11

Prevalence, Diagnosis, and Course of Mesothelioma

In this chapter the same plan will be followed as in that on the Asbestoses (Chapter 9). The text throughout will combine the experience gained in extensive studies at Mount Sinai with that published by other observers.

PREVALENCE

The difficulties in establishing meaningful measures of prevalence that were mentioned for asbestosis in an earlier chapter are still further compounded in the case of mesothelioma. Of particular importance in this respect are: the characteristically long interval after initial exposure before the tumor appears; the small size of the trigger dose that can be effective, and the opportunity for acquiring this dose in situations such as those of associated trades, neighborhood dwellings, or familial association; the unreliability of death certificates and the thorough investigation necessary for the establishment of a firm diagnosis; the difficulties often presented by the histological picture even where unremitting care has been taken in obtaining representative specimens; variability in the degree of conservatism exercised in making a final diagnosis; failure of statistical records in earlier years to distinguish between carcinoma of the lung and mesothelioma, and the continuing practice of condensing the causes of death in published tables so that lung, pleura, trachea, and larynx are lumped together.

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No more than a casual survey of the literature is required to show that prevalence data are reported in a wide and confusing variety of ways with varying degrees of usefulness. At least six types of presentation can be identified, appearing singly or in combination, with information content varying from the incidental to the concrete. In ascending order of utility for indicating prevalence they are: (a) Citation of cases seen in the course of personal or hospital practice without reference to the total number of cases seen or to the size of the population covered. Registries which rely upon the voluntary cooperation of pathologists or practitioners are liable to fall into this category unless special care is taken to acquire ancillary information. (b) The proportion of cases among those diagnosed as having asbestosis that have developed mesothelioma or in which significant concentrations of fibers or asbestos bodies have been demonstrated in the lungs. (c) The proportion of cases among the full spectrum seen in practice or at autopsy that have developed mesothelioma. (d) The proportion of deaths attributable to mesothelioma in a population group with a known risk of exposure to asbestos. Registries to which there is a legal compulsion for entry partake of this category. (e) The proportion of deaths attributable to mesothelioma in a defined cohort of persons exposed to a known risk of exposure. (f) The proportion of cases developing mesothelioma in a cohort of persons exposed to known concentrations of asbestos dust. (Few measurements were made 30 to 40 years ago when today's cases of mesothelioma were experiencing their initial exposure.)

To the extent that the data permit, the available information on prevalence will be reviewed here by population groups in order to give practitioners an indication of the frequency with which they are likely to encounter the disease among the patients that they see. It would be futile, however, to attempt a national estimate from the data given; the same cases may well appear in more than one of the groups reviewed, and may have been reported by more than one investigator, or by the same investigator at various times. On the other hand, many investigators feel that the number of cases actually reported constitute an underestimate of the number that actually occur, partly for lack of listing in registries and partly because of missed diagnoses.

Various attempts have been made to compensate for uncertainties in the originally reported data by sophisticated statistical analysis but the inherent uncertainties remain. We will present the information contained in the original reports with no more than minimum comment, but the user would be well advised to observe the ancient adage of "caveat emptor."

World Locations

The date of Table 11-1 have been taken from a comprehensive review recently prepared by McDonald and McDonald (497). The existence of "hot spots" in the world population is clearly evident but it should not be assumed that other areas are free from risk. Within a general statistic covering a city, county, or country there may well be other smaller "hot spots" of insufficient extent to affect the average but of great importance to the individuals affected.

TABLE 11-1

Observed and Expected Mortality from Mesothelioma in Certain World Areas (497)[a]

Location	Period[b]	Observed	Expected[c]	Ratio
Walcheren, Netherlands	1962–1971	35	1.5	23.3
Wilhelmshaven, BRD	1963–1969	28	1.3	21.5
Somerville, N.J., USA	1963–1972	53	2.0	26.5
Dresden, DDR	1964–1967	62	3.7	16.8
Plymouth, Gt. Britain	1967–1968	14.3	1.0	14.3
Haarlem, Netherlands	1969–1971	10	1.2	8.3
Trieste, Italy	1963–1972	43	5.3	8.1
Malmö, Sweden	1957–1966	35	5.0	7.0
Rotterdam	1969–1971	37	5.3	7.0
Hamburg, BRD	1958–1968	251	36.1	7.0
Nantes, France	1965–1970	30	4.3	7.0
Merseburg, DDR	1955–1967	26	4.3	6.0
Clydeside, Gt. Britain	1967–1968	34.8	6.2	5.6
Merseyside, Gt. Britain	1967–1968	26.7	4.9	5.4
Tyneside, Gt. Britain	1967–1968	11.3	2.8	4.0
Belfast, N. Ireland	1950–1964	42	11.4	3.7
Noord- & Zuid-Holland	1969–1971	78	24.8	3.1

[a] With kind permission of J. C. McDonald.

[b] The varying periods covered during a time of increasing incidence make comparisons between locations difficult.

