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RADIATION-EXPOSURE IN PARENTS OF CHILDREN WITH MONGOLISM (DOWN'S SYNDROME)[1,2]

ARNOLD T. SIGLER,[3] ABRAHAM M. LILIENFELD,[4] BERNICE H. COHEN,[4] AND JEANNETTE E. WESTLAKE

Department of Chronic Diseases, The Johns Hopkins University School of Public Health, and Department of Pediatrics, Harriet Lane Home, Childrens Medical and Surgical Center, The Johns Hopkins University School of Medicine

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With the discovery that the majority of individuals with Mongolism are trisomic for chromosome 21, attention has been focused on the time period prior to conception and on gametogenesis in search of an explanation for the error of non-disjunction.

Because of the known relationship between ionizing radiation and chromosomal aberrations including non-disjunction in Drosophila, laboratory animals and man (1–11), the association of leukemia and Mongolism (12–14), and the widely accepted leukemogenic effect of radiation (15–21), a significant link between ionizing radiation and Mongolism was considered a reasonable possibility.

The recent cytogenetic and epidemiologic observations stimulated the present study of the possible relationships between Mongolism and ionizing radiation prior to or around the time of conception. As part of an epidemiologic investigation utilizing interview technique and medical record analysis, a group of mothers and fathers of children with Mongolism and control subjects were evaluated for exposure to various types of radiation.

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[3] Part of this study performed while Dr. Sigler was assigned to the Research Branch, Division of Radiological Health, U.S.P.H.S.

Address: Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

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MATERIALS AND METHODS

A. *Selection of Cases*

The names of children with a diagnosis of Mongolism were made available by the Maryland State Training School, special Baltimore private, county, parochial and public schools, Baltimore hospitals and private physicians. For the parents of a child to be eligible for interview, the child must have been 1) of Caucasian race, and 2) born in greater Baltimore after January 1, 1946 and prior to October 1, 1962. These criteria were imposed to limit the recall period to more recent events and to facilitate the location of hospital records. Although no attempt was made to ascertain every Mongol born during this period, 419 cases were collected. After eliminating those who did not meet the study requirements, 288 cases of Mongolism (not yet verified by physical examination) were initially available for study. Of the cases eliminated, 17 could not be located in the city directories; 51 were definitely not born in Baltimore; birth certificates could not be found for eight; 38 cases were not Caucasian; and 17 were too old for the study.

B. *Selection of Controls*

The birth certificates of the children with Mongolism were first located and their place of birth and other vital information verified. Controls were then selected by matching, in a systematic manner, each case with another birth certificate for 1) hospital of birth (or at home), 2) sex, 3) date of birth, and 4) maternal age at time of birth of the child.

All 288 cases (100 per cent) were matched with controls of identical sex, race, and hospital of birth (or home). The general results of the matching of maternal age and date of birth are shown in Table I. Because of reasons to be discussed below, a certain number of cases were eliminated from the study, and thus fewer than the original 288 cases were ultimately used in the final analysis.

C. *Contact and Interview of Parents*

After each family was located, a form letter describing the study as an "investigation" of parental and child health factors was mailed. The same letter was sent to both the Mongol and control families, and no mention was made of Mongolism in this communication. The mother and father were then interviewed, usually independently, in the home. The approach to both the families of the Mongols and controls was uniform; the interviewers were not informed which were cases and controls, and recognition

TABLE I

Summary of Matching between Mongols and Controls

Maternal Age Groups	No. of Mongols	Controls Matched By:							
		Same Birth Dates* & Maternal Age†		Same Birth Date, Dif. Maternal Age		Same Mat. Age Dif. Birth Date		Dif. Mat. Age & Birth Date	
		No.	%	No.	%	No.	%	No.	%
19 or less	9	9	100.0	—	—	—	—	—	—
20–24	47	43	91.5	1	5.0	3	6.4	—	—
25–29	40	36	90.0	2	3.3	2	5.0	—	—
30–34	60	55	91.7	2	2.4	3	5.0	—	—
35–39	82	78	95.2	2	4.3	2	2.4	—	—
40–44	46	23	50.0	19	41.3	2	4.3	2	4.4
45 or more	4	—	—	3	75.0	—	—	1	25.0
Total	288	244	84.7	29	10.1	12	4.2	3	1.0

* Same case birth date—within 6 months.
† Same maternal age—within 1 year.

of the Mongol's family was not usually made until the actual interview was conducted.

Out of the 288 cases and 288 controls initially selected for study, interviews were obtained on 87.5 per cent of the mothers and 85.8 per cent of the fathers of the Mongols and on 86.1 per cent and 85.4 per cent of the matched control mothers and fathers respectively. In every case where a family refused to cooperate, the corresponding matched case or control was also eliminated from analysis. There were only minor differences in success of interviewing both groups. Only 5.5 per cent of mothers of Mongols and 7.6 per cent of the control mothers refused to cooperate, while 5.9 per cent of the Mongol fathers and 7.6 per cent of the control fathers also refused.

D. *Method of Questioning*

Questions about radiation exposure were always phrased without reference to the birth of the index child. For instance, "Have you, anytime during your life, had x-rays or radiation for gallbladder disease? If so give the dates and places where this occurred." Only later, during the analysis, were these radiation occurrences enumerated and placed in the time period either prior to or following the birth of the Mongol or control.

E. *Medical Records*

A simultaneous study of several characteristics of the parents was carried out by examining hospital records. A list of every parental name in the study, both married and maiden, was submitted to every hospital in the city of Baltimore. This was performed independently and irrespective of the information obtained on interview. If a record of attendance at the hospital was available, the chart was reviewed in entirety for 1) medical diagnosis during both in and out-patient visits, 2) surgical diagnoses and procedures and 3) x-ray or other radiation exposures.

