

PRIMARY MALIGNANT MESOTHELIAL TUMORS
IN CANADA, 1960-1968

*A Pathologic Review by the
Mesothelioma Panel of the Canadian Tumor
Reference Centre*

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Six pathologists reviewed 119 of 165 cases reported as primary malignant mesothelial tumors, between 1960 and 1968, in a Canadian national survey. Based on histologic observations only, the panel was in favor of the diagnosis in 50%, uncertain in 14%, and against in 36%. This distribution was similar for pleural and peritoneal tumors. In males, the diagnosis was favored more often than in females—61% compared to 26%. Clinical and additional pathologic information changed the pathologists' opinion little. A member of the UK Mesothelioma Panel who reviewed 44 of the 119 cases recorded essentially similar opinions. Subsequently, a further 71 cases were registered between 1968 and 1970, and reviewed pathologically. The 99 cases in all, in which the panel favored the diagnosis of malignant mesothelioma, had been exposed to asbestos slightly more frequently than the rest. Twelve of 26 (46%) tumors classified histologically as mixed were associated with asbestos exposure compared with 8 of 73 (11%) classified as epithelial or mesenchymal.

A SURVEY WAS CARRIED OUT, DURING 1968 and 1969, of all fatal cases of primary malignant mesothelial tumors in Canada diagnosed between January 1960 and June 1968.⁴ Ascertainment was based on replies to an in-

quiry about these tumors received from every pathologist in Canada who was a member of the Canadian Association of Pathologists or of the Quebec Association of Laboratory Physicians. The 165 cases studied were those which the reporting pathologists thought on balance were primary malignant mesothelial tumors. The methods used to assemble the cases and two matched control series and to study them epidemiologically have been described.⁴ In brief, detailed occupational, residential, and smoking histories were sought from relatives and friends of the deceased. The field workers did not know which were cases and which controls, and the information collected was coded "blind." An association between primary mesothelial tumors and an occupational history of asbestos exposure was found in 20% of the 101 male cases for whom a questionnaire was completed compared with 3% of the controls and in 2% of the 51 female cases compared with none in the controls. The survey subsequently has been continued in a similar manner and, between July 1968 and December 1970, 71 cases were registered—39 male and 32 female.⁵ Occupational or domestic exposure was found in 32% of males compared with 11% of controls and 13% of females compared with 3% of controls. Thus, although all rates were higher, the excess asbestos exposure was of a similar order. No

The research was assisted by grants from the Institute for Occupational and Environmental Research of the Quebec Asbestos Mining Association and from the National Cancer Institute of Canada.

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The review was organized by A. D. McDonald, MD and S. Ducic, MD of the Department of Epidemiology and Health, McGill University, who also studied the certified causes of death. P. Bolduc, MD, helped in selecting controls and G. Eysen, MSc, in analyzing the results. Later, W. T. E. McCaughey, MD, of the United Kingdom Mesothelioma Panel reviewed 44 cases.

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The authors wish to thank all pathologists in Canada for their collaboration.

Received for publication September 22, 1972.

differences have been found in occupational exposure of lesser degree and history of residence in an asbestos mining area. Almost all the excess of occupational exposure was in the manufacture and industrial application of asbestos rather than in mining and milling.

Pathologic studies have been carried out in three phases.

Phase 1: A pathologic review of the original 165 cases was planned to find out: 1. the joint opinion of members of the Canadian mesothelioma panel as to whether the cases studied were indeed primary malignant mesothelial tumors; 2. how much weight was given by the panel to histologic appearance alone, and to what extent did clinical, operative, surgical pathology, and autopsy reports modify the histologic diagnosis; 3. how much observer variability there was among members of the panel, and 4. whether a history of asbestos exposure was related to the diagnostic opinion of the panel or to characteristics of the tumor.

Phase 2: The additional 71 cases were reviewed pathologically.

Phase 3: Cases accepted by the panel as mesotheliomas were classified histologically.

