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["... there was a suggested relationship of Mongolism with paternal radar exposure"]

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THE EPIDEMIOLOGICAL STUDY OF MONGOLISM IN BALTIMORE *

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The epidemiological study of mongolism in Baltimore was initiated primarily to determine whether there was a relationship between parental exposure to ionizing radiation and the occurrence of mongolism among offspring. The principal stimuli for this inquiry were the known relationship between ionizing radiation and chromosomal aberrations, the association of leukemia and mongolism, and the leukemogenic effect of radiation. In addition to collecting data for this major objective, information was obtained and analyzed concerning other factors, such as parental age and maternal reproductive patterns, which might be associated with chromosomal aberrations. In this report, we shall summarize the study results [1-3] and briefly describe the procedures of a supplementary investigation undertaken this year and currently in progress.

METHOD

A detailed description of the methods used in the original study has already been reported and will, therefore, be reviewed only briefly here. The names of 421 children with a diagnosis of mongolism were made available from several Baltimore sources. To be eligible for inclusion in the study, the child had to be Caucasian and born in the greater Baltimore area between January 1, 1946, and September 30, 1962. Those who did not meet these requirements were eliminated from the study (51 not born in Baltimore, 38 not Caucasian, 17 too old, 17 whose families could not be located in the city directories, and 8 whose birth certificates could not be located). This left 288 with an initial diagnosis of mongolism. The birth certificates of all the 288 eligible children were then obtained. To select control subjects, the birth certificate of each case was sys-

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tematically matched with another birth certificate on the basis of: (1) hospital of birth, or birth at home, (2) sex, (3) maternal age at the time of birth of the child, and (4) date of birth.

Each eligible child reported to have mongolism was examined by a pediatrician. A set of physical criteria for mongolism was used to determine whether the child should be accepted as a case. Those who did not meet these criteria were eliminated from the study. Of the 288 cases, 18 were excluded because of the absence of diagnostic criteria, and 54 cases were eliminated because of refusal to cooperate, inability to locate the family, or inability to obtain an adequate interview. Consequently, 216 cases were available for the final analysis.

The interviewing of the case and control families was performed by five well-qualified women. Interviewers were not informed which were cases and which were controls; recognition of the family with Down's syndrome did not usually occur until the actual interview was conducted. Questions about radiation exposure were always phrased without reference to the birth of the index child. In addition, medical records—including obstetrical records—were reviewed with regard to reproductive histories and radiation exposure independently of the interview.

Results

Radiation Exposure

A summary of the histories of radiation exposure of the mothers of the cases and controls is presented in Table 1. For mothers with definite "yes" or "no" answers for radiation exposure, 50% of the mothers of mongols reported no radiation as compared to 59.9% of the control mothers—a difference which is statistically significant ($P < .05$). It is clear from this Table that the increased exposure history of mothers of the mongols is mainly a result of fluoroscopic and therapeutic radiation or of combinations of multiple sources of radiation. In contrast to the mothers, the fathers of the mongols did not have significantly greater exposure to radiation than did the control fathers (Table 2). Although a somewhat smaller proportion of fathers of mongols reported no radiation, and a slightly larger proportion had diagnostic radiation as compared to fathers of controls, none of these differences was statistically significant, and there were no differences in the categories in which therapeutic and/or fluoroscopic radiation were included.

In an attempt to determine whether there were any additional differences in exposure to radiation or other energy sources, occupational histories were reviewed: 7.9% of the mothers of mongols, but only 3.3% of the control mothers, had worked in a professional or technical capacity in medical fields ($P < .05$). Eight mongol mothers, in contrast to three control mothers, gave histories of definite x-ray and/or fluoroscopic exposures in all types of occupations, prior to the conception of the index child.

No differences were found in the occupations of the fathers of the mongols and the controls, except for a higher frequency of military service for the fathers of mongol children—63.1%, as compared with 56.6% for control fathers. In addition, a history of radar exposure was obtained from the fathers, which indicated that 8.7% of the fathers of the children with mongolism and 3.3% of

TABLE 1

SUMMARY OF MATERNAL RADIATION EXPOSURE PRIOR TO BIRTH OF INDEX CHILD

Type of Radiation	Mothers of Mongols (%)	Mothers of Controls (%)
No radiation	50.0	59.9
Radiation		
Diagnostic only	24.0	27.1
Fluoroscopic only	4.8	3.4
Therapeutic only	3.3	1.4
Diagnostic and fluoroscopic	6.7	3.9
Diagnostic and therapeutic	3.4	2.9
Fluoroscopic and therapeutic	1.0	0.5
Diagnostic, fluoroscopic, and therapeutic	6.3	0.9
Unknown	3.7	4.2

the control fathers had had contact with radar, both in and outside of the armed forces—a difference which is of borderline statistical significance ($P < .02$).

Two measures of the degree of relationship between maternal radiation exposures and mongolism were computed from the data. TABLE 3 shows that the estimated relative risk is 1.5, that is, mothers exposed to radiation had a 50% greater chance of having an offspring afflicted with Down's syndrome. From this relative risk, it was also possible to determine the attributable risk, that is, the estimated proportion of mongols in the population associated with maternal radiation exposure, using the method proposed by Levin;[4] this was computed to be 17%. It should be understood that this percentage reflects not only the relative risk but also the frequency of radiation exposure in the general population and will, therefore, differ in various population groups.

