840	19, 850	26, 534	25, 818	3, 860	5, 610	5, 580	578	865	850	90	123	114
20–24..	111, 408	111, 833	106, 208	103, 273	114, 498	108, 930	48, 867	63, 185	63, 650	17, 094	25, 338	26, 368	6, 586	11, 632	12, 451
25–29..	49, 714	38, 546	26, 660	86, 094	71, 329	51, 244	67, 665	76, 086	63, 330	34, 672	50, 018	47, 734	26, 834	45, 805	50, 801
30–34..	17, 381	13, 718	8, 388	36, 233	29, 427	17, 568	41, 560	44, 982	30, 758	27, 758	38, 383	32, 160	33, 985	54, 484	61, 490
35–39..	5, 939	4, 951	3, 318	11, 192	10, 510	6, 764	15, 242	17, 114	12, 670	13, 251	17, 678	15, 146	24, 345	37, 445	42, 391
40+...	1, 239	1, 015	798	1, 860	1, 999	1, 516	2, 670	3, 264	2, 726	2, 647	3, 659	15, 180	8, 532	11, 924	14, 047
Total..	252, 212	250, 753	228, 212	258, 502	254, 297	211, 840	179, 864	210, 241	178, 714	96, 000	135, 941	137, 438	100, 372	161, 413	181, 294

*The maternal-age-birth-order distribution for lower Michigan live births was derived from the distribution of all Michigan live births by multiplication of the total live births in a given maternal-age and birth-order category by the proportion of lower Michigan live births (1950–64) to total Michigan live births (1950–64). Because of rounding errors, some totals are incorrect by 1 or 2 live births. The numbers shown here were used in calculations.

TABLE 2.—Number of mongoloid children ascertained at various sources in Michigan, 1950–64

Source	Number of cases found at source	% entire sample	Number of cases unique to source	% entire sample unique to source
Birth certificate	994	39	234	9
State institution	1, 542	61	89	4
University of Michigan Medical Center	429	17	86	3
Kindred files at the University of Michigan Medical Center, Department of Human Genetics	81	3	17	1
Children's Hospital of Detroit	218	9	21	1
Public schools	388	15	37	2

TABLE 3.—Mongolism occurrence rates per 100,000 live births by age of mother and birth order, lower Michigan, 1950–64*

Maternal age	Birth order					Total	
	1	2	3	4	5+	Crude	Adjusted
<20	46. 9	36. 0	(20. 7)	(45. 3)	(00. 0)	43. 2	31. 3
20–24	42. 6	47. 1	40. 2	39. 3	23. 7	42. 8	39. 9
25–29	53. 3	51. 3	51. 7	48. 6	51. 3	51. 2	51. 6
30–34	102. 6	101. 1	84. 1	87. 7	75. 5	86. 6	92. 4
35–39	270. 5	299. 2	242. 2	299. 8	246. 5	263. 8	272. 1
40+	850. 9	753. 6	863. 6	940. 1	851. 7	858. 9	839. 9
Total Crude	56. 7	68. 5	81. 4	114. 4	165. 6	89. 1	
Total Adjusted	93. 2	92. 9	83. 7	92. 4	74. 4		

*Rates in parentheses are based on fewer than 10 cases. Adjusted rates were computed by the direct method. At a given birth order, the adjusted rate shown was obtained by weighting the observed maternal-age-specific rates by the proportion of all births in the study in that maternal-age category. Conversely, the adjusted rate at a given maternal age was obtained by weighting the birth-order-specific rates by the proportion of all births in that birth-order category. The adjusted rates are thus weighted averages of the specific rates.

Adjustment by the indirect method was not feasible because there was no readily defined and appropriate set of standard rates to use for such an adjustment. The crude rates are unsatisfactory because they represent a confounding of maternal-age and birth-order effects. We are investigating a method of indirect adjustment in the presence of such confounding. The principle being considered is that both sets of adjusted rates are to be obtained simultaneously and are to satisfy the condition that either set, when considered as a set of standard rates, yields the other set.

vealed that 15 children born during that period died outside of Michigan. Only a very strong nonrandom relationship between emigration and birth order or maternal age could seriously bias the results.

