PATHOLOGY OF OCCUPATIONAL LUNG CANCER

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The association of environmental factors with lung cancer is well recognized. Among these factors cigarette smoking, air pollution, and occupational exposures to specific industrial agents such as asbestos, arsenic, uranium, chromium, nickel, and chloromethyl ether are considered paramount. Unfortunately for epidemiological purposes, the majority of industrial workers smoke and many live in polluted urban environments; thus separation of risk factors is difficult. The issue is complicated further by synergistic and additive effects between risk factors. Two examples of the former are seen with cigarette smoke and asbestos (35) and cigarette smoke and uranium (6).

The overwhelming majority of lung cancers occur in smokers, and in the United States squamous cell carcinoma is known to be the most prevalent histological type of tumor in males (13)(23)(46) followed by adenocarcinoma, oat cell carcinoma, and large cell carcinoma, respectively (49). The existence of four major histological types of lung cancer is useful as it can be evaluated by pathologists to study the possible influence of smoking, occupational, and other factors on the histogenesis of pulmonary neoplasms. In addition to histological type, the lobe of origin and its position within the lobe (central or peripheral) may also be important.

The majority of studies reporting the distribution of lung cancer by histological type have used the WHO histological classification of lung tumors (24) and its revisions (41)(53).

Histologically, lung cancers can be divided into four major categories: *squamous cell carcinoma, small cell carcinoma, adenocarcinoma,* and *large cell carcinoma.* From the clinical standpoint separation into distinct types is important in view of their different natural histories (28) and responsiveness to therapy (12). These four types together account for approximately 85% of all primary malignant neoplasms of the lung. Lung cancer can be further subdivided into subtypes based on distinct morphological characteristics (53). Subtypes and degree of differentiation may also be important in relation to occupational exposures (29). Other primary malignant tumors of the lung include mixed combined tumors showing features of two or more major types, bronchial gland tumors, carcinoid tumors, carcino-sarcomas, sarcomas, and other rare tumors (Table VIII-15). An association between benign lung tumors and occupational exposure has not been demonstrated; therefore, these will not be considered further. The relationship between malignant tumors of the pleura (mesotheliomas) and occupation are addressed elsewhere.

Grossly, lung cancers may be classified as hilar types (presumed origin within a bronchial wall) or peripheral types (presumed origin in small airways or pulmonary parenchyma).

The majority of *squamous cell carcinomas* are of the hilar type, arising from the major to segmental bronchi. Multicentric origin is also common. These are thought to originate in areas of metaplasia or dysplasia, though this is not always the case (42). Squamous cancers can be further subdivided into: 1) polypoid type, 2) nodular infiltrating type, 3) superficial infiltrating type, and 4) combinations of 1, 2, and 3 (37). The tumors are usually large, pale yellow in color and may show areas of central necrosis. Histologically, the tumors are classified into well, moderately, or poorly differentiated depending on the degree to which they exhibit keratinization and/or intercellular bridges. Hypercalcemia is the most important paraneoplastic syndrome of squamous cell tumors (37).

Small cell carcinomas arise in both major bronchi and in the lung periphery. They typically spread beneath the mucosa to produce raised

Table VIII-15

HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS

I. Epithelial Tumors

A. Benign

1. Papillomas
   a. Squamous cell papilloma
   b. "Transitional" papilloma
2. Adenomas
   a. Pleomorphic adenoma ("mixed" tumor)
   b. Monomorphic adenoma
   c. Others

B. Dysplasia, Carcinoma *In Situ*

C. Malignant

1. Squamous cell carcinoma (epidermoid carcinoma)
   Variant:
   a. Spindle cell (squamous) carcinoma
2. Small cell carcinoma
   a. Oat cell carcinoma
   b. Intermediate cell type
   c. Combined oat cell carcinoma
3. Adenocarcinoma
   a. Acinar adenocarcinoma
   b. Papillary adenocarcinoma
   c. Bronchiolo-alveolar carcinoma
   d. Solid carcinoma with mucus formation
4. Large cell carcinoma
   Variants:
   a. Giant cell carcinoma
   b. Clear cell carcinoma
5. Adenosquamous carcinoma
6. Carcinoid tumour
7. Bronchial gland carcinomas
   a. Adenoid cystic carcinoma
   b. Mucoepidermoid carcinoma
   c. Others
8. Others

Table VIII-15
HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS (Continued)

II. Soft Tissue Tumors

III. Mesothelial Tumors

A. Benign mesothelioma

B. Malignant mesothelioma

1. Epithelial
2. Fibrous (spindle-cell)
3. Biphasic

IV. Miscellaneous Tumors

A. Benign

B. Malignant

1. Carcinosarcoma
2. Pulmonary blastoma
3. Malignant melanoma
4. Malignant lymphomas
5. Others

V. Secondary Tumors

VI. Unclassified Tumors

VII. Tumor-like Lesions

A. Hamartoma

B. Lymphoproliferative Lesions

C. Tumorlet

D. Eosinophilic granuloma

E. "Sclerosing haemangioma"

F. Inflammatory pseudotumor

G. Others

Source: (53)

longitudinal folds (37). The primary tumor may be exceedingly small and the first clinical indication may result from entrathoracic metastases. Necrosis is less frequently seen in small cell carcinomas than in squamous cell carcinomas and cavity formation is rare. Microscopically, the tumors may be divided into oat cell, intermediate cell and combined oat cell carcinoma (53). The oat cell type is characterized by small cells with round or oval hyperchromatic granular nuclei, ill defined borders, and scanty cytoplasm. The cells tend to form trabeculae and rosettes. The intermediate cell type is similar to the oat cell type but has more abundant cytoplasm and distinct cell borders. The combined type is composed of areas of definite oat cell carcinoma with adjacent areas of either squamous cell carcinoma and/or adenocarcinoma. At the ultrastructual level small cell carcinomas can be distinguished from the other types of carcinoma by the presence of dense neurosecretory type granules with limiting membranes. Small cell carcinomas frequently produce polypeptide and biogenic amine hormones which give rise to a number of clinically important syndromes (21).

Adenocarcinomas may arise in the hilar or

peripheral regions of the lung; the majority arise in the latter location. The peripheral type is thought to arise from cells lying distal to the terminal bronchioles. Well differentiated tumors tend to have poorly defined borders whereas the poorly differentiated tumors may secrete copious mucus which may grossly resemble Klebsiella pneumonia (28). Their occurrence in fibrotic lung disease has led to speculation that these tumors arise in areas of cubodial metaplasia adjacent to scars. This theory is difficult to prove, however, as adenocarcinomas may provoke a marked desmoplastic fibrous stromal response. Minute, presumably early, adenocarcinomas have also been demonstrated in areas devoid of fibrosis (37)(38). Because the most common type of metastatic carcinoma to the lungs is adenocarcinoma, it is important to exclude other possible primary sites of origin before a definitive diagnosis is made. Inclusion of metastatic tumors would tend to increase the frequency of adenocarcinomas. Although it is rare, adenocarcinomas can secrete a salivary gland type amylase (1). Histologically, they may be grouped into acinar, papillary, bronchiolo-alveolar, and solid carcinomas with mucus formation. The first two are further classified into well, moderately, and poorly differentiated adenocarcinoma.

