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FUNCTIONS OF MESOTHELIOMA PANELS*

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Lubarsch is quoted[1] as having said in 1895, concerning mesothelioma, "... there is scarcely another variety of tumor which is so ill-defined and which admits of so much doubt as to its true nature." Another half century was required before opposition to its very existence as an entity disappeared. Although its increasing prevalence and a voluminous literature have acquainted many pathologists with its essential characteristics, the morphologic intricacies in the individual case remain a source of difficulty in diagnosis.[2] The pathologic overlap of mesothelioma with other neoplasms continues to give relevance to Lubarsch's comment.

The predominant association of diffuse malignant mesothelioma with exposure to asbestos has made this tumor of unique epidemiologic significance, despite its lower incidence as compared with such polyetiologic malignancies as carcinoma of the lung, gastrointestinal tract, and, apparently, other organs, where exposure to asbestos plays a role.[3]

The occurrence, from the late 1940s on, of a cluster of cases of asbestosis and carcinoma of the lung, and later of mesothelioma, in Paterson, New Jersey, where a large asbestos factory was located, led to clinical and pathologic investigations. These studies were extended to larger populations of asbestos workers and became a stimulus for an international conference on the Biological Effects of Asbestos, sponsored by The New York Academy of Sciences in 1964.[4] At this conference, the International Union Against Cancer Working Group on Asbestos and Cancer proposed the establishment of Pathology Reference Panels on regional and international levels. One of the functions of these bodies would be to serve as consultation centers for the diagnosis of mesothelioma.

In the following years, mesothelioma reference panels were established in England, South Africa, the United States, Canada, and The Netherlands.[5] At a meeting in New York in January 1968, attended by members of the United States Mesothelioma Panel, consultants, and guests, several from abroad, under the chairmanship of one of us (J.C.), it was indicated that in addition to a national panel in England, there were regional panels.[6] The concept of regional panels in the United States seemed particularly appealing because of the size of this country, and plans

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were outlined for their establishment. It was realized that to perform its function adequately, the United States Mesothelioma Panel would have to encourage collection of material from physicians by publicizing its activities in various ways. An ambitious program was suggested, to include the circulation of material from the regional panels and the Armed Forces Institute of Pathology. The collection of epidemiologic data was also anticipated.

The report of the Advisory Committee on Asbestos Cancers to the Director of the International Agency for Research on Cancer, emanating from the meeting on the Biological Effects of Asbestos in Lyon in October 1972,[5] stated that the International Panel of Pathologists and the national panels, established following the 1964 meeting, served a useful purpose. It recommended that panels be formed in other countries. It defined as the main goal of the panels the ensuring of uniformity of diagnostic criteria and recording of histologic types of diffuse mesothelioma. Collaborative study of histologic slides in national panels was also advocated. At both of the international meetings mentioned, the publication of a comprehensive atlas on mesothelioma was urged.

It has not been feasible for us to attempt from personal knowledge, by direct contact, or correspondence, to review the status or experiences of mesothelioma panels in countries other than the United States and Canada. There has been no communication directly from or through the international panel. There have been some relevant publications. McDonald *et al.*[7] presented in detail a pathologic review by the Mesothelioma Panel of the Canadian Tumour Reference Centre in a national survey of primary malignant mesothelial tumors in Canada from 1960 to 1968. McCaughey and Oldham[8] conducted a unique study of the internal workings of a mesothelioma panel, with examination of the extent of and basis for observer variation. Several other articles[9-11] present epidemiologic findings supported by mesothelioma panel review. Most of the reports on the prevalence of mesothelioma or its relationship to asbestos exposure appear to have been independent efforts unrelated to panels, applied to specific cohorts, geographic areas, or medical institutions in a period of time limited by available means or by restricted purpose.