F. *Verification of Diagnosis*

A set of physical criteria for Mongolism based on the most consistently observed findings, as previously reported (22, 23) was established. These "primary" criteria included brachycephaly, slanted palpebral fissues, epicanthic folds, palmar simian lines, malformed ears, broad &/or short neck, malformed fingers &/or hands, nasal abnormality, hypertelorism, abnormal palate, Brushfield spots, and broad &/or short trunk. Each available case of Mongolism was examined by the senior author (A.T.S.).

The diagnosis and inclusion of a child into the study was confirmed if (A) on personal inspection the child appeared mentally retarded and had at least six of the primary signs; or (B) the diagnostic criteria (at least seven in number) were actually listed by a qualified observer on a medical record. The statement on a chart that "this child is a Mongol" did not satisfy the criteria.

On the basis of the study criteria, the diagnosis of Mongolism was verified in 236 or 92.8 per cent of the cases. Of these, 155 diagnoses were based on physical examination alone, 55 on both personal examination plus hospital records and 26 from hospital records alone. Nine cases, or 3.6 per cent, most of whom were deceased, were eliminated because their available medical records did not list the required number of signs to confirm the diagnosis. Another 3.5 per cent were rejected on personal examination because of negative or equivocal diagnosis. The total number of cases is in excess of the 216 Mongols (all verified) ultimately accepted since some cases were later eliminated for other reasons.

G. *Composition of Final Study Group*

Although 288 cases were originally available for study, 72 of these were eliminated for the reasons listed below, leaving 216 Mongol families and matched control families for the final analysis.

Conditionally Accepted to Study:	288
Eliminated because of:	
Incorrect or equivocal diagnosis:	18
Mongol's parents refused to cooperate:	17
Unable to locate Mongol's family:	15
Mongol's family unable to give adequate interview:	2
Control refused to cooperate:	20
Accepted for Final Analysis:	216

RESULTS

I. *Residential History*

It was essential to study residential history to 1) evaluate possible differences in background radiation exposure, 2) rule out differences in medical exposure based on geographical proximity to medical facilities, and 3) insure that the risk of being irradiated in a Baltimore hospital was not affected by differences in the duration of residence in Baltimore.

Sixty-one and one-tenth per cent[5] of the mothers of Mongols and 57.9 per cent of the control mothers were born in Metropolitan Baltimore; 54.6 per cent of both the Mongol and control fathers were born in Baltimore ($\chi^2 = 1.54$, not statistically significant). In addition, there were no other significant differences in areas of birth—either within or outside the United States.

The length of time spent in Baltimore prior to the birth of the index child was very similar for both groups of parents and is summarized in Table II. Mongol and control mothers numbering respectively, 56.5 per cent and 57.0 per cent and 50.5 per cent and 53.7 per cent of the Mongol and control fathers had spent their entire lives in Metropolitan Baltimore, either starting from birth or prior to age 15. There were no significant differences, for residential history between the cases and controls. Furthermore, there were no significant differences in the total number of years spent in other major areas of the United States prior to the birth of the index child.

Analysis of the type of parental residence during the five years prior to the index child's birth demonstrated that there was no concentration of parents either in the rural or urban areas during this period. Ninety-three and one-half per cent of the Mongol mothers and 92.1 per cent of the control mothers lived in cities during this time period, while 89.7 per cent of the Mongol fathers, and 89.0 per cent of the control fathers were in this same category.

There were also no important differences in the kind of construction materials present in the parental dwellings during this period. Brick, stone, wood or combination type dwellings were reported with similar frequency.

II. *Hospitalization History*

Since a separate evaluation was made of radiation exposure occurring only in Baltimore hospitals, it was essential to determine whether differences existed in the frequency of hospital attendance. Sixty-one and one-

[5] All percentage distributions are calculated on the basis of total known positive or negative responses, after "Unknowns" have been subtracted.

TABLE II

Residential History in Baltimore Prior to Birth of Index Child

Type of Residence	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
Lifetime residence since birth	106	49.1	98	45.4	101	46.8	105	48.6
Lifetime residence since 15 yrs. or younger	16	7.4	25	11.6	8	3.7	11	5.1
Not lifetime residence	93	43.0	91	42.1	99	45.8	97	44.9
Total reported	215	99.5	214	99.1	208	96.3	213	98.6
Unknown	1	.5	2	.9	8	3.7	3	1.4
Total	216		216		216		216	

half and 62.8 per cent of the Mongol and control mothers plus 30.3 per cent and 30.8 per cent of the Mongol and control fathers respectively, reported that all their hospitalizations had occurred in Baltimore. Thirty-five and seven tenths per cent and 34.9 per cent of the Mongol and control mothers and 21.6 per cent and 22.9 per cent of the Mongol and control fathers respectively reported hospitalizations to have occurred either in Baltimore or outside of the city. A larger number of hospitalizations outside the city were reported by the fathers, mainly due to illnesses which occurred during military service.

Because the hospital records were searched independently and irrespective of the data acquired on interview, the assessment of the accuracy of the reporting and the success of locating medical records was not available until completion of the study. Analysis then revealed no significant differences between the Mongol and control parents with respect to either the over or under-reporting of hospitalizations (Table III). The medical hospitalizations were reported with most accuracy and as a relative measure, hospitalizations for tonsillectomy and/or adenoidectomy were reported with least reliability. The accuracy of reporting, therefore, was much greater among mothers than fathers, but case and control parents were practically identical. A total of 24 hospitalizations were found on medical records that were not reported by Mongol mothers as compared to 15 for control mothers. Similarly, the Mongol fathers failed to report nine hospitalizations and the controls seven.