MATERIALS AND METHODS

Phase 1: The pathologists who had reported the 165 cases were asked to send in paraffin blocks or tissue in fluid fixative. Material was obtained for 125 cases—in 3 it was known to have been lost and in 37 none could be found. In nearly all cases the specimens received were in the form of paraffin blocks of formalin-fixed tissue, taken at autopsy in 89 cases and at operation in 36 cases. The pleural surgical material varied from small portions of pleura, with or without subjacent tissue, to pneumonectomy specimens. In only one peritoneal tumor had the diagnosis been made on the basis of a surgical specimen. This consisted of a tumor mass measuring 7.0×3.5 cm from the right iliac fossa.

Six sets of slides of each of the 125 cases were prepared at the Canadian Tumor Reference Centre. Slides were stained with hematoxylin and eosin. In each case, one to three

additional slides showing tumor were stained with mucicarmine and by the PAS method after diastase digestion.

The contributing pathologists were asked to furnish a clinical summary including comments on duration of illness, presenting symptoms, presence or absence of pleural or peritoneal effusions, other physical signs, x-ray findings, and therapy. Although the information provided varied in amount and was not extensive, a synopsis of the main clinical events was given in most cases. The pathologists were also asked to describe the gross pathology of surgical specimens and the gross findings at autopsy. This request was usually met by copies of surgical pathology reports or, for autopsies, by a description of the mesothelial tumor and a list of the main autopsy findings, including sites of metastases.

Six members of the Canadian Tumor Reference Centre Mesothelioma Panel, which included an American pathologist who was also a member of the U.S. panel, took part in the review. The study was carried out during a period of 4 days in the Department of Epidemiology and Health, McGill University. The pathologists worked independently in separate rooms and were helped by clerks who checked the case numbers and recorded observations. Each pathologist reviewed cases in the same order, first recording his opinion on histology alone and then, after reading the related clinical information and description of the gross pathology (but *not* any occupational history), his final judgment. The additional information usually allowed pathologists to make some estimate of how closely the macroscopic appearance of the tumor resembled their concept of a typical mesothelioma and to what extent the possibility of a primary tumor elsewhere could be discounted. At each stage the pathologists were asked to classify cases into one of the five categories given below. In order to introduce an element of doubt into each diagnosis, comparable specimens from 17 cases with pleural or peritoneal metastases from known extra-thoracic primary tumors were introduced into the series. It was decided not to search for asbestos bodies.

Classification by pathologists

0. Not a primary mesothelial tumor
1. Unlikely to be a primary mesothelial tumor
 - tending towards unlikely
2. Possibly {
 - unable to decide
 - +tending towards probably
3. Probably a primary mesothelial tumor
4. Definitely a primary mesothelial tumor

Simplified version

- | | |
|---|-----------|
| } | against |
| } | uncertain |
| } | in favor |

If they used category 2 (possible) they were asked to indicate by a — or a + whether they leaned towards unlikely or probable. A simplified version of the classification was derived as indicated above and the six opinions on each case examined. If a majority was against or in favor of the diagnosis the case was classified as such and if opinions were evenly balanced, as uncertain. A panel opinion was obtained for 119 of the 125 cases reviewed. In three of the remaining six cases, no tumor was seen by all six pathologists. In the other three cases, the number of pathologists who found no tumor was five, four, and two, and the cases accepted as a mesothelioma by one, none, and three of the pathologists, respectively. Clinical reports were missing in four other cases so a final diagnosis was made in only 115.

A few months after the panel had finished its work, there was opportunity for a pathologist who was a member of the United Kingdom Mesothelioma Panel to review in the same manner about a third of the series. For this, 44 cases were selected by a random procedure from the three groups in favor, uncertain, against, into which the cases were classified by the panel.

Phase 2: Essentially the same procedure was followed in the classification of the 1968–1970 cases, but material was circulated and no controls used.

Phase 3: All cases accepted by the panel as mesotheliomas for whom a full occupational and environmental history had been obtained—59 in the original series, and 40 in the subsequent series—were classified histologically by one member of the panel (DM) without knowledge of the occupational history.