[c] Calculated by applying average annual age and sex specific rates from a Canadian survey, 1966–1972. (The "expected" rates obtained in this way appear to be higher than would be suggested by reports prepared in the first half of the century—see Chapter 10.)

General Populations

A number of reports, particularly in past decades, have restricted themselves to indicating the prevalence of the disease in a population group with no more than general implications of its composition by trade, residence, or exposure opportunity. Some of these reports are

given in Table 11–2, and serve to extend the information given in the preceding table. [A]

Miners and Millers

As with asbestosis, data on mesotheliomata in miners and millers are limited. The first and third of the reports included in Table 11–3 have widely different implications; they may represent extreme instances.

Factory Workers

Fairly extensive studies have been made in Britain and the United States on the prevalence of mesothelioma in workers in factories that convert asbestos into textiles, insulation material, building material, and an increasingly wide variety of other end products. The data of Table 11–4, published by various authors, are among the best that we have on prevalence.

Construction and Engineering Workers

Insulation and shipyard workers have been fairly extensively studied. Among the latter are many individuals who do not themselves handle asbestos but are subject to a general exposure prevailing in the yards. Representative data on the prevalence of mesothelioma in these employees are given in Table 11–5.

Nonoccupational Groups

Table 11–6 cites series of cases that have been reported as occurring in persons only peripherally associated with asbestos, such as those living or working in the neighborhood of mines or manufacturing plants, or members of asbestos workers' families.

There are, in addition, several reports of single cases developing in no more than peripheral association with asbestos that lead us into the terra incognita of cases in which no history of exposure could be ascertained. These may include up to one-third of the cases reported in some series, as was emphasized in the preceding chapter.

Summary of Prevalence

The diverse nature of the information reported in the literature precludes the compilation of neat estimates of the frequency with which

TABLE 11–2

Reports of Prevalence of Mesothelioma in Communities Served by Hospitals or Some Form of Registry, Without Specification of Occupation or Exposure

Authors	Period	Type of community	Number or proportion[a]	Comment
Roitzsch (625)	1950–1968	Dresden, mfg. city	56m in 28,792 autop	25 had asbestosis
Borow *et al.* (102)	1955–1965	Somerville, N.J. Mfg. 75% of asbestos mined in N. America	17m in 1,330 autop	
Hagerstrand *et al.* (302)	1957–1966	Malmo, port city	37m in 12,763 autop	250,000 inhab., 60% of deaths covered
Knappmann (412)	1958–1968	Hamburg, port city	251m in 79,841 autop	Complete autop
Borow *et al.* (103)	1951–1972	Somerville, N.J. largest asb. plant	72 cases	Incidence increased with time
McDonald and McDonald (496)	1960–1972	Canada	312 cases	Voluntary reporting by pathologists
Roberts (614)	1950–1967	Glasgow, mfg. city	20m in 6,406 autop	Histological asbestosis in 65%
Vigliani *et al.* (759)	1944–1963	N. Italian cities, mfg. asb. products	76m in 24,700 autop	Only persons over 40 yrs of age
Biava *et al.* (78)	1962–1975	Trieste	Pl m./10[6] population: 3.6, 1963—28.9, 1973	Asbestos exposure certain 63%, possible 8%

[a] In this and subsequent tables m denotes cases of mesothelioma, d denotes deaths, autop., autopsies, and w. workers.

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TABLE 11–3

Reports of Prevalence of Mesothelioma in Miners and Millers

Authors	Period	Type of community	Number or proportion	Comment
Wagner *et al.* (772)	1956–1960	N. W. Cape Province S. Africa	11 of 33m seen were in miners and millers	Crocidolite District pop. 43–81 thousand, 1921–1951
Webster (781)	?	Asbestos Tumor Registry	88 of 360m* seen in miners and millers	Crocidolite Majority (81) in 10,161 work force of Cape Province
McDonald and McDonald (497)	To 1974	Quebec Province, Canada	7m in 11,100w studied	Chrysotile Mainly open pit

* For 108 of the 360, exposure history was not known; a better denominator would be 252.

TABLE 11–4

Reports of Prevalence of Mesothelioma in Asbestos Manufacturing Workers

Authors	Period	Type of community	Number or proportion	Comment
Wagner *et al.* (772)	1956–1960	N. W. Cape Province S. Africa	5 of 33m seen were in this category	See Table 11–3
Lieben and Pistawka (459)	1958–1963	Pennsylvania	10 of 42m seen were in this category	From 162 hosp. serving 6½ million
Enticknap and Smither (230)	1958–1963	English factory workers	9m in 52 autop. with asbestosis	9,550 exposed
Newhouse (544)	1931–1970	English factory		
		Men under 2 yr. emp.		
		low–mod. exposure	2m out of 70d in 1,861w	Meso. rate 25*
		severe exposure	8m out of 105d in 2,417w	Meso. rate 71
		Men over 2 yr. emp.		
		low–med. exposure	5m out of 61d in 1,178w	Meso. rate 102
		severe exposure	9m out of 114d in 1,304w	Meso. rate 154
	1936–1970	Women under 2 yr. emp.	6m out of 55d in 557w	
		Women over 2 yr. emp.	5m out of 56d in 239w	
Selikoff *et al.*	1959–1971	United States production and textile workers	15m out of 199d in 689w	Only 4 by 1966; 12, 1966–1971
Selikoff *et al.*	1953–1966	English factory workers	0m out of 15d in 136w	Short exposures
Selikoff *et al.*	1959–1971	United States factory workers	11m out of 87d in 375w	Meso. rate 247
Selikoff *et al.*	1941–1971	United States amosite workers	7m out of 484d in 933w	
Edge (207)	1970	Shipyard community	5m in 100 unselected autop.	