Large cell carcinomas are composed of undifferentiated malignant cells showing no features of the other histological types. They are thus diagnosed by exclusion. Included in this category are tumors showing clear cells or giant cells. On the basis of electron microscopical studies the majority of these tumors probably represent poorly differentiated squamous or adenocarcinomas (37). The frequency distribution of histologic types is probably related to the size of the biopsy available for study. The larger the sample the greater the chance of the tumor showing areas of squamous or adeno differentiation. Large cell carcinomas tend to arise from more distal bronchi, have well defined rounded borders, and show hemorrhage and necrosis on cut section. An inflammatory cellular reaction is frequently seen with the giant cell type. Human gonadotrophic hormone production has been described in association with the large cell variant (17).

Several studies have reported the relative frequencies of the different histological types of lung cancer in the general population and these have largely formed the basis for comparison with occupational groups. Determining the true prevalence of the different histologic types in occupational cohorts has proven difficult due to numerous confounding variables. Some of these will be considered briefly. First, in most studies the occupational histories of the comparison population are not known or are incomplete, thus biases due to occupation may remain undetected. Second, as mentioned earlier, the vast majority of lung cancer cases occur in smokers, thus occupational effects on lung cancer histogenesis are superimposed on the already existing effects of smoking. In many studies smoking histories are incomplete and in most, cumulative exposures are not known. Both of these factors influence cell type frequencies. All types of lung tumor show a dose-response relationship with cigarette smoking. Several studies indicate that this effect is greatest for squamous cell carcinomas (8)(25)(47); other studies indicate oat cell tumors are more responsive (4)(55). Third, it has been shown that the frequency distribution of histological type is dependent on the method of diagnosis. For example, centrally located tumors, which tend to be squamous cell carcinomas, are more easily accessible to bronchoscopy, whereas peripheral tumors, which tend to be adenocarcinomas, are more likely to be diagnosed at autopsy (19). Thus studies based on autopsy material will differ from biopsy based studies. Fourth, the frequency distribution of lung cancer by cell type appears to be changing. In particular, there is evidence that the proportion of adenocarcinomas and possibly squamous cell carcinomas in the general population is increasing (5)(45). While part of this trend may reflect changes in diagnostic criteria, there is also evidence that this is a real phenomena. Fifth, there is considerable inter and intra observer variability in tumor classification by pathologists, particularly for the less well differentiated types (16). Sixth, age at diagnosis appears to influence the frequency distribution of different histological types (48), with a greater proportion of squamous cell carcinomas appearing in the older groups. Finally, there are distinct sex differences with relatively more adenocarcinomas in women (7).

Studies showing the distribution of lung cancer by histological type in the general population categorized by sex and smoking status are summarized in Tables VIII-16-VIII-22. These indicate that in male cigarette smokers (Table VIII-16), the predominant cell type is squamous

with lesser frequencies of adenocarcinoma, small cell undifferentiated carcinoma, and large cell undifferentiated tumors in that order. In female smokers adenocarcinomas predominate (Table VIII-17).

Very few studies of histological type of lung cancer have been reported for nonsmokers. For both males and females, adenocarcinoma appears to be the most common type, although the number of cases is too small to draw a definite conclusion (Tables VIII-18 and VIII-19). In studies in which smoking status is not specified, squamous cell carcinoma is the most frequent tumor type for males whereas in females, adenocarcinoma predominates (Tables VIII-20 and VIII-21). This distribution of types is similar to that seen in smoking populations—suggesting that the majority of these cases are in fact smokers. Table VIII-22 shows the data from studies in which both sex and smoking status were unspecified. These show an excess of squamous cell carcinomas, which probably reflects the proportion of male smokers in these groups.

It is clear from the foregoing that interpretation of studies relating histological type to occupation is difficult without information on sex and smoking status. However, despite these limitations certain occupational exposures do appear to exert an influence on the histogenesis of lung cancer.

Data relating cell type of lung cancer to occupation is shown in Table VIII-23. The pathology of lung cancer in cases with asbestos exposure and/or asbestosis has been studied (22) (52). These investigations indicate a relative increase in the number of adenocarcinomas. Asbestos associated tumors also tend to arise in areas of the lung most affected by asbestosis, i.e., peripherally in the lower zones (22) (39). Although a peripheral, lower lobe adenocarcinoma arising in an area of fibrosis may be considered to be a typical asbestos-associated lung cancer, the majority do not fall into this pattern. Thus in an individual case, knowledge of location or cell type has limited etiologic or medico-legal significance.

Several studies have shown a link between ionizing radiation, such as occurs in uranium miners and an increased frequency of small cell carcinomas (2)(33). Moreover, the relative frequency of this type of tumor increased with increased cumulative exposure to radiation (3)(33). The lungs of uranium miners also showed a slight excess of severe atypia and early primary invasive carcinoma of the bronchial mucosa as compared to matched controls, although the prevalence of carcinoma *in situ* was approximately the same for the two groups (6).

An increase in small cell undifferentiated carcinomas in iron-ore miners (9)(15)(31) may also be due to moderate, but raised levels of radon within the mines, rather than the promoter effect of iron oxides on polycylic aromatic hydrocarbons (34). A similar pronounced excess of small cell carcinomas has been observed in workers exposed to chloromethyl ether (50). There is also a dose-response effect. The authors concluded that small cell carcinoma was a specific response to chloromethyl ether exposure.

Significant but less impressive relationships have been observed in other occupations. Copper smelter workers exposed to arsenic appear to have a relative increase in adenocarcinomas as compared to the general population (51). In another group of copper smelter workers, an excess of poorly differentiated squamous cell carcinomas was observed (29).

Data for coal miners is conflicting: one study indicates almost equal proportions of the three major types of tumor (44) and another indicates an excess of squamous cell tumors (36). The populations were drawn from different geographic regions with either predominantly hard coal (anthracite) exposure (36) or predominantly soft coal (bituminous) exposure (44), and this may account for the differences observed.

There is no evidence to date to suggest that exposure to silica (32) or beryllium (40) exerts an influence on the histogenesis of lung cancer.

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Table VIII-16

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
830	53	10			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977 (Cancer)
662	35	25	25	14	1	1955-72	U.S.A.	Autopsy	Auerbach et al., 1975 (Chest)
138	60	12	15		13	1955-70	U.S.A.	Autopsy	Saccomanno et al., 1971 (Cancer)
121	59	13	14	13	1	1955-70	U.S.A.	Autopsy	Archer et al., 1974 (Cancer)
1237	65	10			25	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-17

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
46	54	26			20	1953-55	U.S.A.	Autopsy	Wynder et al., 1956
163	12	50	10		28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
72	31	21			48	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-18

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
6		100				1955-72	U.S.A.	Autopsy	Auerbach et al., 1975
13	0	85			15	1957-63	U.S.A.	Autopsy	Cooper et al, 1968

Table VIII-19

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
50	32	58			10	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
59	27	49			24	1953-55	U.S.A.	Autopsy	Wynder et al., 1956

