Mesothelioma of Childhood

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Malignant mesothelioma (MM) of childhood is a rare but important neoplasm. Eighty children with a previous diagnosis of MM were identified. Four of the 80 children had exposure to known risk factors (two had history of exposure to asbestos, one had received radiation therapy, and one had been exposed *in utero* to isoniazid). Tissue slides were available for independent and joint review by a panel of three pathologists in 22 of the cases. Ten were accepted as MM, nine were reclassified as other malignancies, and three were considered tumors of uncertain nature. Six of the ten children with MM were boys, and four were girls. Eight had pleural tumors, and two had peritoneal tumors. Four died at 7, 8, 18, and 48 months after diagnosis; three remained alive at 19, 20, and 59 months; and three had no follow-up. This review suggests that MM of childhood is a valid entity with a grave prognosis. The tissue diagnosis is difficult and is best made by a panel of pathologists. The available evidence does not support a causal relationship between MM and asbestos, radiation, or isoniazid.

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NUMEROUS REPORTS on the incidence,[1-6] pathogenesis,[7-10] epidemiology,[11-16] asbestos relationship,[17-30] pathology,[31-35] histochemistry,[36-39] electron microscopy,[40,41] treatment,[42-46] and survival[47,48] of adult mesothelioma have been published over the last 30 years. In contrast, there is little information concerning mesothelioma of childhood. With few exceptions[49-51] this information is limited to individual case reports.[52-60] Moreover, a discussion of mesothelioma of childhood in most contemporary textbooks of general pathology,[61] pediatric pathology,[62,63] and clinical pediatrics[64] is restricted to a brief review or a citation of some of the individual case reports. An authoritative text on cancer[65] states only that cases of mesothelioma do occur in children, while a specialized text on lung pathology[66] makes no reference to the subject. Therefore, it is not surprising that controversy exists regarding the origin, nomenclature, and indeed the very existence of childhood mesothelioma.

We evaluated clinical data and tissue slides from published and unpublished cases of childhood mesothelioma in the United States and abroad in an attempt to clarify the nature of this disease in children. A panel of three pathologists independently reviewed all available tissue slides to confirm the histopathologic diagnosis. In addition, the association of childhood mesothelioma with known risk factors, such as exposure to asbestos,[19] radiation,[67] and isoniazid[68] were assessed.

Materials and Methods

Our group consisted of 80 cases, 38 from the United States and 42 from 15 other countries (Austria, Brazil, Canada, Czechoslovakia, Denmark, France, Germany, India, Israel, Italy, Poland, Rumania, Spain, Turkey, and the USSR). The 80 cases were identified in the following manner: (1) review of the medical literature; (2) analysis of data derived from the United States National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program;[69] (3) correspondence with the chairmen of mesothelioma panels in Australia, Belgium, Canada, Denmark, Federal Republic of Germany, France, Ireland, Italy, The Netherlands, Republic of South Africa, Switzerland, United Kingdom, and the USA; (4) data from the Cancer Registry Division of the Texas Department of Health; (5) search of medical records of The Texas Children's Hospital, The Methodist Hospital, and Ben Taub General Hospital, Houston,

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TABLE 1. Information Sources

Location	TDH	SEER	HMP	POG	CTRC	LIT	IND	Total
Pleura	1 (1)*	0 (0)	4 (3)	0 (0)	3 (3)	45 (6)	1 (1)	54 (14)
Peritoneal	0 (0)	3 (0)	0 (0)	2 (2)	1 (1)	14 (4)	0 (0)	20 (7)
Pericardial	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	5 (1)	0 (0)	6 (1)
Total	1 (1)	4 (0)	4 (3)	2 (2)	4 (4)	64 (11)	1 (1)	80 (22)

TDH: Texas Department of Health; SEER: NCI's Surveillance, Epidemiology and End Results Program; HMP: heads of mesothelioma panels abroad; POC: Pediatric Oncology Group and Society for Pediatric Pathology; CTRC: Canadian Tumor Reference Centre; LIT: medical literature; IND: individual contributors.

* Numbers in parenthesis denote slide availability.