III. *Radiation Exposure—Place of Occurrence*

Distribution of the parents according to the source of the radiation exposures reported on interview are shown in Table IV. There was, again,

TABLE III

Summary of Baltimore Hospitalizations Reported on Interview and Per Cent Verified as Correct on Hospital Records

Maternal or Paternal Age at Interview	Number of Hospitalizations											
	Mothers						Fathers					
	Interview		Verified on Hosp. Records				Interview		Verified on Hosp. Records			
	Mong.	Control	Mongol		Control		Mong.	Control	Mongol		Control	
	No.	No.	No.	%	No.	%	No.	No.	No.	%	No.	%
20-24	5	8	5	100.0	8	100.0	1	—	—	—	—	—
25-29	31	33	23	74.2	25	75.8	3	2	3	100.0	1	50.0
30-34	90	86	82	91.1	70	81.4	24	9	7	29.2	6	66.7
35-39	116	78	95	81.9	63	80.8	31	28	14	45.2	17	60.7
40-44	138	146	95	68.8	113	77.4	27	27	16	59.3	13	48.1
45-49	208	222	168	80.8	168	75.7	27	26	13	48.1	14	53.8
50-54	91	101	73	80.2	57	56.4	20	28	12	60.0	14	50.0
55 or more	39	21	23	59.0	16	76.2	20	21	11	55.0	8	38.1
Deceased	10	—	4	40.0	—	—	2	4	3	150.0	5	125.0
No interview	—	—	2	—	—	—	—	—	—	—	—	—
Total	728	695	570	78.3	520	74.8	155	145	79	51.0	78	53.8

TABLE IV

History of Lifetime Radiation Exposure—Place of Occurrence Taken from Interview

Place of Total Exposure	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
All in Balto. hospitals	47	23.9	45	22.2	23	12.8	26	13.3
Balto. hosps. plus Balto. private physicians	28	14.2	36	17.7	31	17.3	32	16.3
All from Balto. private physicians	40	20.3	35	17.2	23	12.8	35	17.9
All in Balto. and outside hospitals	4	2.0	2	1.0	13	7.3	13	6.6
All in outside hospitals*	7	3.6	9	4.4	25	14.0	28	14.3
Other combinations	9	4.5	7	3.5	19	10.7	19	9.7
Total exposed	135		134		134		153	
No exposure reported	62	31.5	69	34.0	45	25.1	43	21.9
Total known	197		203		179		196	
Unknown	19	8.8	13	6.0	37	17.1	20	9.3
Total	216		216		216		216	

* Outside of Baltimore City.

great similarity between the Mongol and control parents with respect to the number of parents reporting that all radiation exposures occurred in Baltimore hospitals. Because of the magnitude of the task, there was no independent study or verification of sources other than the Baltimore hospitals, and analysis in these cases was confined to the interview data.

IV. *Description of Radiation Exposure*

The history of irradiation as summarized from the interview and medical records is divided into the following categories: 1) diagnostic radiation excluding fluoroscopy, 2) fluoroscopic exposure, 3) radiation for therapy and 4) occupational contact.

The medical radiation data include the exposures from contact with physicians of medicine only and do not include irradiation from dentists, other types of physicians, or from use of shoe fitting apparatus.

Since analysis of hospital records was limited to Baltimore hospitals, the total exposures reported on interview for each kind of radiation is considerably more, for each group, than was found in the medical records alone. (Most of the total radiation exposure occurred at places other than the Baltimore hospitals).

A. *Diagnostic Radiation*

A summary of the total x-ray exposure for diagnostic purposes prior to the index case birth (excluding fluoroscopy) is shown in Table V. The data, as shown, include the total number of individual sessions at which diagnostic x-rays were taken rather than the actual number of x-ray films exposed; the precise number of exposures per session was impossible to estimate in a retrospective study, but the total number of sessions reported is assumed to represent at least one x-ray film exposure. The number of occasions x-rays were taken prior to the birth of the index child was totaled separately from both the interview and hospital records. There was a slight excess of total exposures for the Mongol mothers recorded at interview and also independently, from hospital records. However, in neither case is the difference statistically significant ($\chi^2 = 1.54$ and $\chi^2 = .88$ respectively). In addition, the total diagnostic exposure for the Mongol and control fathers is practically identical and, again, there is close agreement between the interview and medical records. It should be understood, as already explained, that only a portion of the diagnostic radiation exposure occurred at Baltimore hospitals. Therefore, the diagnostic radiation exposure is considerably less than that reported on interview and must be considered as a similar, but separate measure of exposure.

The total diagnostic exposure (excluding fluoroscopy) was further ana-

TABLE V

Total Number of X-rays or Other Radiation for Diagnosis Prior to Birth of the Index Child

(Excluding Fluoroscopy)

No. Times	Interview Data								Hospital Records							
	Mothers				Fathers				Mothers				Fathers			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	45	22.0	40	19.3	38	20.1	32	15.7	31	14.4	22	10.2	12	5.7	14	6.5
2	12	5.9	15	7.3	16	8.5	17	8.3	12	5.6	11	5.0	9	4.3	8	3.7
3	10	4.9	5	2.4	8	4.2	10	4.9	3	1.4	2	.9	4	1.9	7	3.3
4	5	2.5	1	.5	6	3.2	8	3.9	2	.9	5	2.3	4	1.9	3	1.4
5 or more	5	2.5	5	2.4	14	7.4	14	6.9	5	2.3	5	2.4	3	1.4	2	.9
Total positive	77		66		82		81		53		45		32		34	
None reported	127	62.2	141	68.1	107	56.6	123	60.3	162	75.4	171	79.2	179	84.8	181	84.2
Total known	204		207		189		204		215		216		211		215	
Unknown	12	5.6	9	4.2	27	12.5	12	5.6	1	.5	—	—	5	2.3	1	.5
Total	216		216		216		216		216		216		216		216	