Table VIII-20

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
1228	52	11			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977
94	52	22	16	5	5	1956-65	U.S.A.	Autopsy	Weiss and Boucot, 1977
1186	37	25	21	16	1	1955-75	U.S.A.	Autopsy	Auerbach et al., 1979
152	75	9	9	7	0	1963-77	Irish Republic	Surgical	Healey, 1980
50	24	18	28	16	14	1954-71	U.S.A.	Autopsy & Surgical	Kannerstein and Churg, 1972
45	60	7	24	7	2	1954-72	U.S.A.	Autopsy & Surgical	Newman et al, 1976
42	47	12	14	19	7	1950-74	U.S.A.	Autopsy & Surgical	Wicks et al, 1981
1140	60	19			21	1941-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
1017	33	28	22		17	1958-77	U.S.A.	Autopsy & Surgical	Cox and Yesner, 1979
902	38	7			55	1933-48	England	Autopsy & Surgical	Mason, 1949
916	52	4	33		11	1948-52	England	Autopsy	Doll and Bradford, 1952
1404	42	24	18	9	8	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-21

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
98	11	13			76	193 -48	England	Autopsy & Surgical	Mason et al., 1949
79	23	13	48		16	1948-52	England	Autopsy	Doll and Bradford, 1952
164	26	38			36	1955-57	U.S.A.	Autopsy & Surgical	Haenszel et al., 1958
163	22	50			28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
201	16	31	12	22	19	1957-72	U.S.A.	Autopsy & Surgical	Beamis et al., 1975
278	20	38	24	12	6	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-22

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
231	42	20			38	1938-44	U.S.A.		Hollingsworth, 1947
1000	35	7			58	1933-48	England	Autopsy & Surgical	Mason, 1949
351	43	11	14		27	1942-51	U.S.A.		Collins, 1958
849	38	13	9		40	-48	U.S.A.	Autopsy & Surgical	McDonald et al., 1951
199	62	12	8		15	1933-58	U.S.A.	Biopsy & Surgical	Reinhoff et al., 1965
1309	63	11			27	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
81	32	27	27	14	0	1963-77	Irish Republic	Autopsy	Healey, 1980
219	26	39	16		11	1963-76	U.S.A.	Autopsy & Surgical	Valaitis et al., 1981
1682	38	27	19	9	7	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-23

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION SPECIFIED

Occupation/ Exposure	#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Smoking Status	Method of Diagnosis	Reference
Iron Ore Miners/Radon	69			37			1948-67	U.K.	NK	Autopsy	Boyd et al., 1970
Iron Ore Miners/Radon				44				France	NK	Autopsy	Roussel et al., 1964
Coal Miners (Anthracite)	165	79	10				1957-68	U.S.A.	I	Autopsy & Surgical	Scarano et al., 1972
Coal Miners (Bituminous)	202	24	31	28	9	8	1972-77	U.S.A.	S	Autopsy	Vallyathan et al., 1980
Free Silica	16	63	1	18			1960-67	Switzer-land	NS	Autopsy	Ruttner and Heer, 1969
Beryllium Workers	25	20	32	36	12	0	NK	U.S.A.	I	Autopsy & Surgical	Smith and Suzuki, 1980
Copper Smelter Workers/Arsenic	42	31	38	24	7	0	1950-74	U.S.A.	I	Autopsy & Surgical	Wicks et al., 1981
Copper Smelter Workers/Arsenic	25	56	12	28	4		1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Copper Mine Workers	54	61	9	20	9	0	1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Chloromethyl Ether Workers	28	3	18	68	7	3	1960-75	U.S.A.	S	Autopsy & Surgical	Weiss et al., 1979
Asbestos Workers	88	22	34	26	14	5	1962-72	U.K.	S	Autopsy & Surgical	Whitwell et al., 1974
Asbestos Workers	50	22	22	22	12	22	NK	U.S.A.	I	Autopsy & Surgical	Kannerstein and Churg, 1972
Uranium Workers	107	23	7	69		1	1950-70	U.S.A.	S	Autopsy	Archer et al., 1974
Uranium Workers	121	26		61		13	1950-	U.S.A.	S	Autopsy	Saccomanno et al., 1971

BA Bronchioloalveolar
NK Not Known
I Incomplete
NS Nonsmokers
S Smokers

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CLINICAL PRESENTATION

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James M. Melius

The clinical presentation of primary lung cancer due to either occupational or non-occupational causes is varied and depends on numerous factors including cell type, location and extent of tumor, and poorly defined host-tumor interactions. Some patients with lung cancer detected by routine chest radiographs will have no signs or symptoms. In other cases, particularly those with more central lesions, cough, hemoptysis, bronchial obstruction with secondary pneumonia, or other localized findings will be apparent. Intrathoracic spread may involve any structure, causing such symptoms as dyspnea due to pericardial or large pleural effusions, dysphagia due to esophageal compression or invasion, or hoarseness due to invasion of the recurrent laryngeal nerve. Metastasis outside the chest may involve any organ or structure with the most common sites being brain, liver, and bone. Alternatively, patients may present with nonspecific constitutional complaints as anorexia, weight loss, fatigue or weakness. Finally, primary lung cancers (particularly small cell carcinoma) may produce a number of paraneoplastic syndromes such as Cushing's syndrome, cerebellar degeneration, migratory thrombophlebitis, and nonbacterial thrombotic endocarditis.

DIAGNOSIS

The diagnosis of bronchogenic carcinoma usually centers around abnormalities seen on the chest radiograph. Special radiographic exams such as tomograms as well as old x-rays are often helpful in this clinical assessment. In general, cytologic or tissue diagnosis is obtained to confirm the clinical impression. Staging of the tumor is then necessary to determine the appropriate therapy. Interested readers are referred to the following excellent sources of comprehensive discussions of cancer staging:

American Joint Committee for Cancer Staging and End Results Reporting. "Staging of Lung Cancer, 1979." Chicago, Illinois.

D. T. Carr: Diagnosis and Staging. In: Lung Cancer, 1980. II World Conference, Copenhagen, Editors H. H. Hansen and M. Rorth. Excerpta Medica, Amsterdam, pp. 49-70.

Mountain, C. F., Carr, D. T., and Anderson, W. A. D. A System for the clinical staging of lung cancer. Am J. Roent. *120:*130-38, 1974.

Numerous approaches and procedures have been used in the diagnostic evaluation of bronchogenic carcinoma, and each patient must be individualized. The underlying plan in all cases, however, is first to establish the diagnosis, then to determine the tumor's resectability (the chance that it can be totally removed surgically), and if resectible, to determine the patient's operability (the chance that he could survive post-resection cardiopulmonary function). Although the finding of small cell carcinoma is generally considered a contraindication to surgery, staging of this tumor can be useful in determining therapy and prognosis.

THERAPY

The primary mode of treatment of non-small cell bronchogenic carcinoma is surgical resection. Unfortunately, most patients are either unresectable or inoperable at the time of presentation. "Curative" radiotherapy has had some success in limited studies, but for the most part radiotherapy is used for palliation. It may relieve hemoptysis, superior vena cava obstruction, or brain or bone metastases. To date chemotherapy has had little permanent benefit. Combination therapy approaches have been and continue to be tried, including those using immunotherapy, but most well controlled studies again show little benefit.

Although the most lethal, small cell carcinoma is also the bronchogenic cancer most sensi-

tive to both chemotherapy and radiotherapy. Dramatic resolution of tumor masses can be obtained with either mode or with combination therapy. Except in rare cases, however, this remission is short-lived and cannot be maintained.