Although ascertainment was almost complete for 1950–64 leukemia deaths, more leukemia deaths were contributed by earlier birth cohorts, *e.g.*, the 1950 birth cohort, than by later ones, *e.g.*, the 1964 birth cohort. This made calculation of occurrence rates for all cohorts combined inappropriate. And with the occurrence of only small numbers of cases in individual birth cohorts, calculation of leukemia rates for single-year or even 5-year birth cohorts was also inappropriate. Therefore, an analysis of the leukemia data similar to that shown in table 3 for the mongoloid data was not made. Instead, as shown in table 5, the leukemia data were analyzed for birth-order and maternal-age effects in the presence of confounding.

The crude leukemia mortality rates in table 5 for children age 0–15 years suggest an increasing risk with advancing maternal age and a decreasing risk with increasing birth order. These suggested patterns were clarified somewhat when the crude rates were age-adjusted (indirect method), but in either case the rates did not permit any inferences

TABLE 4.—Independent birth-order and maternal-age effects on the risk of a mongoloid birth as indicated by the results of an analysis of the data with an extension of the Mantel-Haenszel chi-square procedure*

Birth cohort	Maternal age																	Summary χ^2
	<20			20–24			25–29			30–34			35–39			40+			
	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	
	Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		
1950–54.....	1. 22	1. 33	0. 76	1. 89	1. 97	0. 68	2. 49	2. 63	1. 56	2. 96	3. 16	2. 92	3. 39	3. 56	2. 50	4. 05	3. 91	1. 30	4. 35
1955–59.....	1. 24	1. 36	1. 83	2. 14	2. 11	0. 10	2. 93	2. 98	0. 21	3. 34	3. 50	2. 40	3. 85	3. 82	0. 08	4. 05	4. 07	0. 07	0. 85
1960–64.....	1. 30	1. 35	0. 12	1. 98	2. 15	2. 65	3. 37	3. 19	1. 96	3. 83	3. 80	0. 04	4. 02	4. 08	0. 38	4. 22	4. 17	0. 48	0. 00
Summary...	—	—	2. 70	—	—	1. 39	—	—	0. 06	—	—	0. 04	—	—	1. 10	—	—	0. 61	2. 49 (Overall)

	Birth order															Summary χ^2
	1			2			3			4			5+			
	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	
	Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		Mongoloid children	All children		
1950–54.....	2. 83	2. 16	58. 78	3. 34	2. 70	70. 70	3. 99	3. 13	102. 13	4. 63	3. 46	131. 66	5. 15	4. 01	154. 33	499. 00
1955–59.....	2. 64	2. 02	62. 32	3. 27	2. 56	92. 42	4. 03	3. 07	145. 24	4. 50	3. 42	185. 54	4. 99	3. 95	267. 37	739. 86
1960–64.....	2. 32	1. 88	25. 86	3. 47	2. 41	137. 46	3. 98	2. 94	127. 85	4. 36	3. 58	44. 09	5. 04	3. 97	307. 78	599. 88
Summary...	—	—	147. 06	—	—	283. 84	—	—	375. 29	—	—	331. 28	—	—	730. 88	1, 840. 19 (Overall)

*Each chi-square value given has one degree of freedom; a value exceeding 3.84 is statistically significant at the 5% level.

TABLE 5.—Crude and age-adjusted 15-year leukemia mortality rates, per 100,000 live births for children age 0–15 at death, Michigan, 1950–64*

By maternal age			By birth order		
	Crude	Age adjusted		Crude	Age adjusted
<20.....	2. 67	2. 66	1.....	3. 32	3. 36
20–24....	2. 94	2. 94	2.....	3. 14	3. 17
25–29....	3. 36	3. 38	3.....	3. 40	3. 40
30–34....	3. 50	3. 50	4.....	2. 78	2. 74
35–39....	2. 87	2. 85	5.....	2. 80	2. 74
40+.....	4. 35	4. 31			
Total....	3. 15	.....	Total...	3. 15	.....