* The *mesothelioma rate* was devised by Newhouse to express the number of deaths from this tumor per 100,000 man-years of risk, excluding the period before the tenth year during which there is no observable excess mortality.

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TABLE 11–5

Reports of Prevalence of Mesothelioma in Construction and Engineering Workers Using Asbestos

Authors	Period	Type of community	Number or proportion	Comment
Wagner *et al.* (772)	1956–1960	N. W. Cape Province S. Africa	3 of 33m seen were in this category	See Table 11–3
Newhouse and Thompson (546)	To 1964	Laggers. London Hosp. series	8 of 76m autopsies were in this category	48% of all cases occurred 1960–1964
Elmes and Simpson (219)	1940–1966	Insulation workers Belfast	7m out of 98d in 170w	Incidence increases with time
Stumphius (724)	1962–1968	Shipyard workers Netherlands	22m in 3,999 men = 1/1,000 per year	Rate varies with job: 0.5–2.8/1000
Harries (318)	1964–1973	Naval dockyard Devonport, England	66m cases	15,000 men
Selikoff *et al.*	1943–1971	Insulators New York and New Jersey	32 m out of 421d in 623w	Meso. rate 291[a]
Selikoff *et al.*	1967–1971	Insulators Canada and United States	77m out of 555d in 17,800w	Meso. rate 89
Ashcroft (51)	?	Shipyard workers Tyneside	41m	
Stossel *et al.* (718)	1963–1969	Shipyard workers Wilhelmshaven	28m	
Webster (781)	?	Railways and other S. Africa	34 of 360m in Asbestos Tumor Registry	History not known for 108 in Registry

[a] For "mesothelioma rate," see Table 11–4.

TABLE 11–6

Reports of Prevalence of Mesothelioma in Nonoccupational Groups

Authors	Period	Type of community	Number or proportion	Comment
Wagner *et al.* (772)	1956–1960	N. W. Cape Province S. Africa	13 of 33m seen were in this category	See Table 11–3
Newhouse and Thompson (546)	To 1964	Relatives worked with asbestos London Hospital series	9 out of 76m autop. were in this category	See Table 11–5
Lieben and Pistawka (459)	1958–1963	Pennsylvania	11 of 42m seen were in this category	See Table 11–4
Lemesch *et al.* (453)	1960–1972	Israel	65m	All but 1 nonoccupational; diagnosis confirmed in 52/65
Anderson *et al.* (18)	1965–1975	Household exposure reported from various countries	37m	Some will have been included in above items; see Table 10–5

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mesothelioma can be expected to appear in various population groups. The inclusion in the denominator of deaths occurring before 1960, when few persons exposed to asbestos had survived long enough after initial exposure for the disease to appear, tends to dilute some of the rates reported. The incidence, moreover, is still increasing. Misdiagnosis, in both directions, and omissions from registries and less formal listings, add uncertainty to the numerator. Nevertheless, it is believed that the data reviewed above will provide the medical practitioner with a realistic idea of the frequency with which he will encounter the disease. From being a very rare disease, diffuse malignant mesothelioma, to give it its full and rightful name, has now become much more common. The McDonalds report that since 1925 the United States and Canada have recorded over 500 cases, the world at large about 4,500 (497); South Africa lists 360 cases in its Registry (781), while Greenberg and Davies consider an annual incidence of 120 in Great Britain a considerable understatement of the true prevalence (293). The same remark could probably be applied with truth to the other figures as well.

It would seem from the incomplete data available, that the prevalence among certain groups of workers in the United States is higher than anywhere else. Compare, for example, the "mesothelioma rates"* of 291 for insulators (Table 11–5) and 247 for factory workers (Table 11–4) in the United States with the highest rate of 154 reported by Newhouse for factory workers with severe exposure (Table 11–4). Insulation workers, asbestos processors, and shipyard employees (not only those handling asbestos) are particularly vulnerable. Persons resident or working near factories handling asbestos, from which fibers can enter the communal environment, are also open to being affected, though to a somewhat lesser extent than the employees themselves. Somewhat surprising to the medical practitioner, perhaps, though not to those engaged in public health, is the liability of workers' family members to effective exposure. The occurrence of family and neighborhood cases is by no means confined to asbestos operations; beryllium, lead, arsenic, polychlorinated biphenyls (PCB's) and other materials can affect wider groups than the industrial employees themselves, principally through contamination carried home on clothing.