PROGNOSIS

The prognosis for bronchogenic carcinoma is poor, and unlike many other cancers, has changed little over the past 30 years. Overall five-year survival rates are less than 10%. Survival is generally better with squamous cell carcinoma; it is much worse with small cell tumors.

Those asymptomatic patients who undergo surgical resection of small peripheral "coin" carcinoma can expect a five year survival rate of approximately 50%. On the other hand, those presenting with advanced disease may survive only a few weeks. While definite advances have been made in the treatment of patients with localized small cell cancer, the five year survival rate for this disease remains near zero.

MESOTHELIOMA

Ruth Lilis

DEFINITION

The primary malignant neoplasm of the pleura —diffuse pleural mesothelioma—has been recognized and accepted as a nosologic entity only during the last 20 years (77), although as early as 1767 Joseph Lieutand (cited by Robertson) reported two cases of probable mesothelioma among 3,000 autopsies, and E. Wagner described the pathology in 1870 (53)(72).

It is not known with certainty when the term "mesothelioma" was first used; one of the early reports indicating a primary and malignant tumor of the pleura and using the term mesothelioma was that by DuBray and Rosson (14).

In 1931, Klemperer and Rabin published a comprehensive description of the distinctive features of diffuse pleural neoplasms and recommended these tumors "should be designated mesothelioma;" since they arise from the surface lining cells of the pleura, the mesothelium (27). The malignant, diffuse pleural mesothelioma arises from the multipotential coelomic mesothelial cell of the pleura. Similarly, malignant tumors originating in the mesothelial cells of the peritoneum are peritoneal mesothelioma.

The definition of pleural mesothelioma thus includes:

- the origin of the tumor in the mesothelial cells of pleura
- the diffuse character of the tumoral growth, often involving a large surface or even the entire pleura of one lung, at the time of diagnosis
- the characteristic rapid growth and extension over the surface of the pleural serosa (closely related to the diffuse character)
- the high degree of malignancy, expressed in rapid growth, local invasiveness (soft tissue and bone structures of chest wall, underlying lung, adjacent pericardium, regional lymph nodes), and frequent metastases to a variety of organs, including brain, liver, kidney, adrenals, etc. These characteristics of pleural mesothelioma have an integrative expression in the mean survival time after diagnosis, which does not exceed 12 months in most reported series, with or without therapeutic attempts.

The association between malignant "endothelioma of the pleura" (mesothelioma) and asbestos exposure was first reported by Wyers (80). Wagner et al., published a report on 33 cases of diffuse pleural mesothelioma from the North West Cape Province of South Africa; most of these cases had occurred over a four year period, and in all but one, exposure to asbestos (crocidolite) could be established (77). Mesothelioma was not necessarily preceded by asbestosis (interstitial pulmonary fibrosis); the exposure was occupational in some cases, but in others, only environmental (residential) exposure had occurred. The long latency period—a mean of 40 years—between initial asbestos exposure and the development of malignant pleural mesothelioma was another striking characteristic of these cases. The carcinogenic hazard of relatively low levels of asbestos exposure; the possibility that pleural mesothelioma associated with asbestos exposure may develop in the absence of preceding pulmonary interstitial fibrosis; and the long latency period between onset of exposure and development of the malignant mesothelioma, were thus outlined.

LIST OF CAUSATIVE AGENTS

Asbestos fiber is widely accepted as the causative agent in the vast majority of mesothelioma cases. So far, asbestos is the only fibrous mineral

where epidemiologic data have shown an association between exposure and pleural and peritoneal mesothelioma in man.

Asbestiform minerals are grouped in two major categories: chrysotile, which is a serpentine, and the amphiboles, which include crocidolite, amosite, anthophyllite, and tremolite.

The first large group of malignant pleural mesothelioma cases due to asbestos exposure was related to crocidolite in South Africa (77). This fact, and subsequent reports on mesothelioma cases from Great Britain where crocidolite had been extensively used, contributed to the empirical and one-sided view that crocidolite was the main or even the only type of asbestos with a specific carcinogenic potential resulting in the eventual development of mesothelioma.

The major increase in mesothelioma incidence in the United States—where chrysotile has been and still is the main type of asbestos used—supports a causal association between chrysotile exposure and development of mesothelioma (4)(31)(59)(63)(64). Epidemiologic evidence for worker cohorts has shown chrysotile to be equally as potent as other fiber types insofar as lung cancer is concerned (13)(49)(80). While the number of mesothelioma cases from populations exposed only to chrysotile has been small, an association with chrysotile exposure has been definitively established. Amosite has also been shown to have a similar carcinogenic effect; a significant number of mesothelioma cases have occurred in a cohort of 933 amosite factory workers(62). Experimental studies on rats using inhalation of five types of asbestos fiber resulted in the development of mesothelioma with chrysotile (Canadian), crocidolite, amosite, and anthophyllite (74). Previous experiments using intrapleural administration of amosite, chrysotile, and crocidolite had given similar results, with chrysotile giving the largest number of mesotheliomas, followed by crocidolite and amosite (73). Shabad et al. also reported on the experimental production of pleural mesothelioma in rats, with intrapleural administration of chrysotile (65). Thus, both epidemiologic evidence and experimental confirmation indicate that chrysotile, amosite, and crocidolite asbestos are causative agents for mesothelioma.

Recently another type of fibrous mineral—naturally occurring zeolites (aluminum silicates) of the fibrous variety (erionite, mordenite)—has come under close scrutiny as a potential causative agent for malignant mesothelioma. The evidence for this association is based on the findings in a rural area of endemic mesothelioma in Turkey, where mineralogic investigations have not found any asbestos minerals, but have identified fibrous zeolites. Although this is still being actively researched and conclusive evidence is not yet resolved, fibrous zeolites are considered highly suspicious at the present time.

Reports on endemic mesothelioma in other parts of the world—such as in a rural area in India—have not yet identified the etiologic agent; the possibility that zeolites may be the causative agent cannot be excluded, since zeolites are known to be present in that area.

Experimental studies using intrapleural application suggest that other fibrous materials, such as fibrous glass, may also induce malignant mesothelioma (68). Epidemiologic evidence for fibrous glass as a causative agent for mesothelioma has not been reported, but fibrous glass has to be included as a suspected causative agent.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Occupations and industries at risk to mesothelioma include all of those listed for asbestosis.

All available information indicates that mesothelioma may be the result of low levels and/or relatively short (of the order of several weeks to several months) asbestos exposure. The dose-response relationship for mesothelioma is therefore different than that for asbestosis (which develops with higher exposure levels over longer time periods) or bronchial carcinoma associated with asbestos exposure (which increases in incidence even after short periods of high asbestos exposure levels, but shows a marked increase in incidence with duration of exposure)(58). Since low asbestos exposure levels carry a significant risk of mesothelioma, occupations and industries characterized by relatively low asbestos levels (auto mechanics and brake repair, tapers in dry wall construction, handling of finished asbestos products including asbestos cement), while at relatively low risk for the development of parenchymal interstitial fibrosis (asbestosis), are nevertheless at high risk for mesothelioma.