FINDINGS

Phase 1: The results of the review of 119 cases are shown in Table 1. The panel was in favor of the diagnosis on histologic grounds alone in 61.3% of males and 25.6% of females and at the final stage they were in favor of the diagnosis in 62.8% of males and 35.1% of females. The panel was against the diagnosis of primary mesothelial tumor in 16 of the 17 cases of secondary pleural or peritoneal tumors with an identified primary elsewhere.

In Table 2, a classification is presented of all 690 individual opinions of the panel members on the 115 cases reviewed both histologically and with clinical and gross pathologic information. When, on histologic appearance, pathologists tended to be in favor of the diagnosis, the additional information resulted in an increased sureness. In cases where they were against the diagnosis, the additional information resulted in some changes equally for and against. Using the simplified classification, in only 21 cases was a change made in the panel opinion after consideration of the clinical and gross pathologic data, 13 being moved up a group and 8 down a group, but the overall proportions remained much the same.

In the 78 male cases with complete clinical and other information, the panel was in favor of the diagnosis in 62% of 63 pleural and 64% of 14 peritoneal tumors. The corresponding figures for females were 37% of 19 pleural and 29% of 14 peritoneal tumors. They also accepted one male, one of two female pleural and peritoneal tumors, and one of two female pericardial tumors. The availability of clinical

TABLE 1. Results of Pathologic Review*

Panel opinion of diagnosis		based on					
		Histology only			Histology and clinicopathologic information		
		Males	Females	All	Males	Females	All
In favor	No	49 (46)	10 (10)	59 (56)	49 (46)	13 (13)	62 (59)
	Per cent	61.3	25.6	49.6	62.8	35.1	53.9
Uncertain	No	12 (11)	5 (3)	17 (14)	8 (7)	4 (3)	12 (10)
	Per cent	15.0	12.8	14.3	10.3	10.8	10.4
Against	No	19 (17)	24 (21)	43 (38)	21 (19)	20 (16)	41 (35)
	Per cent	23.8	61.5	36.1	26.9	54.1	35.7
All		80 (74)	39 (34)	119 (108)	78 (72)	37 (32)	115 (104)

* Figures in parentheses indicate cases studied epidemiologically.

TABLE 2. Classification by the Six Pathologists on Histologic Appearances (115 Cases—690 Observations) before and after Study of Additional Clinical and Pathologic Information

			121	105	64	12	112	156	120	Total
Primary classifica- tion on histologic appearance	Against	{Not	96	9	1				1	107
		{Unlikely	15	67	16	1	9	3		111
		{Possible -	3	19	31	1	17	7		78
	Uncertain	Possible	1	1	4	7	7	4	1	25
	In favor	{Possible +	4	7	11	1	72	44	12	151
		{Probable	2	1	1	2	7	97	59	169
		{Definite		1				1	47	49
Revised classification after review of clinical and pathologic information			Not	Unlikely	Possible -	Possible	Possible +	Probable	Definite	690
			{Against			Uncertain	{In favor			

information and an account of the gross pathology did not raise the proportion of favorable opinions which amounted in males to 61% of 59 autopsy cases and 68% of 19 cases in which there was only a biopsy and in females 33% of 24 autopsy and 31% of 13 biopsy cases.

Variation in opinion between pathologists is shown in Table 3. Using the simplified classification, they each agreed with the panel opinion in about 70% of cases. In the remaining 30%, two members of the panel tended to be more in favor of the diagnosis and two less.

In the 44 cases selected for the British pathologist, there was rather less agreement between individual members and the panel, but the overall picture was similar. The opinions of the pathologist from the British panel resembled those of one of the two pathologists less in favor of the diagnosis than the rest of the panel, but his opinion fell within the range observed among the members of the Canadian panel.