With spreading realization of the hidden dangers of exposure to asbestos, and the progressive tightening of atmospheric standards (see Chapter 19), more and more effective controls have been placed on the dissemination of dust. As indicated in Chapter 7, this action has resulted in a reduction of the incidence of parenchymal asbestosis, but it has not had a comparable effect on that of mesothelioma. When we look at the small or almost trivial doses that some of the mesothelioma cases have had, we can hardly expect much improvement with the levels that have been permitted in recent years. Newhouse and Berry have recently predicted that the mortality for male asbestos factory workers in their British cohort (3,000 men and 700 women) can be expected to rise to between 7 and 11% during the 1980's, but to decline thereafter because of the decreasing size of the residual survivors. The prevalence is expected to be somewhat higher for the women members (545). A further reduction of permitted dust levels may reduce the incidence in years to come, but even then it is doubtful if it will come down to its pristine (19th century) level.

* See Table 11–4 for definition of "mesothelioma rate."

DIAGNOSIS*

There are many difficulties in the diagnosis of the various forms of asbestosis, as indicated in Chapters 7–9, but those encountered in establishing a firm diagnosis of mesothelioma are often much greater. Diagnosis is particularly difficult in the early stages of disease, and many articles have been devoted to the problem (91,215,353,470,501,644,772). From the detailed features of the disease discussed in the preceding chapter we will repeat here just those which are critical to diagnosis, with some comment on techniques involved.

Exposure History

Where there is a history of exposure to asbestos, it is clear from what has been said in preceding pages that the possibility of mesothelioma must be entertained; even where there is no such history the possibility should not be overlooked. Unfortunately, a history of exposure is often lacking, either because one was not sought with sufficient diligence or because the patient was genuinely unaware of the possibility. As has been mentioned before, exposure may be denied in up to one-third of the cases in some reported series. Webster, for instance, indicates that there was no known exposure in 47 of the 360 cases in the South African Asbestos Tumor Registry, and that the history was unknown in 108 others (781). Under these circumstances, one can do little more than reiterate the importance of obtaining a complete occupational and resi-

* See also Chapter 10 on Clinical Manifestations.

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dential history for every patient, and of bearing in mind the possibility of mesothelioma in anyone who has worked with asbestos, has been a member of a family of an asbestos worker, or has resided in the vicinity (up to two miles) of a plant or operation that uses asbestos. Even when great care has been exercised in this respect, there will be a residuum of cases in which the history provides no clue, and these are the ones that are most likely to be missed until the disease is advanced or an autopsy reveals the condition. In Mann's phrase, a high index of suspicion is required. The incidence will probably never be startlingly high; the disease accounts for only 7–14% of deaths even in those who have been occupationally exposed. Mesothelioma may still be a rather uncommon event, but it is of uncommon importance to the affected individual.

Symptomatology

In the early stages of development, the functional impairment produced by mesothelioma is apt to be slight. With its tendency to spread along serous surfaces rather than to invade underlying tissues in the early stages, little more than a gradual restriction of respiratory or alimentary function, with correspondingly vague symptoms, is likely to occur. Attention is commonly drawn to its presence only after it has reached a more advanced stage, involving sensory nerves or interfering with lymphatic drainage. Thoracic pain is often the presenting symptom in pleural cases. Pleural effusion may have occured earlier, but without much in the way of symptoms unless it was of sufficient extent to interfere with respiration. In the peritoneal form, vague discomfort developing later into pain is the usual presenting symptom. Ascites generally does not become noticeable until the disease is fairly well advanced, but there may not have been anything to bring the patient for advice until that point. Loss of weight usually occurs fairly early with the peritoneal form, but later with the pleural.

As the disease progresses and involves other tissues and organs through compression or invasion, corresponding symptomatology develops. In some instances it is only this secondary involvement that leads to presentation, with the underlying mesothelioma discoverable only on careful examination. On rare occasions, the presence of a tumor has been revealed only at autopsy. Sooner or later, however, pain usually becomes a marked feature; it is generally persistent, unresponsive to analgesics, and not particularly related to respiratory movements, even in the pleural form. The onset of pain in a patient with a hitherto silent pleural effusion is highly suggestive of mesothelioma.

Radiography

The presence of mesothelioma must be considered in any case which has already shown pleural reaction to asbestos, as by the development of pleural plaques with or without effusion. A thorough radiological examination is called for in such cases. Rapid extension of pleural thickening, or the reappearance of effusion after tapping, should excite suspicion. In a high proportion of cases, however, there are few if any such prior developments to foreshadow mesothelioma development.