Equally important is the fact that numerous workers in the various trades which do not simply direct asbestos exposure, such as electricians, painters, welders, carpenters, etc., in shipbuilding or ship repair, in construction, in maintenance

work at chemical plants, and even automobile salesmen supervising repair work, are frequently exposed to asbestos due to their mere presence in work areas where asbestos is being handled. This "bystander" exposure has been repeatedly documented to be responsible for numerous cases of mesothelioma (20)(51). It is therefore important to establish the principle that such indirect exposure carries a significant risk of mesothelioma.

Whitwell et al. found that 83% of mesothelioma cases reviewed contained over 100,000 asbestos fibers per gram of dried lung tissue; in cases of asbestosis the number of asbestos fibers was much higher, exceeding 3,000,000 per gram of dried lung tissue (79).

In shipyard workers, more and more mesothelioma cases have been reported; most of these have occurred in trades other than insulation workers, indicating that the risk is widespread (20)(61). The distribution of trades in private shipyards in the United States in 1943 is presented in Table VIII-24. A list of occupational titles in an Eastern U.S. shipyard in 1975 is given in Table VIII-25.

It is difficult to construct a complete list of all occupations in which asbestos exposure may occur at one time or another. Since short-term asbestos exposure (several weeks to several months) is often responsible for mesothelioma occurring 25, 30, 40, or 50 years later, the occupation/industry involved at the time of the diagnosis of a malignant tumor may differ from the occupation/industry where the exposure actually occurred. Therefore, at any point in time, much higher numbers of individuals are at risk for the development of mesothelioma than those working in industries and occupations known to be associated with asbestos exposure. Recollection of remote past exposures and of specific jobs in which they occurred is a formidable task, but crucial when assessing whether one particular case of mesothelioma is related to past asbestos exposure.

Table VIII-24

PERCENTAGE DISTRIBUTION OF TRADES IN PRIVATE SHIPYARDS IN THE UNITED STATES, JUNE 1943

Trade	*Percentage*
Welders	15.3
Shipfitters	11.0
Machinists	8.1
Pipefitters	7.2
Electricians	6.6
Carpenters	6.1
Laborers	5.5
Burners	3.8
Painters	3.1
Sheetmetal workers	3.0
Riggers	2.8
Chippers and caulkers	2.8
Boilermakers	2.3
Crane operators	1.3
Pipe coverers	0.2
All other	21.1

Source: Bureau of Labor Statistics, Bulletin 824, "Wartime Employment, Production, and Conditions of Work in Shipyards," 1945.

EPIDEMIOLOGY

The relationships between asbestos exposure and pleural mesothelioma regarding latency period, dose-response characteristics, populations at risk, and incidence of disease have been presented in the section—List of Occupations and Industries Involved, page 672.

Pleural mesothelioma is a rapidly progressing malignant tumor, the resulting disability is total, and the condition is usually fatal in one to two years. There are no confounding conditions or risk factors which limit the ability to establish cause-effect relationships.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for developing mesothelioma includes:

- all occupations with direct contact and handling of asbestos.
- employees with other occupations (electricians, welders, painters, carpenters, etc.) who work or have worked—even for short periods—in areas where asbestos has been handled by others.
- family members (household contacts) of asbestos workers who have been exposed to asbestos fibers brought into the household by the worker. Household contamination has been found to result in asbestos exposure of family members of asbestos workers, sufficient in magnitude to induce mesothelioma (1)(2)(5)(32)(41)(46)(55)(56).
- individuals who have resided in the vi-

Table VIII-25

OCCUPATIONAL TITLES IN AN EASTERN U.S. SHIPYARD, 1975

Guard & Watchman	Heat Treater	Power House Engineer	Shipfitter
Construction Mechanic	Tool Grinder	Molder	Lead Bonder
Laborer	Tool Room Attendant	Foundryman	Welder
Firefighter	Lathe Operator	Foundry Chipper	Burner
Scrap Material Sorter	Miller	Melter	Rigger
Painter	Drill Operator	Coremaker	Sheetmetal Mechanic
Painter Cleaner	Grinder	Pipefitter	Joiner
Maintenance Painter	Machinist	Silver Brazer	Carpenter
Truck Driver	Engraver	Pipecoverer	Industrial Radiography Technician
Fork Lift Operator	Layout	Electrician	Radiological Control Monitor
Warehouseman	Machine Rigger	Electronics Technician	Clerk
Transportation Locomotive Operator	Make Ready Man	Maintenance Electrician	Data Processor
Toolmaker	Crane Operator	Loftsman	Secretary
	Maintenance Machinist	Blacksmith	Timekeeper
	Dock Crew	Furnaceman	
	Inspector		

cinity (one mile) of an asbestos plant, shipyard, or other source of asbestos contamination.

The population at risk at any point in time has to include all persons who have been exposed *in the past*. Given the long latency period between asbestos exposure and development of mesothelioma (on the average 35-40 years), individuals who have been exposed (even for short periods of time) during the last 50 years have to be considered potentially at risk.

Contributing to the population size at risk is (1) the fact that short duration of asbestos exposure (several weeks to several months) is sufficient to induce mesothelioma; (2) the high job mobility, especially during World War II; (3) the marked increase in the total amount of asbestos used per year; and (4) the diversification of its uses. The estimate of the population at risk is, for the same reasons, a complex and difficult task.

Attempts to assess the incidence of mesothelioma in populations at risk are also fraught with difficulties; these have multiple sources.

1. The complexity of the diagnostic criteria, which require pathologic confirmation; the most rigorous criteria make the diagnosis dependent on a complete autopsy (for the exclusion of another primary site of the tumor, which might have metastasized to the pleural cavity). Only a proportion of all deaths are followed by a postmortem examination. This proportion varies with geographic area, with the time period considered, and with other factors.
2. Even when tissue specimens are examined by experienced pathologists, the diagnosis is not always simple; differences of opinion may persist and result in conclusions on the pathologic characteristics such as "possible mesothelioma" or probable mesothelioma."
3. Evaluation of the incidence of mesothelioma from death certificates has been reported, by all those who have investigated this problem, as incomplete, leading to a marked but quantitatively variable underestimate of the number of cases. This problem is compounded by the fact that the coding of causes of death does not provide a separate code for mesothelioma, but includes it with cancer of the lung or pleura.
4. The most reliable data are those based on the cohort approach: asbestos-exposed employees followed for many years, with a comprehensive assessment of causes of death. The long latency period between

onset of asbestos exposure and mesothelioma has resulted in a limited number of studies with a long enough follow-up period to realistically reflect its incidence. In all these cohort studies, most with several reports published over time, it is a rule without exception that the longer the observation period, the higher the incidence of mesothelioma.

Although the most relevant data on mesothelioma risk in asbestos-exposed populations are derived from long-term cohort studies, other studies following different approaches have also revealed the paramount importance of long-term follow-up and completeness of diagnostic means. The most significant information follows.

By 1965, 160 cases of mesothelioma had been recorded in the United Kingdom, 123 from England and Wales, 36 from Northern Ireland, and only one from Scotland (39). When a systematic review of all necropsy and surgical biopsy reports in all hospitals was undertaken, 80 cases of mesothelioma were found to have occurred in Scotland for the years 1950-1967. Many cases were in employees who had had no direct exposure to asbestos but had been employed in the shipbuilding industry, in a wide variety of trades.