Death certificates were inspected for 107 of the 115 cases classified by the panel on histologic and clinical grounds. Of these, 49 (46%)

TABLE 3. Percentage of Cases in Which Individual Pathologists Agreed with the Panel Opinion

	Pathologist	Agreement	Disagreement	
			-more in favor of diagnosis	-less in favor of diagnosis
1. In 115 cases with clinical information	A	70.4	22.6	7.0
	B	77.2	21.7	6.1
	C	66.0	14.8	18.3
	D	77.2	11.3	16.5
	E	68.7	9.6	21.7
	F	72.2	0.9	27.0
2. In 44 selected cases	A	61.4	27.3	11.4
	B	68.6	29.5	6.8
	C	54.6	15.9	29.5
	D	59.1	18.2	22.7
	E	63.6	13.6	22.7
	F	63.6	0.0	36.4
	W. McC.	59.1	13.6	27.3

deaths were certified as due to mesothelioma or connective tissue tumor, 32 (30%) to other respiratory or gastrointestinal tumors, 16 (15%) to tumors of other organs, and 10 (9%) to non-malignant disease. The 60 cases that the panel accepted as mesotheliomas were a little more often certified as such or as connective tissue tumors (48%) than the 36 cases that the panel rejected (33%).

Phase 2: Of 71 cases registered between July 1968 and December 1970, 42 (59%) were accepted by the panel; they were uncertain in 7% and rejected 34%.

Phase 3: The tumors in which the panel opinion was in favor of mesothelioma displayed patterns which have been described by others.^{1,2,5} Of the 70 pleural tumors accepted by the panel and investigated epidemiologically, 22 were epithelial, 27 mesenchymal, and 21 mixed; of 23 peritoneal tumors, 16 were epithelial, 2 mesenchymal, and 5 mixed. Eight cases showing approximately equal mesotheliomatous involvement of pleura and peritoneum were epithelial and a pericardial tumor, mesenchymal. There were wide variations in the microarchitecture of individual tumors,

even within the three categories listed, but detailed descriptions will not be given here. Several microscopic patterns are illustrated (Figs. 1-8).

In *epithelial* tumors, the cells were generally oval, cuboidal, or polygonal with vesicular nuclei and acidophilic or amphophilic cytoplasm, occasionally vacuolated. These formed tubules, sometimes lined by flattened cells, and wider, irregular spaces into which papillary processes projected. Frequently, the cells grew in solid masses with minimal evidence of tubules, larger spaces, or papillary processes. Evidence of neutral mucopolysaccharide (epithelial mucin) production was not established. The stroma varied in amount and was fibrous. In *mesenchymal* tumors, spindle-shaped or fusiform cells with elongated, oval, vesicular, or hyperchromatic nuclei were arranged in parallel fashion in sheets, fascicles, and whorls. Some tumors were highly cellular; others contained moderate or considerable amounts of collagen, laid down in sheets or enlacing bands, often with hyaline, relatively acellular areas. In *mixed* tumors, epithelial and mesenchymal elements were usually inter-