Fathers $\chi^2 = 1.54$, $P = >.20$ 1 D.F. Mothers $\chi^2 = .88$ $P > .30$ 1 D.F.

lyzed according to the type of the x-ray procedure. The results of parental exposure from abdominal and/or pelvic x-rays are shown in Table VI. There was a greater amount of abdominal and/or pelvic exposures reported on interview for both the mothers and the fathers of Mongols as compared with control parents. However, the differences cannot be considered as significant ($P \cong .10$). Because analysis of the total diagnostic exposures revealed little difference between the cases and controls with respect to multiple exposure episodes, statistical evaluation of the remaining types was based on the total of one or more exposure episodes. Table VII summarizes the results of enumeration of each type of exposure with the χ^2 value based on the total of one or more episodes prior to the birth of the index child. Where the difference was very small, no χ^2 value was calculated. Because of both the scarcity of positive results and the failure to reach higher probability levels, the results in this category of exposure cannot be considered to be beyond the limits of chance.

In all cases, the exposures were spread over a period of one to 20 years without any concentration in the years immediately preceding the birth. In addition, the number of exposures tended to increase with parental age, but there were no major differences between the two groups.

Diagnostic x-ray exposure following the birth of the index child was also studied, using only the interview data. There was no difference in the total number of exposure-episodes for either mothers or fathers. There were also no significant differences found when the total exposure following the index child's birth was broken down by individual kinds of x-rays.

B. *Fluoroscopic Exposure*

The total maternal fluoroscopic exposures reported on interview are summarized in Table VIII and tabulated according to the number of sessions and maternal age at the time of birth of the child; 17.7 per cent of the Mongol mothers had one or more fluoroscopic examinations prior to birth of the index case, as compared to only 8.1 per cent of the controls. This difference is significant at less than the 1 per cent level ($\chi^2 = 8.25$, $P < .01$). As expected, the number of exposures increased with advancing maternal age. However, even though the mothers were matched for maternal age, 58.3 per cent of the Mongol mothers reporting fluoroscopy were over 35 years at the time of the case birth, as compared to 43.8 per cent of the control mothers.

The body area exposed during fluoroscopy as related by the mothers is shown in Table IX. The larger amount of fluoroscopy in the Mongol mothers results from the combined increase of chest, abdominal and "other types" of exposure. The number of Mongol mothers reporting ex-

TABLE VI

Total Diagnostic Abdominal and/or Pelvic X-rays Prior to Birth of Index Child

No. of Instances	Mothers								Fathers							
	Interview				Hospital Records				Interview				Hospital Records			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	28	13.2	20	9.4	23	10.6	16	7.4	9	4.4	6	2.8	4	1.9	5	2.3
2	4	1.9	2	.9	1	.5	3	1.4	4	2.0	1	.5	1	.5	2	.9
3 or more	3	1.4	1	.5	1	.5	2	.9	1	.5	—	—	—	—	1	.5
Total positive	35		23		25		21		14		7		5		8	
None reported	177	83.5	190	89.2	191	88.4	195	90.3	190	93.1	206	96.7	206	97.6	208	96.3
Total known	212		213		216		216		204		213		211		216	
Unknown	4	1.9	3	1.4	—	—	—	—	12	5.5	3	1.4	5	2.3	—	—
Total	216		216		216		216		216		216		216		216	
	$\chi^2 = 2.91$ $P > .05$ (Interview)				$\chi^2 = .38$ $P > .50$ (Hospital Records)				$\chi^2 = 2.76$ $P > .05$ (Interview)				$\chi^2 = .65$ $P > .30$ (Hospital Records)			

TABLE VII

Summary of Diagnostic X-ray Exposure Prior to Birth of Index Child
(Fluoroscopy Excluded)

Type of Diagnostic X-ray	Mothers				Fathers			
	Interview		Hospital Records		Interview		Hospital Records	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Chest X-ray	N.D.*		.82	>.30	N.D.		N.D.	
Gallbladder series	.225	>.50	N.D.		N.D.		5.12	<.05
Kidney, including I.V.P.	N.D.		N.D.		.50	>.30	N.D.	
Abdominal, including G.I. series	N.D.		N.D.		1.18	>.20	N.D.	
Head	N.D.		N.D.		.69	>.30	N.D.	
Spine	−4.81	<.05	N.D.		N.D.		1.36	>.20
Arm &/or leg	.40	>.50	3.88	<.05	.82	>.30	−1.46	>.20
Other organs	N.D.		N.D.		N.D.		N.D.	

Note: (−) (Minus sign) = greater exposure for controls.
* N.D. = No Difference.