Texas; and (6) personal communication with members of the Pediatric Oncology group and the Society for Pediatric Pathology (Table 1).

For our study, only cases arising from the pleura, peritoneum, and pericardium occurring in individuals aged up to 19 years were accepted for consideration. Accordingly, cases of the so-called atrioventricular node mesothelioma[70–77] and cases of mesothelioma of adults, who as children had received radiation therapy for Wilms' tumor, were excluded.[78,79]

Hematoxylin-eosin-stained slides, and in some cases unstained slides and tissue blocks, were available for review in 22 of the 80 cases. The slides were independently reviewed by three examiners without knowledge of the clinical findings. At a later date, the clinical behavior, gross appearance of the tumor, and any other available information such as electron microscopy and histochemistry were made available to these examiners, meeting as a group to rereview the cases. The scoring system used in our study was a modification of that of the European Economic Community International Mesothelioma Panel[80] which used the following categories:

A Definite malignant mesothelioma—no doubt as to the histopathologic diagnosis.

B Probable malignant mesothelioma—some uncertainty exists; this may be due to insufficient material, poor quality, lack of differentiation, or absence of certain histologic features.

C Possible malignant mesothelioma—the diagnosis cannot be denied, but there is insufficient evidence to come to a positive conclusion.

D Improbable malignant mesothelioma—probably not a mesothelioma, but the diagnosis cannot be absolutely denied.

E Definitely not a malignant mesothelioma—in this category an alternate diagnosis is suggested.

During the second review, after the panel members considered all additional information, the results were summarized and coded. In summary groups A and B were coded as positive and groups D and E as negative, while group C represented the doubtful cases. The use of this scoring system made it possible to compare opinions of different observers. The rate of agreement between each of the three pairs of observers was assessed using kappa statistics.[81] Chi-square statistics were used to test for differences in proportions.[82]

Classification of the tumors was based on previously defined criteria.[1,20,32,83,84] The three pathologists independently evaluated each case for the basic histopathologic pattern and other associated patterns. Each tumor was classified as epithelial, fibrous, or mixed. In addition, each case was evaluated for mitotic activity, nuclear atypia, vascular invasion, and available special stains. Subsequently, each pathologist was asked to provide an overall impression in terms of acceptance or rejection of the case and whether it was benign or malignant.

Results

In all, there were 80 cases identified. Forty-seven (58.7%) were boys and 33 (41.3%) were girls: Their ages ranged up to 19 years (mean, 9.7 years). Sixty-four cases (80%) were identified from the literature and the rest through the means listed in Table 1. Risk factors were identified in four of the children. Two had a history of possible exposure to asbestos, one had previous irradiation for a Wilms' tumor, and one had *in utero* exposure to isoniazid.

Fifty-four cases (67.5%) were pleural,[19,49,50–54,67,68,85–106] twenty (25.0%) were peritoneal,[49–51,55–57,108–113] and six (7.5%) were pericardial.[58–60,114,115] These cases are summarized in Tables 2, 3, and 4, respectively. Slides were available for review in 24 cases, but two cases were excluded because of insufficient tissue material in one instance and liver origin in another instance. Thus, 22 cases with adequate material were studied by the panel of three pathologists. Fourteen of the 22 cases were pleural, seven were peritoneal, and one was pericardial. Ten were accepted by the panel as mesotheliomas; nine were reclassified as other recognizable tumors; and three were felt to be tumors of uncertain origin.