*To obtain crude rates we divided the total number of leukemia deaths among children born to mothers in a given maternal-age or birth-order group by the total number of live births to mothers in these categories during 1950–64. Age-adjusted rates were obtained by the indirect method, the standard rates used in the adjustment being the total number of leukemia cases in the study occurring at a particular age divided by the total number of children-years at that age.

about possible independent effects of birth order and maternal age. The positive correlation between maternal age and birth order would tend to obscure an independent inverse birth-order effect. Likewise, if an independent inverse birth-order effect existed, it and the positive correlation between maternal age and birth order would tend to obscure a positive maternal-age effect.

To obtain some measure of the independent maternal-age and birth-order effects on the risk of childhood leukemia, an extension of the Mantel-Haenszel chi-square procedure was employed. As in the analysis of the data for mongoloids, leukemia cases and all live births were distributed by birth order, maternal age, and 5-year birth cohorts (table 1). Also, the same scoring procedure was used. Results of this analysis are given in table 6. In most maternal-age by birth-cohort categories, the average birth-order score for leukemic children was lower than that for all liveborn children, but very few of these differences were statistically significant. When the small differences were permitted to reinforce each other, however, the summary chi-square values indicated that leukemic children had significantly lower birth-order scores in the 20–24, 25–29, and 40+ maternal-age groups as well as in the 1950–54 birth cohort; the highest level of significance was attained for the overall chi square. When the chi-square analysis was repeated with one-time scale position for each of the 15 one-year birth cohorts, the results showed the same pattern of significant and nonsignificant chi-square values. From these results and the age-adjusted rates in table 5, a decrease can be inferred in the risk of childhood leukemia with advancing birth order when maternal age is kept fixed.

Table 6 also shows that in most birth-order by birth-cohort categories the average maternal-age score for leukemic children is higher than that for all children, although very few of these individual differences were statistically significant. However, the summary chi-square value was significantly high for the third birth-order group and for the 1950–54 birth cohort, with significance attained also by the overall chi square. A separate analysis with 15 birth cohorts instead of 3 gave the same pattern of significant and nonsignificant chi-square values. These results and the age-adjusted rates in table 5 indicate that the risk of childhood leukemia increases with advancing maternal age.

The data in table 6 also suggest that the maternal-age and birth-order effects may be more important in children dying of leukemia over age 10 than under age 10. In the 1950–54 birth cohort where leukemia mortality was followed for 10–15 years, both the independent maternal-age and birth-order effects were significant, but in the 1955–59 and 1960–64 birth cohorts this was not true. Although a lack of significance is understandable in the 1960–64 cohort where leukemia mortality was followed for only 0–5 years and the number of leukemia deaths was small (table 1), the reason for lack of significance in the 1955–59 cohort, where leukemia mortality was followed for 5–10 years and the number of leukemia deaths was almost as great as in the 1950–54 cohort (table 1), is not clear. One reasonable explanation of these results is that the independent maternal-age and birth-order effects are particularly strong in children dying of leukemia over age 10. Alternatively, it is conceivable that maternal age and birth order do not affect the risk of leukemia below age 5. If this is true, the absence of discernible maternal-age and birth-order effects in the 1955–59 and 1960–64 cohorts may be explained by the fact that relatively few of the children in the 1955–59 cohort (compared with the 1950–54

TABLE 6.—Independent birth-order and maternal-age effects on the risk of childhood leukemia as indicated by the results of an analysis of the data with an extension of the Mantel-Haenszel chi-square procedure*