TABLE VIII

Total Interview Data for Maternal Fluoroscopic Exposure Prior to Birth of the Index Child by Maternal Age at Birth of IC and Number of Fluoroscopic Sessions

Maternal Age at IC Birth	Number of Sessions													
	Mongols							Controls						
	1	2 or more	Total Positive	None Reported	Total Known	Unk.	Total	1	2 or more	Total Positive	None Reported	Total Known	Unk.	Total
19 or less	—	—	—	6	6	—	6	—	—	—	6	6	—	6
20–24	3	—	3	28	31	3	34	2	1	3	29	32	1	33
25–29	3	—	3	26	29	1	30	1	—	1	29	30	2	32
30–34	9	—	9	34	43	4	47	5	—	5	38	43	5	48
35–39	13	1	14	45	59	4	63	3	2	5	50	55	7	62
40–44	3	3	6	27	33	1	34	2	—	2	30	32	3	35
45 or more	1	—	1	1	2	—	2	—	—	—	—	—	—	—
Total	32	4	36	167	203	13	216	13	3	16	182	198	18	216
% of known	15.8	1.9	17.7	82.3		6.0		6.6	1.5	8.1	91.9		8.3	

$x^2 = 8.25$, $P = <.01$.

posure of the chest or abdomen is almost twice that of the controls. (Chest $\chi^2 = 2.56$, Abdomen $\chi^2 = 2.25$, Other $\chi^2 = 2.69$.)

Because only a small amount of the total radiation exposure occurred in the Baltimore hospitals (the majority from private physicians and other sources), the number of fluoroscopic episodes in these hospitals was very

TABLE IX

Interview Data for Fluoroscopic Exposure Prior to Birth of Index Child by Type and Number of Sessions

Number of Sessions	Mothers											
	Mongols						Controls					
	Chest		Abdomen		Other		Chest		Abdomen		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	20	9.8	13	6.3	6	2.9	8	4.0	7	3.5	2	1.0
2 or more	1	.5	1	.5	1	.5	4	2.0	—	—	—	—
Total positive	21		14		7		12		7		2	
None reported	183	89.7	191	93.2	198	96.6	188	94.0	193	96.5	198	99.0
Total known	204		205		205		200		200		200	
Unknown	12	5.6	11	5.1	11	5.1	16	7.4	16	7.4	16	7.4
Total	216		216		216		216		216		216	

small, and not amenable to statistical analysis. However, the discovery of the small number of exposures after searching the hospital records was verification for the small number of Baltimore hospital exposures reported by the mothers on interview. From medical records, there were reports of only one Mongol and three control mothers with a history of bona fide fluoroscopy prior to birth of the index case. Therefore, most of the excess of fluoroscopy in the Mongol mothers can be attributed to sources other than the Baltimore hospitals. In contrast, the control mothers reported more fluoroscopic procedures following the birth of the index child than the Mongol mothers. However the difference was not statistically significant ($\chi^2 = 2.61$, $P > .10$).

The fluoroscopic history of case and control fathers, both prior to and after the birth of the index child, was strikingly similar. On interview, 7.9 per cent and 8.8 per cent of the Mongol fathers reported chest and abdominal fluoroscopic procedures respectively, while 7.8 per cent and 7.9 per cent of the control fathers reported chest and abdominal exposures before the birth of the index case. The number of exposures for fathers found on medical records for the same time period was also very small and not significant.

C. *Therapeutic Radiation*

The data on maternal and paternal therapeutic radiation exposure are presented in Table X. Of the mothers of Mongols, 14.5 per cent reported

TABLE X

Therapeutic Radiation Exposure Prior to Birth of Index Child Interview Data

Number of Parents Having One or More Exposures

Condition or Area	Prior to Index Child								Post Index Child							
	Mothers				Fathers				Mothers				Fathers			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
Skin	19		5		9		7		2		2		3		2	
Warts &/or birth marks	4		2		1		1		2		1		—		1	
Tumors	1		—		2		2		3		2		—		3	
Sinus &/or adenoids	1		1		1		1		—		2		1		—	
Bursitis	2		—		1		2		3		—		3		5	
Arthritis	1		1		—		—		1		2		—		—	
Menstrual or reproductive disorders	—		1		—		—		2		—		—		1	
Thyroid	—		—		—		—		1		1		—		—	
Polycythemia	—		—		—		—		—		—		—		—	
Other	3		1		2		3		1		—		1		2	
Total positive & percent	31	14.5	11	5.1	16	7.8	16	7.5	15	7.0	10	4.7	8	3.8	14	6.5
None reported & percent	183	85.5	203	94.9	190	92.2	198	92.5	199	93.0	205	95.3	200	96.2	200	93.5
Total known	214		214		206		214		214		215		208		214	
Unknown	2	.9	2	.9	10	4.6	2	.9	2	.9	1	.5	8	3.7	2	.9
Total	216		216		216		216		216		216		216		216	

Mothers Prior

$\chi^2 = 10.54,\ P = <.01$

one or more therapeutic exposures as compared to only 5.1 per cent of the control mothers—a three-fold increase. No differences were noted for the fathers. The increased Mongol maternal exposure constitutes a highly significant difference ($\chi^2 = 10.54$, $P < .01$). The major portion of this difference is contributed by the large number of exposures to the skin reported by the Mongol mothers; 8.8 per cent of the Mongol mothers received skin irradiation and only 2.3 per cent of the controls—a difference that is also significant ($\chi^2 = 8.64$, $P < .01$). Of the 19 Mongol mothers who received skin therapy, six were irradiated for acne, two for eczema, five for various other skin conditions, and six for unspecified diseases. Neither acne nor eczema were reported as a reason for skin irradiation by the control mothers. There were also six control mothers who did not specify the kind of disease for which they were irradiated.

No important differences were found in the time relationship of the exposure to the birth of the index child; most of the skin irradiation to the Mongol mothers occurred more than eight years before the birth of the child.

The number of therapeutic exposures listed in the medical records were extremely few and were not useful for analysis.

The Mongol mothers were also found to have a slight, but not significant excess of therapeutic exposures following the birth of the child. The fathers again failed to reveal significant differences for therapeutic exposure.