Further consideration of the concept of regional panels in the United States has led to the opinion that such a system would probably be extremely difficult to organize and maintain, possibly result in duplication of effort, and actually increase the work of the central panel unproductively. The idea is not now contemplated. The work of the existent central United States panel has been on a limited basis because of restricted support. In recent years, however, requests for panel services in terms of individual consultations and survey and education purposes have been increasing. There has been commendable cooperation from the members of the panel. At any one time, 10 pathologists, interested and experienced in the diagnosis of mesothelioma, have generously served on the panel, with some change in membership over the years.

During a 10-year period, the United States Mesothelioma Reference Panel registry, located at the Barnert Memorial Hospital Center in Paterson, New Jersey, received a large volume of material on asbestos-associated disease, traced occupationally, in addition to mesothelioma. In the earlier years, cases not accepted as mesothelioma were simply assigned to an appropriate category. Later, those submitted as putative mesotheliomas, when rejected, were also listed as "not mesothelioma." There have been approximately 800 cases received, of which 517 were categorized as varying from definitely not a mesothelioma to definitely a mesothelioma. Of these 800 cases, one third were received from various sources as individual consultations, one third through Dr. I. J. Selikoff, most of them derived from occupational studies, and one third as part of a collaborative epidemiologic study. The cases that comprise the first two thirds of those collected were heterogeneous with regard to quantity and

TABLE 1

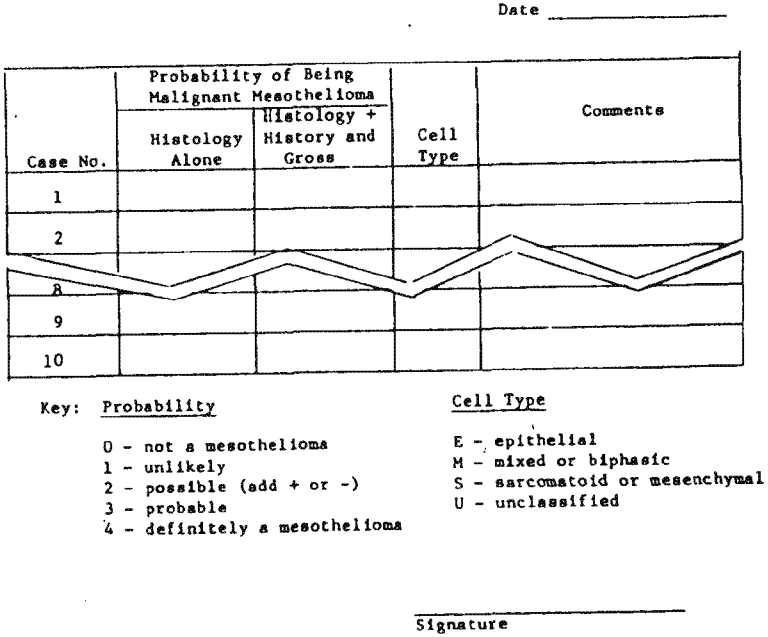
CASES OF MESOTHELIOMA IN BMHC MESOTHELIOMA REGISTRY

Site	Pleura	Peritoneum	Both*	Pericardium	Tunica Vaginalis	Total
Number	253 (60%)	146 (35%)	15	2	3	419

*One or both pleural cavities and peritoneal cavity involved equally.

quality of information and tissue for study. The grading of these cases as to certainty of diagnosis was in many instances affected decisively by deficiencies in the elements of data and/or material for histologic examination. Thus, the grading of many of these cases reflected not the definitive character of the case itself or our fully informed judgment but the failure or inability of the contributing pathologist to submit to us, or our inability to successfully solicit, totally satisfactory information or tissue specimens. Moreover, of these two thirds, the majority were seen by only two of us (J.C. and M.K.), and a relatively small number, usually more complex cases, were referred to the entire panel. To analyze for statistical purposes these two thirds requires a case by case review, which we have not yet completed. Therefore, these cases will not be presented in detail as to certainty of diagnosis at this time. Of the 517 cases referred to above, 419 were considered highly possible to definitely mesothelioma, and these 419 cases are presented merely by site of origin (TABLE 1).