Effusion may be the first condition to come to the radiologist's attention. Oblique views may catch the tumor end-on and reveal protuberances on its surface. A pneumothorax accidentally induced at the time of aspiration, or more deliberately created for diagnostic purposes, may aid in visualization. Persistence of a shadow after removal of fluid is particularly suggestive. The tumor is usually unilateral, at least in its early stages, and appears somewhat more frequently on the right side. When extensive, it may appear as a dense shadow obliterating the affected side. Involvement of the heart shadow, when it occurs, is particularly significant; cardiac tumors are rare, and mesothelioma contributes one-half of them (236). Apart from these features and any preexisting pleural plaques, there is little in the radiological picture to distinguish mesothelioma from other tumors that may be present in the pleura; although massive, diffuse and unilateral involvement is more common with mesothelioma than with metastatic spread from primary tumors elsewhere (644). Angiography has been used with some success in defining a peritoneal tumor (443).

Pathological Confirmation

Demonstration of a histological picture characteristic of mesothelioma is the test that almost every diagnosis must meet. It is, for example, a necessary criterion for entry into the Mesothelioma Registry of Great Britain (293), all other evidence being regarded as suggestive rather than diagnostic. But even histological demonstration is not without its difficulties. The risks and uncertainties attending needle biopsy have been mentioned in earlier chapters. Tissue obtained at open thoracotomy or laparotomy is more reliable, but the severity of the procedure and the possibility that the tumor may spread along the incision limit the applicability of this approach. Something of a compromise is provided by pleuroscopy (452) and peritoneoscopy (619) with visually directed biopsy. Fiberoptic bronchoscopy and transbronchial biopsy may be useful for detecting underlying parenchymal

asbestosis, but the mesothelial tumor usually lies too superficially to be reached by this route until it has invaded underlying tissue. At autopsy, of course, a complete search for relevant tissue can be made, and the possibility of an extension or metastatic implant from a primary tumor elsewhere can be checked.

Diagnosis is left in little doubt when the characteristic tubopapillary histological structure is seen, but when the appearance is nonspecific, i.e., consistent with mesothelioma but not excluding the possibility of another tumor, the decision is less certain. This uncertainty increases with very anaplastic or pleomorphic neoplasms. The appearance of adenomatous structures, on the other hand, would introduce the possibility of the tissue having come from a bronchial carcinoma. The uncertainties of the histological picture were described in the preceding chapter. Tissue from several areas of the tumor need to be examined since seemingly benign tissue may be interspersed with the malignant. Variations in histology themselves strengthen the probability that the tumor is a mesothelioma.

The following extract from the Appendix to a recent paper by Greenberg and Davies describes the procedures used by the British UICC Panel of Pathologists for resolving doubts (293):

> In mid-1971 the following protocol was designed for combined panel diagnosis. Two opinions are necessary for diagnosis and these two opinions should be combined as below:

First opinion	Second opinion: Definite	Probable	Possible	Not
Definite	Definite	Definite	—	—
Probable	Definite	Undecided	Undecided	—
Possible	—	Undecided	Undecided	Not
Not	—	—	Not	Not

> If the two opinions lead to a blank entry above then the specimen should be sent to the two other readers and a combined diagnosis made on the basis of four readings. There are many possibilities from four readings but the combined diagnosis should follow the majority if there is a clear one and otherwise be undecided. The following rule is sufficient to determine all cases of four readings: score a definite as 1 point, probable as ½, possible as 0, not as −1; then add up the four scores and if the total is greater than or equal to 1½ the diagnosis is Definite, between −1 and +1 inclusive it is Undecided, less than or equal to −1½ is Not a mesothelioma.

The fact that this complicated procedure has been found necessary after eight years of experience testifies to the difficulties of histological diagnosis. McCaughey and Oldham found 18% disagreement between the more experienced pathological examiners, rising to 32% among the less experienced (492). Panels in general find they have to reject a considerable percentage of the submitted cases.

The identification of malignant cells in pleural or peritoneal fluid is equally if not more difficult. Nevertheless it has been found at Mount Sinai to be useful in one-half to two-thirds of the cases investigated. It has been recommended that a diagnosis of probable mesothelioma should not be made from fluid cytology unless the cells that are identified as being malignant also show the characteristics of mesothelial cells (125,615). The absence of such cells, however, does not negate a diagnosis made on other grounds. Butler and Berry describe four patterns of cells seen in serous fluid: papillary pleomorphic, papillary nonpleomorphic, a mixed pattern, and single cells (125). They give guidelines for distinguishing benign mesothelial, malignant mesothelial, and carcinomatous cells. Legrand and Pariente find examination of cells by electron microscopy useful (450).

Kannerstein and his associates have summarized their experience with histochemical aids to diagnosis at Mount Sinai (389,390). Two tests are applied to histological sections. The first is the reaction of cytoplasmic and luminal secretion to the periodic acid–Schiff reagent after removal of glycogen by diastase (DPAS), which gives positive results with the neutral mucin characteristic of epithelial cells, and is thus likely to be shown by adenocarcinomatous but not by mesothelial cells, in which the mucin consists of acid mucopolysaccharides. The second is application of the Hale colloidal iron stain with and without prior removal of the hyaluronic acid component of the acid mucopolysaccharide by a hyaluronidase preparation. Their experience with 82 mesotheliomas with varying degrees of diagnostic probability by other evidence, as well as with 26 carcinomas, is summarized in Table 11-7.