D. *Occupational Exposure*

The occupational histories of the parents were scrutinized for indications of possible exposure to radiation or other energy sources. Seven and nine-tenths per cent of the Mongol mothers and 3.3 per cent of the control mothers worked in a professional or technical capacity in medical fields. This difference is significant at the 5 per cent level. Mongol mothers numbering 82.4 per cent were employed for more than one year in medical fields. Eight Mongol mothers and three control mothers gave actual histories of x-ray and/or fluoroscopic exposures in all types of occupations prior to the index child.

The experience of the fathers prior to the index case in various occupations was very similar, except for an excess of military service for the fathers of children with Mongolism. There were only four fathers from each group who had been involved in professional or technical work in the medical fields prior to the child.

Because of extensive history of paternal involvement in the armed services, an analysis of military experience was carried out. This revealed that 63.1 per cent of the Mongol fathers as compared to 56.6 per cent of the control fathers had service experience prior to the birth of the index child; the difference is not statistically significant. Eleven and one-half per cent of the Mongol fathers and 7.9 per cent of the control fathers were in military service within two years prior to the conception of the index child. Only two Mongol and two control fathers had military duty following the conception of the index child. One hundred and four Mongol fathers and 100 control fathers had their military experience more than two years prior to the conception of the index child. There was an increased but not statistically significant number of Mongol fathers in the Army during this military service.

There were no important differences in the professional or industrial radiation exposures for the fathers prior to the birth of the index child.

As an additional source of radiation energy, though non-ionizing in nature, a history of radar exposure was elicited from the fathers. A significantly increased amount of radar exposure was obtained from the Mongol fathers. Eighteen, or 8.7 per cent, of the fathers of children with Mongolism and seven, or 3.3 per cent, of the fathers of controls reported intimate contact with radar both in and outside of the armed forces ($\chi^2 = 5.37$, $P \cong .02$). The military radar contact occurred when the father was either a radar technician or radar operator. The increase in military radar exposure in the Mongol fathers is supported by their histories of increased military service.

E. *Summary of Exposure*

A summary tabulation and analysis of the parental diagnostic, therapeutic and fluoroscopic exposure is presented in Table XI. Of those parents with definite "yes" or "no" answers for radiation exposure, 50 per cent of the Mongol mothers reported "no radiation" as compared to 59.9 per cent of the control mothers. This difference is significant ($\chi^2 = 4.13$, $P < .05$). Hospital record analysis revealed that 72.7 per cent of the Mongol mothers had no radiation whatsoever, as compared to 78.2 per cent of the control mothers ($\chi^2 = 1.80$, $P > .10$). As shown in previous tables, the increased exposure of the Mongol mothers, as reported on interview, is mainly a result of fluoroscopic and therapeutic radiation. Thirteen Mongol mothers and only two control mothers reported a combination of one or more each of diagnostic, fluoroscopic and therapeutic exposures—a difference which is significant ($\chi^2 = 8.30$, $P < .01$). The summary of hospital radiation experience again demonstrates the sparse amount of fluoroscopic or therapeutic radiations recorded. However, an increased amount of diagnostic exposure for the Mongol mothers is evident, though not statistically significant ($\chi^2 = 2.86$, $P \cong .10$).

The Mongol fathers also demonstrated a slight total increase of radia-

TABLE XI

Summary of Parental Diagnostic, Fluoroscopic, & Therapeutic Radiation (One or More Exposures) Interview and Medical Records Prior to Birth of the Index Child

Type of Exposure	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
Interview								
No Radiation	104	50.0	124	59.9	86	43.7	102	50.0
Radiation								
Diagnostic only	50	24.0	56	27.1	62	31.5	52	25.5
Fluoroscopic only	10	4.8	7	3.4	11	5.6	11	5.4
Therapeutic only	8	3.3	3	1.4	4	2.0	4	1.9
Diagnostic & fluoroscopic	14	6.7	8	3.9	17	8.6	21	10.3
Diagnostic & therapeutic	7	3.4	6	2.9	11	5.6	10	4.9
Fluoro. & therapeutic	2	1.0	1	.5	2	1.0	2	1.0
Diag., fluoro., & therapeutic	13	6.3	2	.9	4	2.0	2	1.0
Total known	208		207		197		204	
Unknown	8	3.7	9	4.2	19	8.8	12	5.6
Total	216		216		216		216	
Hospital Records								
No radiation	157	72.7	169	78.2	184	85.6	182	84.2
Radiation								
Diagnostic only	59	27.3	44	20.4	31	14.4	31	14.4
Other types	—	—	3	1:4	—	—	3	1.4
Total known	216		216		215		216	
Unknown	—	—	—	—	1	.5	—	—
Total	216		216		216		216	

tion exposure. Of those with a definitive interview response, 43.7 per cent of the Mongol fathers reported "no radiation" as compared to 50.0 per cent of the control fathers. This difference, however, is not significant ($\chi^2 = 1.62$, $P > .20$). The paternal hospital records, in contrast, are strikingly similar for radiation exposure. An almost identical number of both Mongol and control fathers were found to have no radiation exposure whatsoever.

DISCUSSION

The findings of several studies designed to determine the relationship of parental radiation exposure and the occurrence of Mongolism are somewhat contradictory. Uchida and Curtis (24) in 1961, reported a striking relationship between radiation and Mongolism—that 28 per cent of a group of 81 mothers of Mongols were exposed to four or more abdominal x-rays or fluoroscopies prior to the Mongol's birth, as compared to 4 per cent of mothers of cleft lip children and 14 per cent of neighbors. In contrast, Lunn (25) reported no significant difference between the x-ray exposure of the mothers of Mongols and controls; similarly, Carter *et al.* (26) found no differences in the maternal abdominal radiation prior to conception in a study based on interview data, and Schull and Neel (27) reported no association in the data based on offspring of survivors of atomic bomb explosions in Hiroshima and Nagasaki. However, except for the Japanese data which represent a unique type of radiation exposure, each of these studies is concerned primarily with diagnostic radiation experience, or has not separated out diagnostic and other types of radiation. Furthermore, each study has limitations of a methodological nature.