TABLE 2. Pleural Mesotheliomas

Year/sex/age	Gross	Microscopic	Malignancy	Risk factor	Outcome (mo)	Reference
1869/F/10	Local	Epithelial	NS	NS	Dead (1)	85
1885/M7	Local	Mixed	Yes	NS	Dead (1)	86
1904/M/5	Diffuse	Mixed	Yes	NS	Dead (2)	87
1932/M/6	Local	Fibrous	Yes	NS	Dead (7)	52
1932/F/3	Local	Fibrous	Yes	NS	Dead (1)	88
1939/M/8	Local	Epithelial	NS	NS	Dead (7)	89
1939/M/2	Local	Epithelial	NS	NS	Dead (1)	90
1950/M1½	Diffuse	Fibrous	Yes	NS	Dead (1)	91
1950/M/12	Diffuse	Epithelial	Yes	NS	Dead (3)	92
1951/M/7	Local	RE	Yes	NS	Dead (5)	53
1953/F/5	Diffuse	RCT	Yes	NS	Dead (5)	93
1954/F/8	Diffuse	Epithelial	Yes	NS	Dead (4)	94
1955/F/3	Diffuse	Fibrous	Yes	NS	Dead (1)	95
1956/M/1	Local	Fibrous	No	NS	Alive (72)	96
1956/F/4	Local	Fibrous	Yes	NS	Alive (24)	96
1956/F/	Local	Fibrous	Yes	NS	Dead (1)	96
1956/M/6	Diffuse	Epithelial	NS	NS	Dead (14)	97
1956/M/10	Local	Epithelial	Yes	NS	Dead (5)	98
1958/M/9	Diffuse	Unknown	Yes	NS	Dead (6)	99
1959/F/12	Diffuse	Mixed	Yes	No	Dead (4)	100
1961/M/5	Diffuse	Unknown	Yes	NS	Dead (8)	54
1964/M/12	Local	Fibrous	Yes	NS	Dead (18)	49
1964/M/9	Local	Fibrous	Yes	NS	Dead (12)	49
1964/F/12	Local	Fibrous	Yes	NS	Dead (10)	49
1964/M/14	Diffuse	Fibrous	Yes	NS	Dead (6)	49
1967/F/3	Unknown	Unknown	NS	Asbestos	Unknown	19
1970/M/19	Diffuse	Epithelial	Yes	No	Dead (7)	101
1970/F/1	Diffuse	Fibrous	Yes	No	Dead (7)	101
1970/M/	Local	Mixed	Yes	No	Dead (46)	101
1972/M/4	NS	Undifferentiated	Yes	No	*	50
1972/M/9	NS	Mixed	Yes	No	*	50
1972/M/11	NS	Undifferentiated	Yes	No	*	50
1972/M/14	NS	Fibrous	Yes	No	*	50
1972/M/1	NS	Fibrous	Yes	No	*	50
1972/M/1	NS	Fibrous	Yes	No	*	50
1972/F/17	NS	Undifferentiated	Yes	No	*	50
1972/F/17	NS	Fibrous	Yes	No	*	50
1972/F/17	NS	Fibrous	Yes	No	*	50
1972/M/17	NS	Fibrous	Yes	No	*	50
1972/M/17	NS	Fibrous	Yes	No	*	50
1974/M/14	NS	NS	NS	NS	Dead (few)	102
1974/M/11	NS	NS	NS	NS	Unknown	102
1974/F/7	NS	NS	NS	NS	Dead (2)	102
1975/F/12	Unknown	Unknown	NS	NS	Unknown	51
1975/F/15	Unknown	Unknown	NS	NS	Unknown	68
1980/F/1	Unknown	Mixed	Yes	NS	Dead (<12)	103
1980/M/9	Diffuse	Unknown	Yes	Isoniazid	Dead (7)	103
1980/F/17	Diffuse	Fibrous	Yes	Asbestos	Alive (59)	104
1985/M/15	Diffuse	Fibrous	Yes	No	Dead (156)	105
1985/M/1	Diffuse	Epithelial	Yes	Radiation	Alive (19)	67
1986/M/18	Unknown	Epithelial	Yes	No	Unknown	106
1986/F/19	Unknown	Epithelial	Yes	No	Unknown	106
1986/M/17	Unknown	Mixed	Yes	No	Unknown	106
1986/M/16	Unknown	Epithelial	Yes	No	Unknown	106

RE: reticuloendothelial; RCT: round cell tumor; NS: not stated.

* In eight of these cases death occurred within 12 months; the longest survival was 24 months, one child survived only 3 weeks.