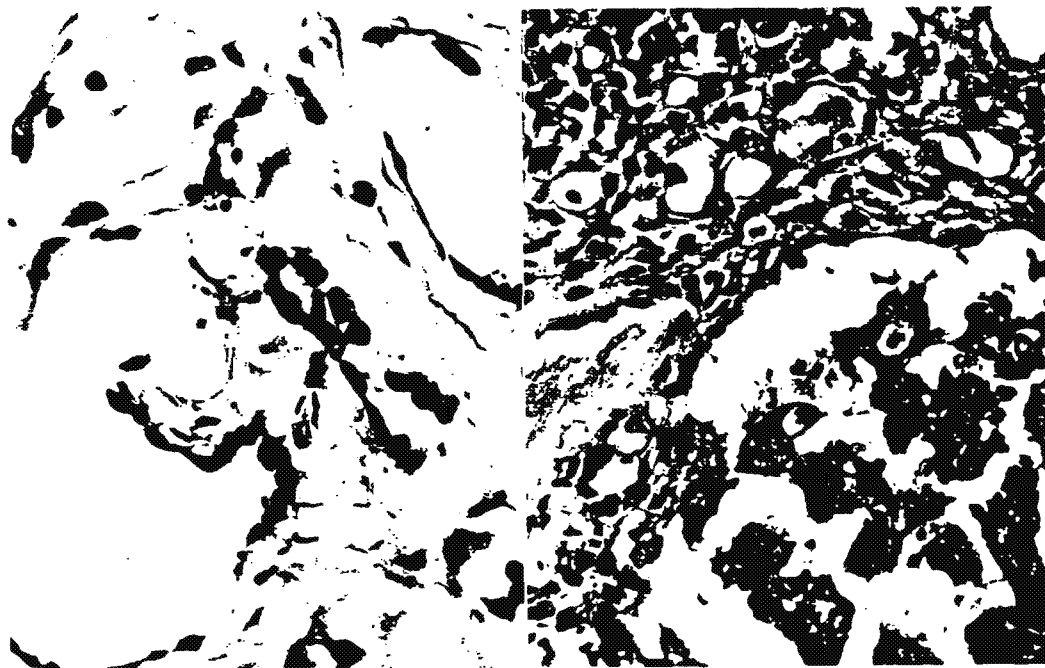


FIG. 1 (left). CTCRC 14037. Malignant pleural mesothelioma, tubular epithelial pattern. The tubules are lined by cuboidal and flattened cells ($\times 400$).

FIG. 2 (right). CTCRC 14065. Malignant pleural mesothelioma, tubulopapillary