In the last third of cases mentioned above, which comprises 168 cases submitted in


Date _____

Case No.	Probability of Being Malignant Mesothelioma: Histology Alone	Probability of Being Malignant Mesothelioma: Histology + History and Gross	Cell Type	Comments
1				
2				
8				
9				
10				

Key: Probability

0 - not a mesothelioma
1 - unlikely
2 - possible (add + or -)
3 - probable
4 - definitely a mesothelioma

Cell Type

E - epithelial
M - mixed or biphasic
S - sarcomatoid or mesenchymal
U - unclassified

_____
Signature

FIGURE 1. Mesothelioma review project score sheet used by panel.

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TABLE 2

MESOTHELIOMA REVIEW PROJECT: DIAGNOSTIC GRADING OF 168 CASES

	Pleural					Peritoneal					One or Both Pleurae and Peritoneum Involved Equally					Pericardium		
Panel median grade	0,1	2	2	2+	3,4	0,1	2	2	2+	3,4	0,1	2-	2	2+	3,4	0	3,4	
Number of cases	15	5	2	13	81	6	1	1	3	33	0	1	0	1	3	1	2	
Total	116 (69%)					44 (26%)					5 (3%)					3 (2%)		

a national survey of mesothelioma cases in the United States in 1972, pathologists supplied adequate clinical histories, gross pathologic descriptions, and tissues for the preparation of sections for panel distribution. All of these cases were submitted to the panel. This group of cases is reviewed here briefly as an example of panel function. The panel members recorded on a score sheet (FIGURE 1), grading the case in terms of *certainty of diagnosis* before and after reading the history and gross pathology findings, with space for comment. Grading was expressed in terms of a 0-4 numerical system employed earlier in the Canadian surveys. The meanings of these numbers are indicated in FIGURE 1. The numeral 2, possibly a mesothelioma, indicates a position of no preference for mesothelioma or for any other tumor. Panel members were given the option of signifying if, in fact, they inclined somewhat less (2-) to the diagnosis of mesothelioma or somewhat more (2+), without wishing to take a more positive stand. The median of the panel members' opinions was used for the final evaluation of the case (TABLE 2). Seventy percent of the cases were accepted as probable or definite mesotheliomas; 13% were rejected and 16% were considered possible over a span of less to more.

When the median of the panel's judgment was compared to the individual members' gradings and the degree of agreement among the panel members was evaluated, it was found that there was essentially strong agreement in the 3 and 4, and good agreement in the 0 and 1, categories (TABLE 3). However, in the "possible" group (2-, 2, 2+), the agreement was not good. Even in the 2+ grade, the median indicating a preference for the diagnosis of mesothelioma, there was disagreement among the panel members in more than half of the instances at this level. However, this group of cases constitutes less than 10% of the total series.

Another aspect of the panel's study of the cases was the assignment to a cell type as indicated in FIGURE 1. The greater association of the mixed cell character with asbestos exposure has been reported.[6] In the present series, as yet no correlations with asbestos exposure have been made, but it is interesting to note that in 64% of the cases, the majority opinion favored an epithelial character and in only 13% a mixed cell type.

TABLE 3

PANEL'S MEDIAN JUDGMENT VERSUS PANEL MEMBERS' AGREEMENT

Panel's median judgment	0	1	2-	2	2+	3	4	Total	%
Number of Cases									
Strong agreement	8	5	1	0	0	54	48	116	69.0
Lesser agreement	2	6	3	0	7	14	1	33	19.6
Disagreement	0	1	3	3	10	2	0	19	11.4

In 14% of cases, no majority was reached. These and other phases of this study will be described further in another publication.

The Mesothelioma Panel of the Canadian Tumour Reference Centre is one of 15 specialized pathology diagnostic panels of that organization, which is a unit of the National Cancer Institute of Canada, located in Ottawa. Founded in 1968, this panel has reviewed almost 300 cases of diffuse mesothelioma or suspected mesothelioma. It has collaborated also with the McGill University group in epidemiologic surveillance studies of mesothelioma in Canada. The panel, a five-member body, reviews sections and histories in all cases submitted. A Canadian member of the Canadian panel has been a member of the United States panel since its inception and an American member of the United States panel is also a member of the Canadian panel. The present Canadian member of both panels has also served on the United Kingdom panel.