TABLE 11-7

Histochemical Reactions of 82 Mesotheliomas and 26 Carcinomas (390)

	Mesotheliomas				Carcinoma
	Definite 30	Probable 24	Possible 28	Total 82	26
DPAS positive	0	0	0	0	12
DPAS questionable	1	4	3	8	0
CI positive	23 (77%)	13 (54%)	6 (21%)	42 (52%)	13
CI questionable	1	1	4	6	0

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Their comments on this procedure are as follows:

> In the definite cases, where the likelihood of a positive reaction is greatest, it serves as a reassurance and a check on initial classification. Unfortunately, in the merely possible cases, where demonstration of the presence of hyaluronic acid would be most helpful, a positive reaction is least likely to be present. However, in this area the demonstration of a positive DPAS and of nonhyaluronic acid mucosubstance were helpful in some cases in weighing the decision against a mesothelioma and in favor of a carcinoma. One might mention that some of those mesotheliomas that showed a questionable DPAS also showed acid mucosubstances that were only in part hyaluronic acid, and these cases must be evaluated with caution.
>
> It is in the intermediate group that the method may be most frequently of value. A little over one-half of these cases were positive, and in this category the presence of hyaluronic acid may be of particular significance in confirming the evaluation of the case (389).

Boersma and colleagues describe a method for the measurement of hyaluronic acid in serous fluids by electrophoresis after its liberation by a reducing agent (87). Supporting evidence for the nature of the substance measured is given by its reaction with toluidine blue and its sensitivity to hyaluronidase. They find this material consistently absent from fluid induced by secondary tumors. Possible sources of confusion are purulence, antimitotic medication, and heparin in the fluid. An alternative method is by fractionation of the fluid and measurement of the carbazol : orcinol ratio in the eluted material. The authors suggest that this method may be applied to tissues after hydrolysis by papain and pronase. In a later paper they discuss their findings in 1,580 samples of pleural fluids (88). In 100 cases in which hyaluronic acid was found, 57 had pleural mesothelioma confirmed by pathology, 17 were diagnosed as having the disease by clinical and radiological criteria, but pathological examination was not done or was uncertain, 12 had tissue diagnosed as probable secondary growth but a primary tumor was not found, 4 had mesothelial hyperplasia, 2 had lung cancer, 6 had tuberculous pleurisy, 2 had pleural asbestosis, 1 had a benign pleural tumor, and 1 had subpleural fibroblastic sarcoma. They emphasize the absence of any false negative finding in the 1,580 samples. The number of effusions studied was extended to 2,339 in a later paper (89).

Most of these tests, of course, depend upon the mesotheliomatous cells continuing their biochemical behavior as mesothelial derivatives, perhaps with some exaggeration as in the production of mucin. But the more sarcomatous or anaplastic that the cells become, the less they retain of these characteristics, and the more difficult they are to identify by histochemical as well as by morphological methods. The tests also require the services of a fairly sophisticated laboratory, which may limit their widespread applicability.

Differential Diagnosis

Nonmalignant Pleural Asbestosis

It may be difficult to distinguish between a benign increase in pleural plaque formation and the supervention of malignant growth. Any rapid increase in the amount of pleural thickening, or the appearance of irregularities on the surface, should be regarded as highly suggestive. A pleural effusion which increases in size, reappears after tapping, or fails to show signs of spontaneous resorption is also suggestive of malignant change. Histological examination of a satisfactory biopsy specimen (see above) may provide the necessary evidence, but a surgical procedure, other than thoracocentesis to obtain fluid for cytological examination, is not to be undertaken lightly.

Carcinoma

A bronchogenic carcinoma from which there is a direct or metastatic spread will usually be found to lie in the substance of the lung on radiographic examination, in addition to its presence in the pleural cavity. A carcinoma spreading on the pleura, however, may be indistinguishable from mesothelioma; only histology can provide the answer, and then not invariably. Bilateral radiological opacities are more consistent with metastases from a carcinoma, but would need to be distinguished from pleural plaques as mentioned in Chapter 8. [A]

Tuberculosis

In the early years of the century, when tuberculosis was common and could coexist with asbestos disease, confusion could occur; the possibility, however, is less likely today. Pleural thickening from tuberculosis is more apt to appear in the upper part of the thorax; mesothelioma in the lower part until it spreads. Biopsy or cytological examination of effusion fluid will usually settle the diagnosis. Much the same may be said for peritoneal developments of the two diseases.