epithelial pattern. A group of small tubules are present at the top of the photograph. Below, papillary processes project into a space lined by tumor cells ($\times 400$).

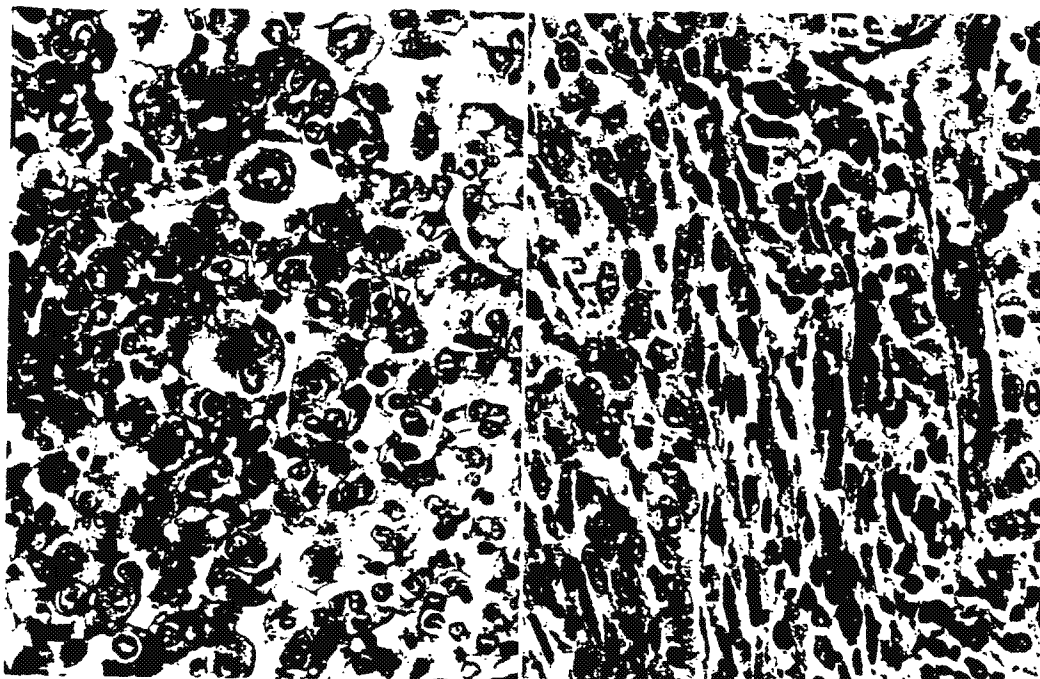
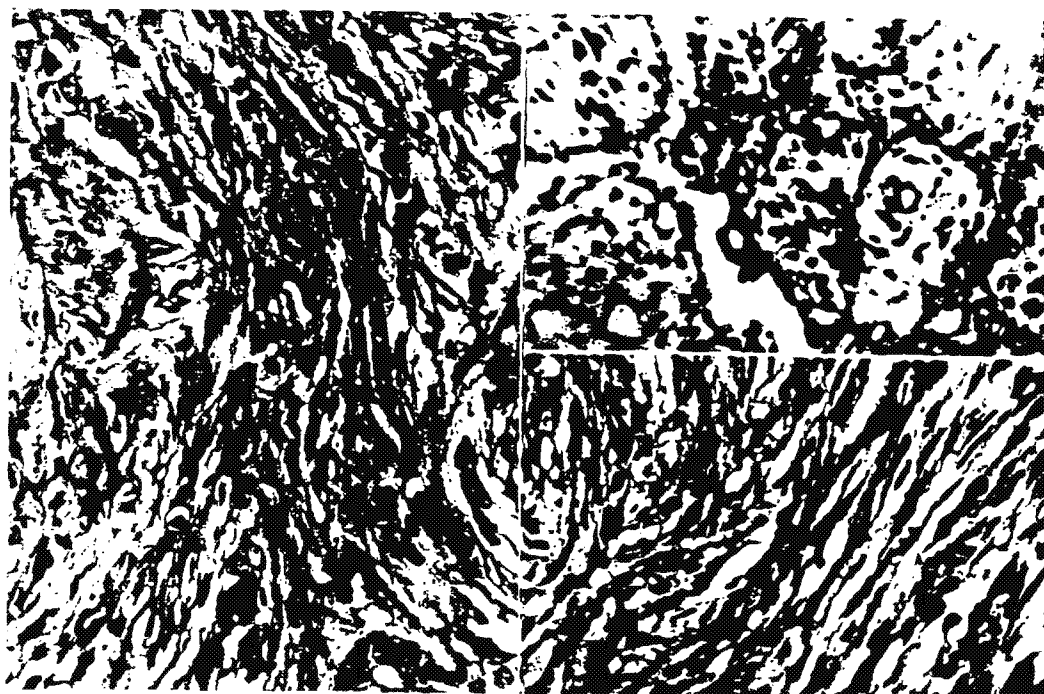