DISCUSSION

From the Third National Cancer Survey tables, one would infer an annual occurrence of about 500 cases of mesothelioma per year in the United States during the years 1969–71.[12] The sources employed in this survey were very varied and numerous. Questions can be raised as to the precision of case determination from these various derivations. There may be disagreement as to whether this figure represents an over- or underestimation and by what degree. However, the literature has indicated an increase in diffuse malignant mesothelioma in recent years, and a further increase is anticipated for some period of time. Thus, the continued epidemiologic monitoring of prevalence is of fundamental importance. In any case, it is agreed that it is essential that the diagnosis be confirmed by pathologic examination. Dr. Alison McDonald[13] has told us that continuing registration through pathologists in Canada has provided a reasonably complete ascertainment of mesothelioma.

The pathologist must be capable of making the diagnosis or at least of suspecting it. We have the impression from the example of the survey previously cited that, as judged by the mesothelioma panel, the majority of pathologists have such a capability. In an undetermined proportion, the original pathologists, suspecting mesothelioma, had independently availed themselves of more expert opinion.

One may ask why, if most pathologists have the ability to make the diagnosis or can obtain consultation, panels are really necessary. First, there is a not insignificant segment of error. Second, we do not know whether the cases diagnosed correctly, or at least suspected, represent the contribution of those pathologists most conversant with the entity through study or previous experience. It is entirely conceivable that cases are attributed to other origins by pathologists who lack appropriate information on mesothelioma.

The primary duty of the panels is to render a decision, which is the more reliable because it is that of a group, whose members are experienced in the diagnosis of mesothelioma, and in estimating the degree of certainty attributable to that diagnosis. Acting as a consultant body in individual cases for individual pathologists faced with a trying problem or collaborating with epidemiologists in surveys of prevalence, usually with the element of asbestos exposure under consideration, panels have performed a useful function. However, it would seem evident that their potential would be greater with more extensive organization, possibly increased membership, more widely distributed geographically, and presupposing substantial support. With these advances, their ability to collaborate with the pathologists of individual medical

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institutions would be enhanced. An additional panel function is suggested here: the stimulation of more complete case detection and reporting.

This suggestion implies still another function, not yet undertaken, essentially educational: to persuade pathologists of the importance of maintaining a high index of suspicion and to give them helpful morphologic and technical information and ready access to reliable consultation. The more extensive panel system could help to accomplish these ends by the use of appropriate publications, seminars, or workshops at professional society meetings and by making available study sets of suitable slides. The preparation of an atlas of mesothelioma morphology has not yet been accomplished, but a start has been made. Pathologists could be persuaded of the importance of soliciting from clinicians thorough occupational and environmental histories and adequate general clinical histories. They must also be convinced of the necessity of ascertaining, as far as study performed on the individual case permits, a knowledge of the gross pathologic state in that case. Through the panels, the development of facilities and routines for determining the asbestos content of lung tissue would be an objective. It may be pertinent to mention at this point that the establishment of any etiologic association with asbestos must be predicated on diagnosis independent of that consideration. The diagnosis must be based on gross and microscopic pathology with relevant clinical and radiologic features, not including any reference to asbestos exposure.[2]

At the panel level itself, it is apparent that circulation of material to its members by mail does not permit full realization of the panel's potential. Periodic meetings are really requisite. One example of what can be attempted in direct group exchange is the reduction of observer variation, manifest particularly in the category of cases designated as possible: not only have the panel median verdicts been indecisive, but wide disagreement among its members also has been manifest, as previously pointed out.

There has been evident recently in this country a significant arousal of general interest in mesothelioma, because cases associated with indirect occupational, bystander, incidental, neighborhood, and domestic asbestos exposure have been apparent. There has been interest particularly in those who have worked in shipyards.

The appropriate governmental agencies are concerned, and action is being planned. The mesothelioma panel can play a critical role in the assessment and management of the problem of case detection and confirmation.

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