Accepted Cases

There were ten cases accepted by the panel as mesothelioma. Six patients were boys, and four were girls. Eight tumors were pleural, two were peritoneal, and there were no pericardial. Two of the ten tumors were localized, five were diffuse, and three were undetermined. Four of the ten were mixed, six were epithelial, and none were fibrous. Three cases were studied by electron microscopy, and three were evaluated histochemically. Four of the ten children died of disease at 7, 8, 18, and 46 months after diagnosis; three were alive at

TABLE 3. Peritoneal Mesothelioma

Year/sex/age	Gross	Microscopic	Malignancy	Risk factor	Outcome (mo)	Reference
1962/F/2	Diffuse	Epithelial	Yes	No	Dead (1)	55
1963/F/5	Diffuse	Epithelial	Yes	No	Alive (72)	49
1970/F14 mo	Diffuse	Epithelial	Yes	No	Dead (5)	101
1972/M/12	Unknown	Mixed	Yes	No	Dead (6)	50
1972/M/16	Unknown*	Mixed	Yes	No	Dead (6)	50
1972/M/15	Diffuse	Unknown	Yes	NK	Unknown	108
1976/F/19	Diffuse	Epithelial	Yes	NK	Unknown	108
1976/F/3	Diffuse	Epithelial	Yes	No	Dead (20)	56
1979/M/2	Diffuse	Unknown	Yes	No	Dead (3)	107
1980/M/3	Unknown	Mixed	Yes	No	Dead (<12)	51
1980/M/11	Unknown	Mixed	Yes	No	Dead (<12)	51
1980/F/12	Unknown	Mixed	Yes	No	Dead (<12)	51
1983/F 7 mo	Cystic	Epithelial	Yes	NK	Unknown	108
1983/F/6 wk	Cystic	Epithelial	Yes	No	Alive (36)	57
1985/M/2	Multifocal	Mixed	Yes	No	Dead (3)	109
1985/F/8	Localized	Mixed	Yes	No	Alive (30)	109
1985/F/13	Diffuse	Epithelial	Yes	No	Dead (8)	110
1985/M/16	Unknown	Fibrous	No	NK	Unknown	111
1985/F/15	Unknown	Epithelial	Yes	No	Alive (20)	112
1986/M/7	Diffuse†	Epithelial	No	NK	Alive (7)	113

NK: not known.
* Combined pleural and peritoneal tumor.
† Tumor of tunica vaginalis, regarded as extension of peritoneum.

19, 20, and 59 months after diagnosis; and the outcome was unknown in the remaining three cases. Risk factors were identified in two of the ten children. One had a history of possible exposure to asbestos in a school environment, and the other had previous irradiation for a Wilms' tumor. Both were alive at last follow-up, 19 and 59 months after diagnosis. None of the ten children had exposure to isoniazid. The salient histopathologic features and the outcome are summarized in Table 5.

Reclassified Cases

Nine cases were reclassified as having tumors other than mesothelioma. Five patients were boys, and four were girls. Four tumors were pleural, four were peritoneal, and one was pericardial. Six of the nine tumors were diffuse, one was localized (cystic), and two had unknown gross tumor morphology. Three patients had epithelial, four had fibrous, and two did not fit in either category. All epithelial tumors had papillary or tubulopapillary components. Seven of these children died of their disease, most within 12 months of diagnosis. One infant girl with a cystic peritoneal tumor remained alive 36 months after diagnosis. Follow-up was not available in one patient. None of these patients had known exposure to irradiation or isoniazid. The salient histopathologic features, proposed diagnosis, and outcome are summarized in Table 6.

Doubtful Cases

Three cases were felt to be of doubtful or uncertain nature. One patient was a boy, and two were girls. Two tumors were pleural and one was peritoneal. One tumor was localized, and two were diffuse. One was fibrous, and two were epithelial. Two patients died of their disease, 7 and 12 months after diagnosis, and one was alive at last follow-up, 72 months after diagnosis. None of the three children had a history of exposure to asbestos, radiation, or isoniazid. The salient histopathologic fea-

TABLE 4. Pericardial Mesothelioma

Year/sex/age	Gross	Microscopic	Malignancy	Risk factor	Outcome (mo)	Reference
1958/F/14 mo	Diffuse	Epithelial	Yes	No	Dead (2)	58
1964/M/20 mo	Diffuse	Mixed	Yes	No	Dead (3)	59
1971/M/4	Diffuse	Fibrous	Yes	No	Dead (6)	60
1974/F/2	Unknown	Unknown	NS	NS	Unknown	114
/M/1	Unknown	Unknown	NS	NS	Unknown	114
1970–80/M/16	Diffuse	Fibrous	Yes	No	Dead (1)	115

NS: Not stated.