FIG. 3 (left). CTTC 13056. Malignant pleural mesothelioma, solid epithelial pattern. The tumor cells vary in size, some being very large with abundant cytoplasm. Nucleoli are prominent in many nuclei ($\times 400$).

FIG. 4 (right). CTTC 14051. Malignant pleural mesothelioma, mesenchymal pattern. The elongated tumor cells are arranged with their long axes parallel. Nuclei are oval or fusiform. Collagen fibers are inconspicuous ($\times 400$).



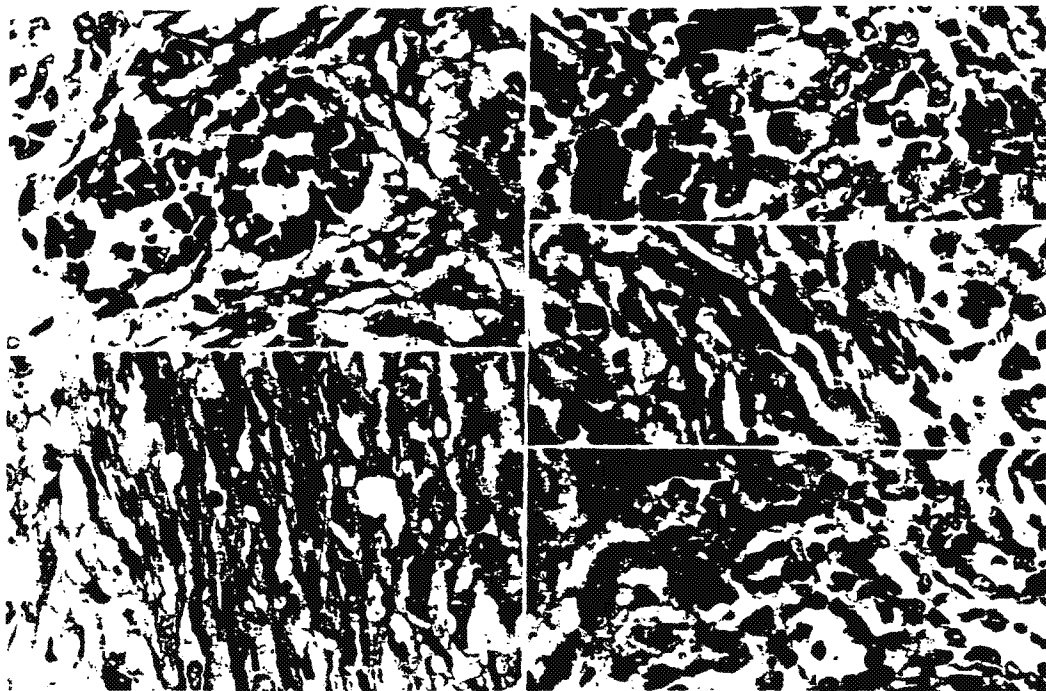


FIG. 7 (left). CTCRC 14066. Malignant pleural mesothelioma, mixed pattern. The top half of the photograph shows the tubules formed by tumor cells of epithelial type. The bottom half, from an area in the same tumor, shows spindle-shaped tumor cells of mesenchymal type ($\times 400$).

FIG. 8 (right). CTCRC 14031. Malignant pleural mesothelioma, mixed pattern. The top third of the photograph shows a solid epithelial area with one multinucleated tumor cell. In the middle third, from an area in the same tumor, are spindle-shaped tumor cells of mesenchymal type. In the bottom third, from a hilar lymph node in the same case, metastatic mesothelioma forms a tubular epithelial pattern ($\times 400$).

mingled throughout the tumor but sometimes occupied different but adjacent territories.

In several tumors, particularly those of pleural origin, undifferentiated areas were en-

countered in which the cells were pleomorphic and varied considerably in size and nuclear characteristics. However, even in these cases there were zones of sufficient differentia-

TABLE 4. History of Definite or Probable Occupational or Domestic Exposure to Asbestos Related to Panel Opinion of Diagnosis

Panel opinion of diagnosis	Males			Females		
	Total	Asbestos No.	Exposure Per cent	Total	Asbestos No.	Exposure Per cent
In favor	67	17	25.4	32	3	9.4
Uncertain	10	4	40.0	5	1	20.0
Against	32	6	18.8	27	1	3.7
All	99	27	27.3	63	5	7.9

FIG. 5 (left). CTCRC 12092. Malignant pleural mesothelioma, mesenchymal pattern. Elongated tumor cells form encasing strands with moderate collagenization ($\times 400$).

FIG. 6 (right). CTCRC 13503. Malignant pleural mesothelioma, mixed pattern. The top half of the photograph shows spaces lined by cuboidal tumor cells of epithelial type. The bottom half, from an area in the same tumor, shows spindle-shaped tumor cells of mesenchymal type ($\times 400$).

TABLE 5. Histologic Classification and History of Asbestos Exposure in the 99 Cases Accepted by the Panel (1960-1970)

Definite or probable exposure to asbestos	Males			Females		
	Epithelial	Mesenchymal	Mixed	Epithelial	Mesenchymal	Mixed
Occupational	3	3	11*	—	—	—
Domestic	—	—	1*	1	1	1
Number	3	3	11	—	—	—
Percent	11.5	17.6	45.8	5.2	9.1	50.0
Total cases	26	17	24	19	11	2

* One man who worked as a geophysical explorer for an asbestos company had also been exposed domestically.

tion to allow classification into one of three histologic types with fair certainty.

EXPOSURE TO ASBESTOS

A history of definite or probable asbestos exposure was slightly more frequent in cases in which the panel, after consideration of all available information, was in favor of the diagnosis than in cases in which they were against it or uncertain (Table 4).

Table 5 shows the histologic classification and history of asbestos exposure in all 99 accepted cases. Mixed tumors were more often associated with asbestos exposure than the other two groups, and this type of tumor was infrequently found in women. Six of the 11 occupationally exposed men with mixed tumors had worked in insulation or asbestos products manufacture compared with one of the 6 men with epithelial or mesenchymal tumors.

ADDENDUM

Since this paper was submitted for publication, some of these data were included in a letter to the editor of the *New England Journal of Medicine*, 287:570-571, 1972.

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