Birth cohort	Maternal age																		Summary χ^2
	<20			20–24			25–29			30–34			35–39			40+			
	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	Average birth-order score		χ^2	
	Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		
1950–54.....	1. 32	1. 33	0. 00	1. 85	1. 97	1. 44	2. 30	2. 63	8. 02	3. 00	3. 16	1. 07	3. 68	3. 56	0. 11	3. 11	3. 91	2. 82	9. 50
1955–59.....	1. 28	1. 36	0. 32	1. 94	2. 11	1. 62	2. 86	2. 98	0. 65	3. 40	3. 50	0. 26	4. 22	3. 82	2. 03	4. 38	4. 07	0. 31	0. 85
1960–64.....	1. 80	1. 35	1. 64	1. 96	2. 15	0. 62	3. 21	3. 19	0. 00	4. 27	3. 80	1. 28	3. 73	4. 08	0. 74	2. 00	4. 17	14. 24	0. 48
Summary...	—	—	0. 00	—	—	3. 89	—	—	6. 28	—	—	0. 61	—	—	0. 60	—	—	3. 86	9. 17 (Overall)

	Birth order															Summary χ^2
	1			2			3			4			5			
	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	Average maternal-age score		χ^2	
	Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		Leukemic children	All children		
1950–54.....	2. 26	2. 16	0. 97	2. 78	2. 70	0. 67	3. 49	3. 13	9. 63	3. 45	3. 46	0. 00	3. 87	4. 01	0. 44	5. 12
1955–59.....	2. 00	2. 02	0. 01	2. 61	2. 56	0. 10	3. 19	3. 07	0. 64	3. 39	3. 42	0. 01	4. 25	3. 95	3. 33	1. 49
1960–64.....	2. 23	1. 88	1. 53	2. 76	2. 41	2. 43	3. 00	2. 94	0. 01	3. 64	3. 58	0. 00	4. 08	3. 97	0. 06	2. 60
Summary...	—	—	0. 97	—	—	1. 89	—	—	7. 92	—	—	0. 00	—	—	0. 99	8. 65 (Overall)

*Each chi-square value given has one degree of freedom; a value exceeding 3.84 is statistically significant at the 5% level.

cohort) and none of the children in the 1960–64 cohort were over age 5 at death.

DISCUSSION

The incidence data in this study indicate that mongolism occurred less frequently in Michigan than other places around the world (*5*, *6*, *11*) or that ascertainment was incomplete. If case finding was incomplete, at least four possible explanations exist. High death rates among mongoloids may have prevented many from being registered at the sources used in this study. Also, out-of-State migration, a recent trend in Michigan to "home care," and missed diagnoses could have diminished ascertainment precision. The important question is, did any of these case-finding deficiencies—which are common to all retrospective studies of mongolism—introduce significant bias into the measurement of the maternal-age and birth-order effects?

Deaths among mongoloids prior to registration at one of the sources could bias the maternal-age and birth-order results, if deaths due to all causes are affected by maternal age and birth order. Data from British Columbia, Canada, published by Newcombe (*25*) indicated that the probability of death due to all causes in 0–6-year-old children increased with advancing birth order, although for mothers over age 30 the risk curve by birth order was J-shaped. If Michigan mongoloid children have a similar pattern of mortality risk, preregistration deaths among mongoloid children would tend to reduce observed rates more at the higher than lower birth-order levels. Correction of the present data for this bias would tend to make the curve for risk of mongolism by birth order virtually horizontal. Certainly any preregistration bias due to death could not be masking an inverse birth-order effect like that observed for children dying of leukemia.

Newcombe's data (*25*) also showed that risk of childhood death due to all causes generally decreased with advancing maternal age. If risk of death among Michigan mongoloids followed the same pattern, relatively more mongoloids born to younger mothers would die and be unascertained. This would lower the observed occurrence rates more for younger mothers than older mothers, and the observed increase in risk of mongolism with advancing maternal age would be more precipitous than indicated in previous reports (*4*). Apparently this potential source of bias was not operating, because Michigan rates did not rise more rapidly with advancing maternal age than has been reported in previous studies (*4*).

Biases in the maternal-age and birth-order distributions contributed by out-of-State migration and home care probably have a leveling effect on the birth-order curve. Migration is no doubt more frequent in young and relatively small families where migration is easier than in older and larger households. This circumstance would tend to diminish the number of mongoloids ascertained in the early birth orders. Mongoloids who are last born to older parents are likely to be cared for at home because they interfere less with the care of older siblings than younger siblings. This would tend to reduce the number of ascertained mongoloids in the higher birth orders. It is difficult to imagine how diagnoses of mongolism would more likely be missed for one birth order or maternal age than another.