TABLE 2

SUMMARY OF PATERNAL RADIATION EXPOSURE PRIOR TO BIRTH OF INDEX CHILD

Type of Radiation	Fathers of Mongols (%)	Fathers of Controls (%)
No radiation	43.7	50.0
Radiation		
Diagnostic only	31.5	25.5
Fluoroscopic only	5.6	5.4
Therapeutic only	2.0	1.9
Diagnostic and fluoroscopic	8.6	10.3
Diagnostic and therapeutic	5.6	4.9
Fluoroscopic and therapeutic	1.0	1.0
Diagnostic, fluoroscopic, and therapeutic	2.0	1.0
Unknown	8.8	5.6

Reproductive and Menstrual History

An analysis of the lifetime reproductive histories showed striking similarities in menstrual history, fertility experience, and pregnancy wastage in mothers of both the cases and controls.[6] No significant differences were noted in the number of pregnancies, abortions, or stillbirths, before or after the birth of the index child. No statistically significant differences were observed with regard to the pregnancy order or birth order of the index child, interval of time between the preceding pregnancy and birth of the index child, or from the latter to subsequent births. Moreover, the frequency of neonatal deaths and childhood deaths among siblings of the mongoloid children was similar to those among the controls.

TABLE 3

COMPUTATION OF RELATIVE RISKS FOR MATERNAL RADIATION EXPOSURE *

Maternal Radiation History	Mothers of Mongols	Mothers of Controls
No radiation	104	124
Radiation	104	83
	208	207

* Estimated relative risk $= \frac{124 \times 104}{83 \times 104} = 1.5$

Marital History

A significantly greater number of multiple marriages before the birth of the index child was recorded for the mothers of the mongols. There were 16.2% of mothers of affected children who were married two or more times, as compared to only 6.9% of mothers of controls. Of the multiple marriages, 6 in the case group and 5 in the control group had remarried because of the death of the previous spouse; however, 28 marriages in the case group had ended in annulment or divorce as compared to only 9 in the control group.

Because of the higher frequency of radiataion exposure among mothers of mongols, it was considered desirable to determine whether multiple marriages were also associated with radiation exposure. Perhaps, the higher frequency of multiple marriages among mothers of mongols is merely a reflection of a higher frequency of radiation exposure among those who have had multiple marriages. However, an analysis indicated that these two were independently related to mongolism (TABLE 4). Among mothers who had not been irradiated, 14.4% of mothers of mongols but only 5.6% of control mothers had multiple marriages ($P < .05$).

Other Factors

The cases and controls were compared with regard to several other variables, including residential history,[2] religion,[3] and educational background.[3] No statistically significant differences between the two groups were observed in these factors.

Maternal and Paternal Ages

The relationship of mongolism to maternal age has been well substantiated, and did not require any additional confirmation in this study. In fact, the controls were matched to the mongol children by maternal age, thereby eliminating the possibility of analyzing these pairs for a maternal age effect.

We were, however, interested in the possibility of a paternal age effect, since there was a suggestion from some recent studies that such an effect might exist, and we were also not satisfied that earlier studies had completely excluded such a possibility.[5–7] The difficulty in analyzing data for a paternal age effect stems from the high correlation of paternal with maternal ages. The approach in the present study, however, permitted the examination of the effects of maternal and paternal ages independently, in a separate analysis.

TABLE 4

FREQUENCY OF MULTIPLE MARRIAGES AMONG STUDY MOTHERS WITH KNOWN MARITAL AND RADIATION HISTORIES

	Mothers of			
	Mongols		Controls	
Radiation History	Total	Multiple Marriages (%)	Total	Multiple Marriages (%)
No reported history of radiation	104	14.4	124	5.6
Reported history of radiation	104	18.3	83	9.6
Reported history of fluoroscopic and/or therapeutic radiation	54	18.5	27	11.1

In this study, the matching of the birth certificate of each mongol with that of a subsequent birth with respect to maternal age, permitted us to determine whether there were differences with respect to paternal age distributions. Then a different series of controls was obtained by selecting another set of birth certificates matched to the certificates of the mongol cases with respect to paternal age to determine whether there were differences in maternal age distributions.

The results of this analysis clearly indicated the presence of a maternal age effect but no paternal age effect. TABLE 5 shows the maternal age effect with paternal age controlled. Note that in every paternal age group except the youngest, the mothers of the mongols were older than those of the controls, the

TABLE 5

MATCHED PAIR ANALYSIS OF MATERNAL AGE WITH PATERNAL AGE CONTROLLED (PAIRED t TEST)

Paternal Age Group	No. of Mothers	Mean Differences *	t	P
20–24	22	−0.09	0.14	NS
25–29	40	+0.73	1.03	NS
30–34	41	+3.4	3.09	<.01
35–39	53	+2.3	6.28	<.001
40–44	39	+4.9	6.20	<.001
45+	20	+0.8	0.53	NS
All cases	215	2.3	6.05	<.001

* Mongol maternal age minus control maternal age.

mean differences attaining statistical significance in the older age groups, 30–45 years. The group over 45 years of age is not significant, probably because of its small size, although the difference is in the same direction. When all age groups are pooled, the maternal age difference is statistically significant at the .001 level.