Other Abdominal Tumors

Evidence of functional interference by invasion or constriction usually develops more rapidly and is more localized in cases of carcinoma, but diffuse carcinomatous processes may mimic mesothelioma in this respect. We have seen metastases from occult gastric carcinoma simulating it, for example. Subdiaphragmatic mesothelioma may imitate carcinoma of the pancreas, a tumor which seems to be appearing more frequently, just as is mesothelioma. In contradistinction to carcinoma, mesothelioma usually gives rise sooner or later to marked ascites. Endometriosis is more apparent in the pelvic area, but mesothelioma is

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sometimes found in a hernial sac (of either sex) or even in the tunica vaginalis. Peritoneoscopy and perhaps celiac angiography may help in establishing the diagnosis.

Other Causes of Ascites

Distinction from ascites of cardiac or renal causation is usually provided by the other manifestations of those diseases. Liver function tests and the presence of collateral circulation should help to differentiate ascites attributable to hepatic cirrhosis. Rapid reappearance of ascites after paracentesis is characteristic of mesothelioma.

CLINICAL COURSE (P. Chahinian)*

The disease is invariably fatal, death resulting from restriction of ventilation, involvement of pericardium, internal hemorrhage from invasion of a large blood vessel, malnutrition, or intestinal obstruction depending upon the original site of the tumor and the path of local or metastatic growth. Pneumonia of the contralateral side is a frequent cause of death.

A large proportion of patients die within a year of diagnosis (Tables 11–8 and 11–9). Nevertheless, Whitwell and Rawcliffe, who report one of the lower speeds of death (53% survival 12 months from onset of symptoms), found that only 4% of bronchogenic carcinoma cases had survived that length of time (792). They insist that the duration of illness is much longer than is usually thought. The treatment given to patients has been very varied.

Palliative Surgery

Under this term may be included thoracotomy with biopsy, partial resection, and decortication. In addition to providing opportunities for improved diagnosis, these procedures may improve the quality of survival by limiting the reaccumulation of pleural fluid, or by relieving pain. There is very little evidence, however, that the duration of survival is increased.

Curative or Radical Surgery

This term designates the cases where the entire tumor was apparently removed. The procedures include total pleurectomies and radical pleuropneumectomies. They are infrequently performed. Involvement

* Principal author of this section.

TABLE 11–8

Overall Survival of Patients with Diffuse Malignant Mesothelioma of Pleura (Including Treated Patients)

Authors		Year	No. of cases	Survival in months from onset of symptoms: Mean	Median	Range	% Patients dead at 1 year
Dufray and Rosson	(201)	1920		6–9			
Geschickter	(268)	1936	25	>24			
Saccone and Coblentz	(639)	1943	19[c]			3–24	84
Hochberg	(337)	1951	43[c]			3–48	86
Godwin	(282)	1957	9	14	7	1.5–66	
Poulsen and Sorensen	(586)	1959	27	9.9			
Caffrey and Lucido	(126)	1961	5	6		2–10	100
Sleggs *et al.*	(692)	1961	28				61
Manguikian and Prior	(477)	1963	5	12		3–24	60
Semb	(674)	1963	10	16.8	13	2–48	40
Newhouse and Thompson	(546)	1965	42	14.6	12	2–30	50
Reisner and Huzly	(605)	1967	33	<12			
Ratzer *et al.*	(598)	1967	15[a] 15[b]	21 19	19 13	11–58 3–82	
Porter and Cheek	(583)	1968	7		7	2–96	86
Roberts	(614)	1970	20			<15	85
Oels *et al.*	(558)	1971	28				78
Whitwell and Rawcliffe	(792)	1971	36				47
Elmes	(217)	1972	250[c]	12			
Borow *et al.*	(103)	1973	72[d]		15–16		only 1 survival >19 mos.
Lilis and Selikoff		1974	48	12.5		1–31	

[a] Epithelial type.
[b] Fibrosarcomatous type.
[c] Cumulative literature series.
[d] Including 21 patients with peritoneal mesothelioma.

of the chest wall, the diaphragm, or the lung usually necessitates that the surgery be extensive and thus difficult. While some surgeons favor this approach, the majority find that survival is not prolonged and that the patients die from early recurrence. In this connection, reference may be made to a recent paper by Butchart *et al.*, in which the experience with pleuropneumonectomy in 29 cases is analyzed (123). The authors conclude that the operation does not appear materially to affect the

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TABLE 11-9

Overall Survival of Patients with Diffuse Malignant Mesothelioma of Peritoneum (Including Treated Cases)

Authors	Year	No. of cases	Survival in months after onset of symptoms: Mean	Median	Range	% Patients dead at 1 year
Godwin (282)	1957	4	12	11	1–26	86
Winslow and Taylor (796)	1960	12*	18	11	1–60	58
Newhouse and Thompson (546)	1965	21	14.8	12	3–54	50
Elmes (217)	1972	45*	6			
Lilis and Selikoff	1974	68	9.5		2–29	

* Cumulative literature series

course of the disease in cases of mixed epithelial and mesenchymal type, but that a better prognosis can be expected in those cases where the histological structure is of pure epithelial type, especially those in which the tumor consists entirely of abundant edematous mucoid stroma with loosely arranged tumor cells. The hospital mortality for the whole group was 31% and only 3 patients survived 2 years or longer; 2 of these were alive and well with no evidence of recurrence 3½ and 6 years, respectively, after the operation.