In the present study, attempts were made to eliminate or control those factors which might involve bias in a retrospective study as well as to evaluate various types of maternal and paternal exposure; and there appears to be a definite association between maternal exposure to ionizing radiation and Mongolism. A sample derived from almost all of the cases of Mongolism born in Baltimore between 1946 and 1962 was obtained, and the diagnosis in each case included was verified either by physical examination or on the basis of standardized criteria from reliable medical records. To the Mongols determined eligible for inclusion in the study, controls were matched with regard to sex, race, date of birth, hospital of birth and maternal age at time of birth of the child. On interview an objective questioning procedure was used with equal emphasis on each sibling and pregnancy in each family.

The very close matching of maternal age (the mean age of mothers of Mongols was 32.6 as compared to 32.5 for the control mothers) eliminated the possibility that any greater radiation exposure in the mothers of Mongols might be a function of a greater number of years at risk for these mothers as compared to the mothers of the controls. The absence of any significant paternal age effect in Mongolism, as shown previously, made it unnecessary to correct for paternal age in evaluating the data on the father (28).

A striking similarity between the parents of Mongols and of controls demonstrated from the study of several other variables lends further emphasis to the observed radiation differences. Since both groups of parents spent very similar amounts of time in Baltimore, and other geographical areas, prior to the birth of the index child, differences in proximity to institutions where radiation was easily accessible, could not account for the observations. In addition, the uniformity of residential history tended to eliminate other local environmental factors, including background radiation, from having an important role in the etiology of this condition.

Moreover, the close agreement between the parents of both groups regarding the number of Baltimore hospitalizations reported, tended to exclude the biased recollection of serious illnesses as an explanation for differences in radiation exposure in this study.

By far the best measure of the accuracy of the interview data and the absence of any significant retrospective bias from the Mongol parents clearly came from the actual verification of the hospitalization history. There were no significant differences between the Mongol and control parents with respect to either the over or under-reporting of hospitalizations. In fact, the Mongol parents *forgot* to report more hospitalizations that had actually occurred than did the controls. Even in the older age groups, there was no memory advantage demonstrated for the parents of Mongols, further eliminating any differences in recall, as is sometimes suggested as a source of bias in interview studies.

Finally, there was no evidence of an increased willingness of the parents of the Mongols to cooperate in the study since the refusal rates were very similar in both groups. When a refusal did occur, the matched case or control was always eliminated.

From this preliminary examination to ascertain the validity of the collected data and evaluate any possible bias, it therefore seems reasonable to assume that whatever relationships are observed in this case-control study would not result from any artifact introduced through the sources, selection, completeness or mode of collection of the data.

The tabulated results already described in detail, clearly indicate that the mothers of Mongoloid children received significantly more radiation (in particular, fluoroscopy and therapeutic radiation) than the mothers of the control children. In fact, in the case of combined irradiation from one or more diagnostic, fluoroscopic and therapeutic sources, mothers of Mongols had seven times as many radiographic procedures as the control mothers. This highly significant difference represents an accumulated exposure prior to the index child from various radiation sources. Moreover, significantly fewer mothers of Mongols than mothers of controls failed to receive any radiation prior to the index child.

Because the actual date of conception was impossible to determine, the parents were questioned and medical records searched for the entire period "prior to the *birth* of the index child." However, there was very little radiation exposure reported around the time of conception and practically no exposure during intrauterine life.

The observation that the major maternal radiation exposure occurred over many years prior to the index child's birth is consistent with the views concerning cumulative radiation damage to genetic material. Since, unlike in the male, the full complement of germ cells is present in human females from the time of birth, they are susceptible to repetitive damage either from the same or different environmental sources. The association of Mongolism with advanced maternal age adds credence to this cumulative radiation effect.

Most noteworthy is the fact that the substantially greater exposure to the mothers of Mongols was contributed by those radiation sources expected to provide large doses. Although dosimetry is lacking in this study, a description of the type of exposure is valuable and useful for relative dosages within wide ranges. While there was a greater total diagnostic exposure demonstrated for the mothers of the Mongols, the difference was not statistically significant. The major difference came from fluoroscopic and therapeutic sources. A significantly greater number of fluoroscopic sessions was reported by the Mongol mothers, with fluoroscopies of the abdomen and chest contributing the major excess. The duration of each exposure was impossible to determine, and the number of bona fide fluoroscopic procedures found on the medical records was too small to be useful for comparison.

Therapeutic radiation for a variety of conditions was partly responsible for the greater exposure in the mothers of Mongols, with therapy many years prior to the index child's birth for acne, eczema and other dermatologic conditions contributing heavily to the significant differences between mothers of Mongols and mothers of controls. Again, although no dosimetry was available, it is recognized that therapeutic irradiation—especially from sources used in past years—produces high exposure with scatter over much of the body area.

Of additional interest was the observation that significantly more mothers of Mongols were employed in professional or technical occupations in the medical field prior to the birth of the index child. Although no greater radiation exposure was reported by these mothers, the possibility of inapparent or accidental exposure is likely.