The Mesothelioma Register in Great Britain (Employment Medical Inspector's Advisory Service)—with data sources in death certificates, Cancer Bureau registrations, Pneumoconiosis Medical Panels (claims for benefits under the National Insurance Acts), chest physicians, surgeons, pathologists and coroners—had 413 cases reported for 1967-1968; 75% of the confirmed cases with definite asbestos exposure came from shipbuilding, asbestos factories, and insulation work; the other 25% from a variety of occupations (welders, electricians, gas workers, mechanics, chemical workers, etc.). The highest rate/million per year of mesothelioma (confirmed cases) figures were 8.93 and 8.24, both in shipbuilding areas. The incidence of definite mesothelioma in the United Kingdom for the period 1967-1968 was 120 per year. It was concluded that this figure may considerably understate the true incidence.

McDonald and McDonald reviewed evidence published between 1959 and 1976, including cohort studies of asbestos workers; "population studies" (mesothelioma surveys in Canada and the United States describing "case-series referable to some kind of denominator"); case reports unrelated to any denominator; and mortality statistics, mainly in Canada, the United States, and the United Kingdom (37). Data from the Third U.S. National Cancer Survey (42) was also reviewed. A total of 4,539 cases had been published after 1958. (This figure did not include cases from official mortality statisitics and Third U.S. National Cancer Survey.) The incidence of mesothelioma for the period preceding 1958 had been very low: in 1957 Hachberg mentioned 43 cases in 60,042 autopsies over the 40-year period, 1910-1949, i.e., less than 1 case per year and only 0.07% of the autopsies performed (Philadelphia, Baltimore, Minneapolis, New York, and Toronto in North America and Munich, Prague, and Copenhagen in Europe).

The marked increase in the incidence of mesothelioma over the last 20 years is evident when comparing the total number of reported cases (436) for the period 1955-1959, with that of 1,697 cases of mesothelioma for the period 1965-1969 (an almost fourfold increase). Interestingly, 9% of cases were due to neighborhood or household-family exposure.

In the Third National Cancer Survey (1975), a thorough ascertainment was done using hospital records and pathology material, besides death certificates, in selected areas comprising approximately 10% of the population of the United States (deaths in 1971). The annual rate per million for males 45 and over was 11.20 and for females in the same age range, 3.53.

Reports from other countries, such as Germany, Sweden, the Netherlands and Great Britain, indicate much higher rates than those published for Canada by McDonald (10 per million for males and 4 per million for females, over 45-years-old) for some cities and regions, most with large shipyards: Walcheren had a death rate 23.3 times higher than that expected according to the Canadian rates; Wilhelmshaven (21.5 times higher); Plymouth (14.3 times higher); and Rotterdam, Harlem, Hamburg, Malmo, Nantes, and Trieste (with rates 7-8 times higher) (38)(51)(69). These data indicate that annual incidence rates for mesothelioma in geographical areas with shipyards and/or other important asbestos industries or uses are of the order of 200/1 million or higher, for men aged 45 or over.

The most relevant data on the incidence of mesothelioma in exposed populations are derived from cohort studies of occupational groups. But

only studies with long follow-up (30-40 years) can provide comprehensive information, although even these might not include all the cases. It has been estimated, from the relatively limited number of such studies, that between 5% and 11% of all deaths in asbestos-exposed workers are due to mesothelioma (16)(26)(43)(45)(61)(62)(63). In a cohort of 632 asbestos insulation workers observed prospectively from January 1, 1943 to December 31, 1976, 38 out of a total of 478 deaths were due to mesothelioma (see Table VIII-26) (60). The mortality experience of a large cohort of 17,800 asbestos workers in the United States and Canada (Table VIII-27) observed from 1967 to 1977 indicates that 175 out of 2,270 deaths were due to mesothelioma. In a cohort of amosite asbestos factory workers employed from 1941-1945, and observed until 1977, 16 out of 594 deaths were due to mesothelioma (Table VIII-28) (62). In another cohort of 689 asbestos factory workers employed before January 1939, and observed from 1959 through 1975, 26 out of 274 deaths were due to mesothelioma (48)(60). Newhouse reported the mortality experience of workers in an East London asbestos factory, 1931-1970; out of a total of 461 deaths, 35 were due to mesothelioma (43).

The importance of long-term observation is shown in Tables VIII-29, VIII-30, and VIII-31.

Two further problems are: 1) the correct assessment of all those at risk for developing mesothelioma in various occupations, or who have had such exposure even for short periods of time sometime during the last 40-50 years; and 2) quantification of the risk for "bystander" exposure, neighborhood or other types of environmental exposure (buildings, schools, etc.), and household-family exposure.

Although no firm data are as yet available for these types of asbestos exposure, according to the information available on cases occurring after short (several weeks) and relatively low levels of exposure, it has to be assumed that the risk is of the same order of magnitude as that for occupationally-exposed groups.

PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

The pathology of mesothelioma is largely determined by the potential of the mesothelial cells to produce tumors of epithelial, mesenchymal, or most commonly a mixed type. This potential is related to the embryologic origin of the mesothelium, which is derived from coelomic epithelium developed from the mesoderm and underlined by mesenchymal tissue (27).

The macroscopic features of pleural mesothelioma are those of a gray-white or yellow-gray mass, varying in extent from a part of the lung's surface to a complete, or almost complete, encasement of the lung. The tumor has a rapid growth rate, extending along the serosa, with a tendency to grow along the interlobar fissures. Both the parietal and visceral pleura are involved; often the tumor seems to have originated in the visceral pleura (for example, in the minor fissure).

Two types of mesothelioma can be observed: 1) the scirrhous type, presenting as a hard sheet, with variable thickness often exceeding one inch, rapid encasement and compression of the lung, partial or total obliteration of the pleural cavity, and contraction of the hemithorax; and 2) the encephaloid type, presenting as large tumor masses, often multiple, sometimes with extremely rapid growth (seen on chest x-rays as "scalloping").

Continuous spread—with local invasion of the pericardium, mediastinum, chest wall, diaphragm, and, through it, the liver and peritoneum, or into the controlateral pleura—is frequent. The underlying lung can be invaded directly, into the pulmonary parenchyma immediately underlying the pleura, or by spread into septal and perivascular lymphatics, with lymph node involvement in about 50% of cases. Distant metastases, thought in the past to be rare, are, on the contrary, quite frequent, affecting the brain, liver, kidney, adrenals, thyroid, lung, or other organs in more than 50% of cases. Tumor growth along the needle biopsy track or surgical scar after thoracotomy is common.