Radiotherapy

Opinions concerning conventional radiotherapy are contradictory. The lack of controlled studies and the possibility of some isolated long survivals do not allow any firm conclusion.

High doses and high energy radiotherapy have given some encouraging results. Schlienger, Eschwege, and colleagues obtained a mean survival after first symptoms of 25 months, and mean survival after treatment of 13 months, as compared with 17.4 and 9.8 months, respectively, for cases given only palliative doses; the cases were not randomized, and only 8 were given the curative as compared with 24 of the palliative treatment (237,650). Other authors are more pessimistic (762). Objective improvements that were noted include relief of pain (but not of dyspnea), regression of vascular compression that may have been present, and some tumor necrosis seen at autopsy.

There is no good evidence that radiotherapy is effective in peritoneal mesothelioma, although we have seen isolated cases that suggest clinical improvement and apparent lengthening of life.

Chemotherapy

Isolated cases of mesothelioma have been reported which were treated with chemotherapy. No general conclusion is yet possible, due to the paucity of cases, the lack of information on the dosage and schedules of administration, and the lack of controlled studies. Nitrogen mustard has generally failed. Cyclophosphamide seems to have given some palliation in some cases. 5-fluorouracil resulted in a remission lasting several months in two patients (267). Numerous other drugs have been tried but conclusive results are not available.

McGowan *et al.* have obtained complete remission of several months with oral melphalan (502), and Waxman at Mount Sinai has treated nine patients with metastatic mesothelioma, using a combination of 5-fluorouracil, cyclophosphamide, and Velban (vinblastine sulfate). Five of the nine experienced symptomatic improvement and four of the nine an objective response with decrease in tumor size. The mean survival time was 17 months from diagnosis.

So far, adriamycin seems to be the most promising single agent (99,423,424). Since clinical and experimental data suggest that it has a radiosensitizing effect, seven patients have been treated at Mount Sinai with a combination of adriamycin and radiotherapy. All had recurrent or surgically incurable mesothelioma. In three cases there was complete failure of response; three showed a definite symptomatic improvement, and one had both symptomatic and objective improvement (137).

Local Therapies

Various local applications have been tried, such as nitrogen mustard and radioactive gold, without much success. One treatment should be mentioned if only for its novel nature. Esposito (238), acting on experimental evidence that RNA extracted from normal tissues inhibits tumor growth, injected RNA from hog's liver into the pleural sac after complete aspiration of the fluid; 8 out of 10 cases were reported in 1969 to have lost their symptoms and to be well 11.5 months after treatment. Further reports, however, have not been forthcoming.

Combined Therapies

Martini *et al.* (484) combined removal of the pleural tumor with external radiation to the entire hemithorax and with systemic chemotherapy. They state that 11 of 14 patients were alive after 1 year, and that the median survival time after pleurectomy was 16 months.

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Rogoff *et al.* treated four cases of peritoneal mesothelioma with intraperitoneal radioactive phosphorus and abdominal radiotherapy; three of them with some chemotherapy as well (619). Two patients survived more than 10 years, one was alive 2 years after treatment, and the fourth survived 1.5 years. [A]

Comment

The conclusions to be drawn from reports of treatment so far tried are disappointing. Not only are the results generally poor, but the various treatments have been applied in haphazard fashion and the reports are generally lacking in the detail which would permit systematic evaluation. It would appear most profitable at this juncture for two or three of the most promising regimens to be applied systematically to a series of cases under agreed protocols. To obtain a sufficiently large series for immediate treatment, the study would probably need to be organized on international lines. In the meantime, one must agree with Elmes that mesothelioma "is a disease in which prevention is far more effective than the cure (217)."

12

Characteristics, Etiology, and Prevalence of Asbestos-Associated Carcinoma

DEFINITION

The high prevalence of carcinoma in the population at large during the last three decades and the increased incidence of pulmonary carcinoma in particular are only too well known. Persons exposed to asbestos, like any other occupational group, share in this general risk but are open to any other carcinogenic factor peculiar to their environment. In what is coming to be recognized as a disease of multifactorial origin, any additional causative factors call for special investigation. It has become progressively clear, as will be seen later, that the appearance of pulmonary carcinoma in persons exposed to asbestos is significantly more frequent than that which may be expected from general population data. There is also some evidence that the prevalence of carcinoma in other bodily sites may also be greater than expected. (We will use the term "carcinoma" here rather than the simpler word "cancer" to make it clear that we are excluding mesothelioma and other neoplastic developments. Past use of the phrase "lung cancer" to include both carcinoma and mesothelioma sometimes led to confusion that we wish to avoid.)

For the purpose of our discussion we have defined asbestos-associated carcinoma as that which occurs in members of population groups that have been demonstrated to have an exposure to asbestos

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