TABLE 5. Accepted Cases

Case/sex/age	Location	Gross	Type	Subtype	Malignancy	MIT	NA	VI	EM	Histochemistry	RF	Outcome (mo)	Reference
4/M/12	PL	L	M	P	Yes	2	2	No	No	No	No	Dead (18)	49
9/M/16	PL	D	E	P	Yes	1	1	No	Yes	PAS+ MU−	RT	Alive (19)	67
10/F/13	PT	D	E	S	Yes	5	2	No	Yes	PAS+ AB+ MU−	No	Dead (8)	110
11/M/19	PL	D	E	T	Yes	4	2	No	No	No	No	Dead (7)	101
14/M/5	PL	L	M	TP	Yes	6	3	No	No	No	No	Dead (46)	101
21/F/15	PT	D	E	S	Yes	0	2	Yes	No	PAS+ KER+ MU−	No	Alive (20)	112
22/F/17	PL	D	M	P	Yes	1	1	No	Yes	No	ASB	Alive (59)	104
23/M/18	PL	U	E	TP	Yes	1	1	No	No	No	No	Unknown	106
24/F/19	PL	U	E	S	Yes	0	1	No	No	No	No	Unknown	106
25/M/17	PL	U	M	S	Yes	3	2	No	No	No	No	Unknown	106

PT: Peritoneum; PL: pleural; PC: pericardial; M: mixed; S: solid; D: diffuse; U: unknown; P: papillary; TP: tubulopapillary; MIT: mitosis/40 high-power fields (HPF); NA: nuclear atypia; VI: vascular invasion; EM: electron microscopy; PAS: periodic acid-schiff; F: fibrous; AB: Alcian blue; MU: mucicarmine; RF: Risk factors; L: localized.

tures, alternate diagnosis, and outcome are summarized in Table 7.

Discussion

In this study, ten of 22 (45%) cases previously diagnosed as mesothelioma of childhood were accepted by the panel. Our acceptance of only 45% of cases submitted as mesothelioma is not without precedent. Similar difficulties in pathologic diagnosis have been encountered in studies in adult mesothelioma. Discussing a review of 114 cases of mesothelioma reported to a Canadian National Survey, McDonald[116] indicated that a group of six pathologists disagreed with the diagnosis in 36% of the cases. Greenberg and Lloyd-Davies[117] reported on a review of 413 cases of mesothelioma submitted to the Mesothelioma Registry of England, Scotland, and Wales. This reviewing panel considered the pathologic material to be insufficient in 11% of the cases and concluded that the diagnosis was definitely not mesothelioma in 18% of the cases. Hasan[118] reviewed 22 cases of adult mesothelioma on file in a major urban

TABLE 6. Reclassified Cases

Case/sex/age	Location	Gross	Type	Subtype	Malig-nancy	MIT	NA	VI	EM	Histo-chemistry	RF	Proposed Diagnosis	Outcome (mo)	Refer-ence
3/F/6 wk	PT	C	E	—	No	0	0	No	Yes	PAS+ AB−	No	Benign cystic malformation	Alive (36)	57
6/F/12	PL	D	F	—	Yes	1	1	No	No	No	No	Embryonal sarcoma NOS	Dead (10)	49
7/M/14	PL	D	RCT	—	Yes	1	1	Yes	No	No	No	Granulocytic sarcoma	Dead (6)	49
12/M/14 mo	PT	D	E	P	Yes	1	3	No	No	No	No	Yolk sac tumor	Dead (<12)	101
15/M/3	PT	U	E	TP	Yes	5	1	No	No	No	No	Yolk sac tumor	Dead (<12)	51
16/M/10	PT	U	F	—	No	0	0	No	No	No	No	Soft tissue fibromatosis	Unknown	111
17/M/4	PC	D	F	—	Yes	12	2	No	No	PAS+ AB− MU−	No	Malignant triton tumor	Dead (6)	60
18/F/2	PL	D	H	—	NoX	2	2	No	No	PAS− AB− MU−	No	Histiocytic proliferation, Langerhan's cell type	Dead (<12)	51
19/M/15	PL	D	F	—	Yes	0	1	No	No	No	No	Malignant fibrous histiocytoma	Dead (156)	105