Microscopic features are characterized by diversity of appearance, not only from case to case, but also in the same tumor, where both epithelial (or tubulo-papillary) and mesenchymal (or fibrosarcomatous) areas can be observed. According to the microscopic pattern, mesothelioma can be classified into four types: 1) epithelial or tubulo-papillary, with the epithelial cells usually cuboidal or flattened, tending to form tubular and papillary structures, separated by a more or less abundant matrix; 2) mesenchymal or fibrosarcomatous, appearing as a spindle cell sarcoma, but sometimes with extensive areas of acellular collagen; 3) mixed, the most frequent form, containing both epithelial and fibrosarcomatous areas; 4) the undifferentiated type, with polygonal, less often spheroidal cells, with large nuclei and scanty mitotic figures. These cells resemble those of the tubulo-papillary

Table VIII-26

EXPECTED AND OBSERVED DEATHS AMONG 632 NY-NJ ASBESTOS INSULATION WORKERS OBSERVED PROSPECTIVELY JANUARY 1, 1943 - DECEMBER 31, 1976

Number of Men	**632**
Man-years of observation	**13,925**

	Deaths 1.1.43-12.31.76	
Cause of death	*Expected**	*Observed*
Total deaths, all causes	328.9	478
Total cancer, all sites	51.0	210
Lung cancer	13.3	93
Pleural mesothelioma	**	11
Peritoneal mesothelioma	**	27
Cancer of esophagus	1.4	1
Cancer of stomach	5.4	19
Cancer of colon - rectum	8.3	23
All other cancer	28.06	36
Asbestosis	**	41
All other causes	262.6	227

*Expected deaths are based upon age and sex-specific U.S. death rates of the National Center for Health Statistics, 1949-1975 actual rates, 1943-1948 extrapolated from 1949-1955 rates, and 1976 extrapolated from 1967-1975 data.
**These are rare causes of death in the general population.

Table VIII-27

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 — JANUARY 1, 1977

Number of Men	**17,800**
Man-years of observation	**166,855**

	*Expected**	*Observed*	*Ratio*
Total deaths, all causes	1,660.96	2,270	1.37
Total cancer, all sites	319.90	994	3.11
Lung cancer	105.97	485	4.58
Pleural mesothelioma	**	66	—
Peritoneal mesothelioma	**	109	—
Cancer of esophagus	7.01	18	2.57
Cancer of stomach	14.23	22	1.55
Cancer of colon - rectum	37.86	59	1.56
All other cancer	154.83	235	1.52
Asbestosis	**	162	—
All other causes	1,351.06	1,114	0.82

*Expected deaths are based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.
**These are rare causes of death in the general population.

Table VIII-28

EXPECTED AND OBSERVED DEATHS
AMONG 933 AMOSITE FACTORY WORKERS EMPLOYED
1941-1945, OBSERVED TO DECEMBER 31, 1977

	Deaths 1941-1977		
	Expected[a]	*Observed*	*Ratio*
Total deaths	368.62	594	1.61
Cancer, all sites	73.35	195	2.66
Lung cancer	19.16	100	5.22
Pleural mesothelioma	[b]	8	—
Peritoneal mesothelioma	[b]	8	—
G.I. cancer	21.55	32	1.48
All other cancer	32.64	47	1.44
Asbestosis	[b]	30	—
Other noninfectious respiratory disease	8.47	19	2.24
All other causes	286.80	350	1.22

[a] Expected deaths based upon age-specific death rate data for New Jersey white males in corresponding years. In 4 cases, ages were not known; omitted from calculations. 39 men partially traced and 890 traced to death on December 31, 1977.

[b] Death rates not available, but these have been rare causes of death in the general population.

type.

A property of mesothelial cells is the production of acid mucopolysaccharides, especially hyaluronic acid, which stains strongly with colloidal iron, but not with periodic acid Schiff (PAS). This last characteristic is useful in differentiating mesothelioma from adenocarcinoma; the latter usually gives a positive stain with PAS. The hyaluronidase test (digestion of hyaluronic acid by the enzyme) is useful in a limited number of cases, since the tubulopapillary type of the tumor is the only form which consistently produces hyaluronic acid. Therefore a negative hyaluronidase test does not exclude the diagnosis of mesothelioma.

The pathogenesis of mesothelioma is not yet completely understood. Nevertheless, the following facts of major theoretical and practical consequence have been established:

- mesothelioma may result from exposure to crocidolite, chrysotile and/or amosite; the evidence is derived from epidemiologic and experimental animal studies.
- relatively low levels and short duration of exposure can produce mesothelioma.
- while a dose-response relationship may exist, it has not been quantitatively clarified, and therefore available information can only be interpreted to indicated that any asbestos exposure, given a long enough period of follow-up, may induce mesothelioma.
- the hypothesis according to which polycyclic aromatic hydrocarbons adsorbed on asbestos fibers are important in the induction of mesothelioma has not been confirmed, nor has that attributing a similar effect to adsorbed trace metals (19).
- cigarette smoking has no etiologic relationship with mesothelioma.
- in experimental studies, intrapleural administration of asbestos, but also of similarly sized fibers of fibrous glass and fibrous aluminum oxide, resulted in pleural mesothelioma (66)(67)(68). This seems to indicate that fibrous characteristics, rather than the chemical composition, are crucial for this specific carcinogenic effect.
- a special selectivity in the distribution of asbestos fibers, relevant to the problem

Table VIII-29

EXPECTED AND OBSERVED DEATHS AMONG 689 ASBESTOS FACTORY WORKERS, EMPLOYED BEFORE JANUARY 1, 1939 DURING THE SEVENTEEN YEARS FROM JANUARY 1, 1959 THROUGH DECEMBER 31, 1975

	1959-1964		1965-1970		1971-1975		1959-1975		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs./Exp.
All causes	59	52.41	123	69.85	92	65.93	274	188.19	1.46
Cancer, all sites	21	10.47	45	14.70	33	14.73	99	39.92	2.47
Lung cancer	6	2.96	18	4.65	11	4.92	35	12.53	3.91[a]
Pleural mesothelioma	1	n.a.	5	n.a.	7	n.a.	14	n.a.	—
Peritoneal mesothelioma	1	n.a.	6	n.a.	4	n.a.	12	n.a.	—
Cancer of esophagus, stomach, colon and rectum	4	2.23	5	2.92	3	2.83	15	7.99	1.88
Cancer, all other sites	9	5.28	11	7.13	8	6.98	23	19.40	1.19
All respiratory disease	14	3.01	10	4.56	18	4.60	42	12.16	3.45
Asbestosis	12	n.a.	8	n.a.	15	n.a.	35	n.a.	—
Other respiratory	2	(b)	2	(b)	3	(b)	7	(b)	—
All other causes	24	38.93	68	50.59	41	46.60	133	136.11	0.98
Person-years of observation	3,962		3,411		2,273		9,646		

(a) Pleural mesothelioma included with cancer of bronchus in calculating ratio since expected rates are based upon "cancer of lung, pleura, bronchus, trachea."
(b) This rate is virtually identical with that of "all respiratory disease."
n.a.—not available.

Table VIII-30

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

	Number of men	**17,800**							
	Man-years	**166,855**							
		Duration from onset of work exposure (years)							
Cause of death	*Total*	*<10*	*10-14*	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45+*
All causes	2,270	51	85	188	320	388	340	253	203	442
Cancer, all sites	994	7	17	59	125	193	186	128	95	184
Lung	485	0	7	29	59	104	112	66	39	69
Pleural mesothelioma	66	0	0	2	6	15	10	16	4	3
Peritoneal mesothelioma	109	0	0	3	3	18	22	18	16	29

Table VIII-31

EXPECTED AND OBSERVED DEATHS AMONG 933 AMOSITE ASBESTOS FACTORY WORKERS EMPLOYED 1941-45 OBSERVED TO DECEMBER 31, 1977

		Deaths of lung cancer and mesothelioma				
Time from onset (years)	*Man-years*	*Lung cancer*			*Mesothelioma*	
		Exp.	*Obs.*	*Ratio*	*Pleural*	*Peritoneal*
<5	4,331	0.95	0	—	0	0
5-9	4,095	1.78	3	—	0	0
10-14	3,784	2.57	13	5.06	0	0
15-19	3,362	3.19	20	6.27	0	0
20-24	2,837	3.49	18	5.16	1	0
25-29	2,250	3.59	25	6.96	2	4
30-34	1,553	3.16	17	5.38	5	3
35+	192	0.41	4	—	0	1
	22,404	19.14	100	5.22	8	8

of mesothelioma induction, has been demonstrated by Roe et al. (54). After subcutaneous injection in mice (experiments with three types of asbestos), wide dissemination from the site of injection and a highly selective distribution were observed; the main sites of asbestos accumulation were the visceral and parietal pleura and the serosal surface in the abdominal cavity.