The radiation history of the fathers of the Mongols provides a marked contrast to that of the mothers. There was striking similarity and in some cases almost identical medical radiation exposure reported by the fathers of Mongols and of the controls. Only minor differences were reported for diagnostic, fluoroscopic and therapeutic exposures. Except for more radar exposure to the fathers of Mongols along with more military service where this exposure occurred, there was no evidence for any association between paternal irradiation and Mongolism. Moreover there was no indication of any increased exposure of the fathers of Mongols in the period around the time of conception of the abnormal child. This similarity of the radiation exposure of fathers of Mongols and of controls is also consistent with the failure to demonstrate a correlation between Mongolism and paternal age and provides additional evidence against the presence of any bias in reporting of retrospective data in this study (28).

Ever since the discovery and confirmation of the existence of a chromosomal abnormality in Mongolism (29-33) it has been clear that whatever environmental agents may lead to that chromosomal defect must act on parental germ cells prior to conception or, in rare cases, on zygotes not later than several days after fertilization.

It is well established on the basis of evidence in experimental organisms that radiation can cause non-disjunction (1–5, 34–39) as well as chromosomal breaks leading to various types of aberrations (38–42). In every plant and animal species adequately investigated, ionizing radiation has proven to be mutagenic with no known threshold dose in studies that have carried the total dosage down to 5 r (38–49).

While there are no direct experimental data relating either specifically to the radiosensitivity of human female germ cells in the dictyotene stage or specifically to non-disjunctional events in human females, there now exists not only substantial support from a wide range of other organisms, but also a growing body of data from mammals concerning the various types of damage to germ cells (37, 53-62). Rapidly accumulating data have also demonstrated chromosomal aberrations in the somatic cells of humans following exposure to ionizing radiation. Tough *et al.* (6) reported a 20 per cent increase in the number of circulating leukocytes with 47 chromosomes 24 hours after x-ray treatment of a patient with ankylosing spondylitis. Similarly, extensive observations by Buckton *et al.* (7) on blood cultures from 58 patients with ankylosing spondylitis treated with one course of x-ray therapy to the spine showed chromosomal damage with persistence of some abnormalities up to 20 years after irradiation. Furthermore the frequency of the chromosomal abnormalities increased significantly in subjects irradiated at age 35 or over. Bender and Gooch (8) reported chromosomal abnormalities present in a small group of men after they were irradiated with gamma and fission neutron irradiation.

Chromosomal aberrations have been reported following lower dosage diagnostic radiation. Stewart and Sanderson (9) and Conen *et al.* (10) described the appearance of chromosomal defects in subjects exposed to as little as 0.8 rads. Bloom and Tjio (11) studied the pre and post-abdominal fluoroscopy, or fluoroscopy with cardiac catheterization and reported aberrations in each of five patients exposed to between 12 and 35 r following abdominal fluoroscopy.

It is therefore not only likely but probable that chromosomal abnormalities occur in human germinal tissue exposed to therapeutic and diagnostic levels of radiation. On the basis of known patterns of human gametogenesis, the radiosensitivity of human tissues, and the genetic effects of radiation in experimental animals there appears to be remarkable consistency between the findings of this study and what might be expected biologically.

Increased radiosensitivity may also contribute to the maternal age effect. Evidence from experimental organisms indicates that with increasing age there is increased susceptibility to chromosomal damage from radiation and other agents (36, 38, 63). Even more important have been Russell's recent observations of age associated increased radiosensitivity of oocytes in female mammals (61).

Finally, the only truly puzzling association is the suggested relationship between Mongolism and paternal radar exposure. Recent studies have revealed that radar, a form of microwave energy, can cause tissue damage in humans and laboratory animals (64, 66). In addition, microwave radiation has been reported to have a deleterious effect on rat testis (67).

The increased radar exposure of fathers of Mongols as compared with controls raises the question as to whether ionizing radiation, in addition to the known heating effect, may be involved in radar operations. Since, however, no greater exposure to medical radiation was observed among fathers of Mongols as compared to fathers of controls, radar, under special circumstances, must involve some unique and potent effect that overcomes the male advantage of continuous spermatogenesis. One can only speculate concerning possible mechanisms, but the association between Mongolism and radar exposure deserves further investigation.

The acknowledged association of Mongolism and leukemia (12–14) and radiation and leukemia (15–21) is additional evidence consistent with the hypothesis that radiation is of etiological importance in Mongolism.

The conclusion derived from the present study is that Mongolism is statistically associated with maternal radiation. The likelihood that the radiation association is a causal relationship is considerably enhanced by the evidence—experimental and other kinds—which has already been reviewed. In addition comparisons of several other characteristics, including medical and surgical histories, of the mothers of Mongols and controls did not reveal any differences, except for a higher frequency of divorce among Mongol mothers. These additional results will be reported in detail later. It should therefore be emphasized that although a causal interpretation does not mean that radiation must be implicated in every case, the results do suggest that certain physical energy sources, such as ionizing radiation, are involved in the pathogenesis of some cases of Mongolism.

SUMMARY

As part of an epidemiologic study in Baltimore Maryland, a population of parents of both Mongoloid and control children was evaluated for exposure to various types of ionizing radiation. Utilizing interview technique and medical record analysis, the study demonstrated a statistical association between maternal radiation exposure and Mongolism. The mothers of the Mongoloid children were found to have a significantly increased exposure to both fluoroscopic and therapeutic irradiation prior to the birth of the index child.

In contrast, there were no significant differences in ionizing radiation exposure found in the fathers of the Mongol and control children. However, a surprising increase in radar exposure was discovered in a significant number of fathers of the Mongol cases.

These results suggest that maternal ionizing radiation exposure may be one etiological factor responsible for some cases of Mongolism. It is emphasized, however, that ionizing radiation may be only one of several important factors in the pathogenesis of the condition.

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