PT: Peritoneum; PL: pleural; PC: pericardial; C: cystic; F: fibrous; D: diffuse; U: unknown; P: papillary; TP: tubulopapillary; E: epithelial; MIT: mitosis/40 high-power fields (HPF); NA: nuclear atypia; VI: vascular invasion; EM: electron microscopy; PAS: periodic acid-Schiff; X: Biologically malignant; NOS: not otherwise specified; AB: Alcian blue; MU: mucicarmine; RCT: round cell tumor; RF: risk factors.

TABLE 7. Doubtful Cases

Case/sex/age	Location	Gross	Type	Subtype	Malig-nancy	MIT	NA	VI	EM	Histo-chemistry	RF	Alternate Diagnosis	Outcome (mo)	Refer-ence
5/M/9	PL	L	F	—	Yes	8	1	No	No	No	No	Rhabdomyosarcoma	Dead (12)	49
8/F/5	PT	D	E	P	Yes	2	1	No	No	No	No	Extraovarian serous tumor with calcification	Alive (72)	49
3/F/19	PL	D	F	—	Yes	1	1	No	No	No	No	Vascular embryonal tumor	Dead (7)	101

PT: Peritoneum; PL: pleural; L: localized; D: diffuse; P: papillary; RF: risk factor; MIT: mitosis/40 high-power fields HPF; NA: nuclear atypia; VI: vascular invasion; EM: electron microscopy.

hospital. Using strict histologic and histochemical criteria, 14% of the cases were rejected as not fulfilling the criteria for mesothelioma. Lieben[19] studied 34 pleural and eight peritoneal mesotheliomas identified from the records of 163 hospitals serving a population of 6.5 million people. In this study, an independent pathologist reviewed 33 of the 42 cases. The pathologist agreed with the previous diagnosis in 17 of the cases, rejected seven cases as unacceptable histologically, and had serious doubts concerning the diagnosis of mesothelioma in the remaining nine. In 1972, the US Mesothelioma Panel reviewed 168 cases of (adult) mesothelioma; 70% were considered either probable or definite mesothelioma, and 16% were thought to be possible mesotheliomas. In the remaining 14%, the diagnosis of mesothelioma was rejected.[119] In the 22 childhood cases we reviewed, 45% of the cases were accepted as mesothelioma, and 14% were of doubtful or uncertain nature. In the remaining 41%, the diagnosis of mesothelioma was rejected. The discrepancies between the original pathologic diagnosis and the revised diagnosis in the previously cited studies and in our study illustrate that the difficulties encountered in the diagnosis of childhood mesothelioma are similar or perhaps more pronounced than those found in adults.

Kappa calculations were carried out to determine the rate of agreement between the three pairs of observers (A to B, B to C, and A to C) while reviewing the 22 childhood cases in which slides were available. Kappa values of less than 0.40 have been interpreted to represent poor agreement beyond chance.[81,120] Only one of the three observer pairs had a kappa value as high as 0.40, which was statistically significant ($P < 0.01$). The other kappa values were not statistically significant.

The overall rate of agreement between individual observers and the panel in this study of childhood mesothelioma varied from 50% (11/22) for observer 1 to 68% (15/22) for observers 2 and 3. The composite rate of agreement for the three observers and the panel was 62% (41/66). The mean rate of agreement between the panel's opinion and that of individual observers was highest in the accepted cases (73%), intermediate in the reject category (63%), and lowest in the doubtful category (22%). McCaughey and Oldham[121] studied interobserver variation in the histologic diagnosis of adult diffuse mesotheliomas. They measured the percentage of agreement among the first two members of a panel of three experienced pathologists. The percentage of agreement in their study varied from 68% to 82%. This variation in initial interobserver agreement underscores the need for using panels in which members initially review slides independently and then meet as a group to review all available data jointly to develop a consensus agreement.