On the other hand, as shown in TABLE 6, when paternal age was examined with maternal age controlled, there were no significant differences, except for one maternal age group (30–34 years) in which the fathers of mongols were younger than the fathers of controls. Thus, no consistent age pattern is discernible in the fathers. Naturally, in such a study, the number of cases imposes limitations with regard to the detection of a small effect. It would appear, however, that the absence of a significant finding with regard to paternal age probably eliminates at least a moderate effect of paternal age. The detection of a smaller paternal age effect would require a larger series of cases.

TABLE 6

MATCHED PAIR ANALYSIS OF PATERNAL AGE WITH MATERNAL AGE CONTROLLED (PAIRED t TEST)

Maternal Age Group	No. of Fathers	Mean Difference *	t	P
15–19	6	0	0	NS
20–24	34	0	0	NS
25–29	30	−0.07	0.07	NS
30–34	46	−3.07	3.79	<.001
35–39	62	+0.45	0.66	NS
40+	37	+1.1	1.05	NS
All cases	215	−0.34	0.79	NS

* Mongol paternal age minus control paternal age.

Discussion

The results of this study indicate that the mothers of mongol children received significantly more radiation, particularly fluoroscopy and therapeutic radiation, than the mothers of control children. In fact, for combined radiation from one or more diagnostic, fluoroscopic and therapeutic sources, the frequency of mothers of mongol children that had such procedures was seven times that of control mothers. Of additional interest was the observation that significantly more mothers of mongols were employed in professional or technical occupations in the medical field. The consistency of these relationships is notable.

The only other two associations that appeared in the analysis were the well-documented association of mongolism with maternal age, and the higher frequency of multiple marriages among the mothers of the mongol children as compared to the controls. Although broken marriages might be expected following the birth of a defective child, they are not as easily explained when they occur before the birth. It is quite possible, however, that in a study in which a great many factors are examined, one or more chance associations will appear. Whether this multiple marriage association is a chance finding remains to be determined. With respect to pregnancy wastage, fertility, and menstrual irregularities, the mothers of the mongol children did not differ from the control mothers nor did they show a higher frequency of other offspring with congenital abnormalities.

The radiation history of the fathers provided a contrast to that of the mothers. There was a marked similarity in the history of radiation exposure reported by the fathers of mongols and of the controls, except for the suggested relationship between mongolism and paternal radar exposure. Although, with the small numbers available, it is possible that this finding may be a chance observation, it clearly appears worthy of additional investigation, especially since recent studies have also indicated that a small amount of ionizing radiation may be involved in high voltage radar equipment.

In view of the need to confirm the positive findings, the original study was extended, beginning in June 1969, to include additional mongol children born from October 1962 through December 1968. We estimate that it will be possible to obtain an additional 140 cases. The procedures for control selection and interviewing in the current study are essentially the same. However, two features are being added: a validation of military service history and a chromosome study.

All of the names of the fathers of the cases and controls will be checked against armed forces records to determine whether they, in fact, had been in military service and the branch of service. Moreover, information will be obtained on the MOS (Military Occupation Specialty) classification of fathers and, insofar as is discernible from records, whether they worked with radar or at a radar installation.

The chromosome studies are being carried out on all fathers who reported a history of radar exposure in the original series as well as on those reporting such exposure in the current series, in order to determine whether any aberrations (such as aneuploidy, translocations, dicentrics or other aberrations or evidence of breaks) are observed. For a comparison group, the chromosomes of unexposed fathers of the children matched to the exposed fathers are also being studied. As a result of these additions, both series together will probably yield

60–70 radar-exposed fathers, so that a total of approximately 120 chromosome analyses will be performed.

Thus, the investigation in progress not only will serve as an independent replication of the earlier study but will also allow validation of the military service histories as well as explore possible chromosomal changes. Hopefully, the current phase will be completed by the end of 1970.

Summary

An epidemiological study encompassing a population of parents of mongols and matched control children born in Baltimore, Maryland 1946–1962 confirmed the well-documented association of mongolism with older mothers and indicated that the mothers of mongols had been exposed to significantly more radiation, particularly fluoroscopy and therapeutic radiation, than the mothers of control children. Another association, the higher frequency of multiple marriages among the mothers of the mongol children, as compared to the controls (independent of the radiation association), is difficult to interpret and may be a chance finding.

Although there were striking similarities in the diagnostic and therapeutic radiation histories of fathers of mongols and controls, there was a suggested relationship of mongolism with paternal radar exposure.

In order to confirm the findings, an extension of the investigation to include mongols born October 1962 through December 1968 was initiated last June. The current study is an independent replication of the previous study with two added features: (1) a validation of military service and radar exposure, and (2) a chromosome study of radar-exposed fathers and unexposed fathers of matched controls.

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