In summary, the possible sources of bias in the maternal-age and birth-order distributions of the mongoloids in the present study could not seriously alter the overwhelming maternal-age association, and the bias in the birth-order distribution is more likely to be a leveling effect on a truly J-shaped curve than the masking of an inverse birth-order effect.

Leukemia.—The leukemia data show that the risk of death from childhood leukemia increased with advancing maternal age and decreased with advancing birth order. This pattern of variation in leukemia risk is virtually opposite to that indicated by Newcombe's data on childhood deaths due to all causes (*25*). Risk of death from all causes in childhood increased with advancing birth order and decreased with advancing maternal age until age 34. After maternal age 34, risk of death from all causes rose slightly with advancing maternal age. The degree of contrast in the maternal-age and birth-order effects on risk of leukemia and risk of death from all causes suggests these variables may be closely associated with the etiological agents of childhood leukemia. Also, the inverse effect of birth order

on the risk of childhood leukemias appears to be unique among the more common childhood cancers (*1*, *3*).

Mongolism and leukemia.—The probability of leukemia in mongoloids is very high (*26–31*), and both the probability of childhood leukemia and the probability of mongolism increase with advancing maternal age (*1–3*); therefore, it is reasonable to speculate that some factor associated with advancing maternal age is common to the etiology of both mongolism and leukemia. Miller (*32*) has observed that mongolism, leukemia, and the occurrence of miscarriages are all related to advancing maternal age, and all have a high frequency of chromosome abnormalities. These observations and the evidence for the increasing frequency of aneuploidy in lymphocytes of the peripheral blood with advancing age (*33*) give some credence to the notion that both mitosis and meiosis become less precise with increasing age. It therefore seems reasonable to postulate that, as a potential mother becomes older, an increasing number of her gametes become genetically imperfect. Some of these imperfections are lethal; others result in postnatal selective disadvantages in the form of mongolism or a predisposition to childhood leukemia.

Although progressive genetic disorganization offers a plausible explanation of the maternal-age effect in both mongolism and leukemia, the mechanism by which birth order affects leukemia mortality rates, but not the probability of a mongoloid birth, remains to be explained. It is difficult to imagine how the genetic material of children born early in the birth sequence could be less perfectly organized—and, therefore, more likely to lead to leukemia—than in subsequent children. Perhaps the disorganization of genetic material responsible for the association of birth order with risk of leukemia is acquired postnatally. Existing data are compatible with this possibility. MacMahon and Newill (*3*) have shown that in childhood leukemia the birth-order effect increases with increasing age at death due to leukemia. The present data are compatible with the possibility that the birth-order effect is greatest in children over age 10, and a recent study of childhood leukemia in Minnesota (*34*) failed to demonstrate any birth-order effect in children dying of leukemia between ages 0 and 4.

Although postnatal or antenatal factors which vary with ordinal position at birth are numerous, the field is narrowed considerably by the fact that the inverse parity effect on leukemia mortality is not found for any childhood cancer (*1*, *3*) or deaths due to all causes (*25*). Any factors inversely associated with parity and found more frequently in leukemic than nonleukemic children can be considered etiologically important. Examples of conditions which could be inversely associated with advancing parity include the following: 1) number of exposures to diagnostic radiation during gestation, 2) number and extent of exposures to drugs and radiation in early-born children compared to later-born children, 3) frequency of infection and age at infection with the common childhood viruses, and 4) number and extent of drug treatments during gestation. Likewise, inhibitors of potential leukemogenic agents which are positively associated with increasing parity must be considered. For example, higher levels of maternal antibodies in later pregnancies—a result of secondary responses in mothers exposed to infections in their living children—could more effectively protect later-born children from the potentially leukemogenic effects of virus infections acquired in the first 6 months of life.

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