In the group of ten accepted cases of childhood mesothelioma, there were more boys than girls (60% *vs.* 40%), and a pleural location was more common than a peritoneal or pericardial one. The composition of these accepted cases included eight (80%) pleural tumors and two (20%) peritoneal tumors. These figures are similar to those reported by Greenberg and Lloyd-Davis.[117] In a study of 413 adult mesotheliomas, these writers found that only 12% of all confirmed cases were of peritoneal origin. Diffuse tumors were encountered in 50% of the ten accepted cases and localized tumors in 20%. The gross morphology of the tumor was not known in the remaining 30% of the cases. Epithelial tumors (60%) predominated over mixed (40%) and fibrous (0%) types. This finding differs significantly from that of Wasserman[51] who reported a prevalence of mixed types. Thirteen of the 22 cases reviewed by our panel died of their disease, most within 1 year of diagnosis. Five remained alive at 19, 20, 36, 59, and 72 months after diagnosis. The status was unknown in the remaining four cases. The mortality of the subgroups of reclassified cases (7/9) and of doubtful cases (2/3) was greater than that of the accepted cases (4/10), but this difference was not statistically significant ($P = 0.24$). We believe that the higher mortality in the reclassified and doubtful categories represents the malignant nature of childhood tumors which may be misclassified as mesothelioma.

Asbestiform fibers are ubiquitous in nature and in the urban environment[1] and are commonly referred to by the commercial term asbestos. Recent reports have drawn attention to the occurrence of asbestos in play sand[122] and in lungs of infants aged 2.5 to 10 months.[123]

Nevertheless, only two of the 80 children reported here had a history of possible exposure to asbestos. One was a 3-year-old girl with a pleural mesothelioma. She was the daughter of a ceramics engineer who worked in a Pennsylvania insulation plant handling chrysotile and amosite asbestos. We did not review the tissue slides for this case, but a reviewing pathologist agreed with the initial diagnosis.[19] The other patient, a 17-year-old girl, was identified through a hospital reporting to the Cancer Registry of the Texas Department of Health. To our knowledge, the case had not been previously reported.[104] This patient lived in Central Texas at the time of diagnosis, but had earlier resided in Ohio where she had possible exposure to asbestos in a school environment. She had a diffuse malignant mesothelioma of the pleura with a mixed microscopic morphology. Our panel reviewed the slides and concurred with the initial diagnosis of mesothelioma.

Adult mesotheliomas have a peak occurrence in the sixth to seventh decade often following brief high-dose or prolonged low-dose exposure to asbestos[23-25,124,125] and long latency periods of 20 to 40 years between initial exposure and tumor manifestation[23,118,126] have been reported. However, no similar data are available in childhood cases. Initial exposure in some cases of adult mesothelioma may have taken place during childhood. A case in point is the patient reported by Arul.[126] This patient was a 43-year-old woman who had lived and played near an asbestos factory between the ages of 5 and 7. The asbestos dust from the factory settled on houses, and after heavy winds, floors and furniture had to be cleaned. She subsequently left the factory district and had no other known exposure to asbestos for the next 37 years.

Recently, the presence of asbestos-containing materials in public buildings, and particularly schools, has been the focus of considerable attention. Removal or disruption of these materials can result in markedly increased levels of asbestos fibers in the air. For children in the school environment, it has been said that factors such as a high level of physical activity and higher breathing rates may result in an increased level of exposure. Opinions vary as to the degree of exposure children may experience in the school setting. Some risk assessment studies have indicated that asbestos in buildings does not represent a major public health threat. Hughes and Weill[127] assessed quantitative risk of exposure to asbestos in schools and estimated the occurrence of only five lifetime excess cancers per one million school children exposed to asbestos, during an average school enrollment of 6 years. These authors also provide for risk assessment comparison other causes of death in children, *e.g.*, annual rates (per million) of ten deaths from high school football and 14 from bicycling. The overall significance of school asbestos exposure in the school environment remains unclear because of the variation in type of asbestos fibers used, the frequent mixing of fiber types, the varying length of stay by children at any given school, and the difficulties inherent in the quantitative assessment of asbestos-fiber concentration in ambient air.[128]

Another possible causative or predisposing factor in mesotheliomas is radiation. Thirteen radiation-related cases have been reported in adults. Three of these followed radiation therapy for Wilms' tumor during childhood,[78,79] two occurred after extravasation of contrast material during diagnostic procedures,[129,130] and the others developed after therapeutic radiation of other primary malignancies.[4,131-133] Anderson[67] reported on a mesothelioma after radiation therapy in a child. The patient, a 16-year-old boy, had a Wilms' tumor diagnosed at 18 months of age which was treated with chemotherapy and radiation therapy. Subsequently, at age 15 he developed a diffuse malignant pleural mesothelioma. This well-documented case, which was accepted as a mesothelioma by our panel, represents the only childhood case of mesothelioma after radiation therapy. This patient had no history of exposure to asbestos or other known risk factors. Despite the evidence of a relationship between radiation and mesothelioma, the precise role of radiation in the induction of mesothelioma remains unknown and awaits further clarification.

Isoniazid administered in high doses to rats and mice has been shown to induce tumors of the lung, liver, lymph nodes, and other sites.[134] When administered to pregnant animals, it may also induce pulmonary tumors in the offspring.[135] Hammond[136] studied children exposed to therapeutic doses of isoniazid *in utero* and found that there was no increase in the incidence of cancer in these children 10 to 15 years later. However, a mesothelioma has been reported in a 9-year-old boy whose mother was given isoniazid during pregnancy.[68] The mother had a history of exposure to asbestos but did not live near a construction site, factory, or shipyard. The boy developed a pleural tumor which was reported as malignant mesothelioma. The morphology and histochemistry for this case were not discussed, and no photomicrographs were provided. We were also unable to obtain the slides for review.

It is also possible that childhood mesothelioma may not be related to any of these factors. Wagner and others[137] are of the opinion that childhood mesotheliomas represent a different entity from adult mesotheliomas. We concur with this view and believe that asbestos is not a factor in the sporadic cases of childhood mesothelioma. Peterson *et al.*[138] have discussed the role of other possible causes of nonasbestos-related mesothe-

liomas (nickel, silica, beryllium), man-made fibers (zeolite, erionite, mordenite), organic chemicals (polyurethane, sterigmatocystin, ethylene oxide, nitrosamine), viruses (avian leukosis virus), chronic inflammation (tuberculosis), and hereditary predisposition (occurrence of mesothelioma in several members of a family).

While the potential for exposure to asbestos or other risk factors can occur in childhood, we believe there is insufficient evidence to support a causal relationship between these factors and childhood mesotheliomas. Grundy,[50] in his study of 13 children with mesothelioma, also concluded that the available evidence appeared to rule against asbestos or other industrial exposure as causative agents. A similar lack of association between asbestos and mesothelioma has been reported in a substantial number of adult cases.[138-141]

Although very rare, we conclude that mesothelioma of childhood is a valid pathologic entity. Although only a few of the cases we reviewed were evaluated by histochemical methods or electron microscopy, these diagnostic techniques are extremely useful in the differentiation of mesothelioma from tumors with overlapping features and should be done whenever feasible. The diagnosis of mesothelioma, particularly in children, remains difficult; however, the use of a uniform, reproducible light-microscopic classification, together with mesothelioma panels may ease this problem. A thorough microscopic study of individual cases needs to be supplemented by a careful assessment of the clinical findings and environmental risk factors. The available data thus far do not support a clear causal association between mesothelioma of childhood and asbestos exposure, radiation, or isoniazid.

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Erratum

A technical error was made. "DNA Analysis in the Differential Diagnosis of Osteosarcoma" by Bauer *et al.*, which appeared in the April 1, 1988 issue of *Cancer* (61:1430–1436), also appeared with slight editorial alterations in the June 15, 1988 issue (61:2532–2540).