- the fiber size (cross-sectional diameter and length) seems to be important, since smaller fibers penetrate deeply into the periphery of the lung and subpleural areas (21)(22)(67)(68)(70)(75).

The evidence for marked effects, including the carcinogenic mesothelioma inducing effect of small fibers (length less than 5 um) has emerged relatively recently (122)(24)(75). This is important in view of the fact that handling or treating asbestos as well as use of asbestos products gen erates fragmentation (both longitudinally and transversely) of fibers resulting in a larger number of shorter and thinner fibers or even fibrils. Chrysotile is especially prone to undergo such

fragmentation.

CLINICAL DESCRIPTION

Symptoms

Chest pain (unilateral) and shortness of breath are the most common presenting symptoms. The chest pain may be diffuse and dull or it may be of the pleuritic type; it often progresses to be severe. Shortness of breath may rapidly progress, especially with the development of a pleural effusion.

Other relatively frequent symptoms are loss of appetite, weight loss, fatigue, and in some cases fever; cough is infrequent.

Physical Signs

Pleural effusion occurs in the majority of cases, with dullness on percussion and decreased breath sounds. Rapid recurrence after aspiration of pleural fluid is the rule. The pleural fluid may be serous and clear but sometimes is hemorrhagic.

Retraction of the affected hemithorax, and shifting of the mediastinum to the side of the lesion may occur.

Natural History

Rapid tumor growth—often after pleural biopsy, i.e., needle biopsy or thoracotomy—with subcutaneous tumor nodules may involve the chest wall, the ribs and vertebrae, the mediastinum (sometimes with superior vena cava syndrome), and/or the pericardium with pericardial effusion. Distant metastases to the liver or other intra-abdominal organs, sometimes with ascites, can be clinically detected.

The metastatic spread of mesothelioma is much more frequent than previously thought and has been shown to occur in the majority of cases in which an autopsy was performed; both lymph node metastases and distant hematogenous metastases can be found. Spread of the mesothelioma to the opposite pleural cavity, and also to the peritoneum, is frequent; most often this is the result of a local invasive process, through the mediastinum or through the diaphragm.

The natural history of the disease is that of a rapid downhill course; death occurs in the majority of cases after an interval of months to one or two years. The mean survival from first diagnosis does not exceed 12 months. Although all therapeutic methods have been used, often in combination (surgery, radiotherapy, chemotherapy), no significant difference in survival of patients with pleural mesothelioma has been consistently achieved.

Laboratory Investigations

Radiographic changes are characteristically unilateral and progressive. The two main modalities of radiologic changes in pleural mesothelioma are: 1) unilateral pleural effusion; 2) large, nodular, protuberant opacities projecting from the pleura into the pulmonary parenchyma. Most often a combination of these changes is found.

Aspiration of the pleural fluid may be helpful in revealing underlying solid tumoral opacities. Extension of the tumoral growth over the apical pleura and into the mediastinal pleura is frequent. PA chest radiographs should be complemented by oblique views of the chest whenever a suspicion of pleural mesothelioma arises. Other radiographic evidence of asbestos-related parenchymal and/or pleural changes may or may not be present. Pleural plaques or calcifications are a useful marker of past asbestos exposure.

Pulmonary function studies are irrelevant for the diagnosis of mesothelioma.

Pleural fluid aspiration, while often necessary to alleviate respiratory distress, is of limited diagnostic use. Cytology of the pleural effusion is often fraught with the difficulty of distinguishing between mesothelial malignant cells and "atypical" mesothelial cells. The detection of hyaluronic acid in the pleural fluid is useful, although it can be found with other malignant tumors of the pleura; a negative result does not discard the diagnosis (6)(25)(76).

Needle biopsy specimens are insufficient for tissue diagnosis, since tissue specimens so obtained might not include malignant changes (although such changes may well be present in adjacent areas of the pleura) and since there is marked variability of pathologic changes.

Thoracotomy with surgical pleural biopsy, although providing adequate tissue specimens for diagnostic purposes, is often followed by local extension of tumor growth into the chest wall.

Treatment

There is no effective therapeutic approach, although surgery to reduce the tumor mass (9), radiotherapy (17)(57)(71), chemotherapy, single drugs (7)(18)(29)(30)(40), or combinations of two, three, or four drugs, and all possible combinations of these methods have been attempted (35).

Wanebo et al. reported on 66 cases with

malignant mesothelioma (78). For the epithelial type, pleurectomy combined with irradiation and chemotherapy seemed to be more effective; in the fibrosacromatous type, surgery resulted in longer survival.

Prognosis

The disease is fatal, and progression is usually rapid, with marked deterioration over short periods of time. In exceptional cases, longer survival (several years) can occur even in the absence of any therapeutic procedure.

DIAGNOSTIC CRITERIA

The diagnostic criteria for pleural mesothelioma are:

- a history of asbestos exposure in the past. Occupational exposure (even for short periods) or household or neighborhood exposure has to be actively searched for and can be established in the vast majority of cases if histories are taken by a physician with experience in occupational medicine (11).
- long latency period, usually more than 20 years from onset of exposure, most often between 30 and 40 years.
- clinical symptoms: unilateral chest pain and/or significant increase in dyspnea over a short period of time (weeks or months).
- physical findings: consistent with pleural effusion.
- radiographic abnormalities presenting as pleural effusion or pleural thickening often with large nodular opacities projecting from the pleura. Rapid increase in pleural thickening or the the appearance of irregularities of the pleura are highly suspicious. Rapid progression of radiologic changes.
- tissue diagnosis on an adequate specimen (thoracotomy with pleural biopsy). Microscopic findings consistent with the epithelial (tubulopapillary), mesenchymal (fibrosarcomatous), or mixed or undifferentiated type.

The complexities and difficulties of the pathologic diagnosis have been discussed. The finding of hyaluronic acid in the pleural fluid of tissue specimen is useful, but the diagnosis cannot be discarded when the test is negative.

In the differential diagnosis of pleural mesothelioma, the following problems are of practical importance: (a) Benign pleural effusions may occur in a patient with present or past asbestos exposure. The clinical course is usually indicative, since benign pleural effusions tend to resolve spontaneously over several weeks. Nevertheless, such a "benign pleural effusion" has been observed, in some cases, to be a precursor of pleural mesothelioma. (b) Pleural fibrosis is a common finding in persons with present or past asbestos exposure; the prevalence increases with time since onset of exposure. In cases with extensive pleural fibrosis, especially when the width on chest x-ray exceeds 10 mm, the differential diagnosis between pleural fibrosis and pleural mesothelioma may be difficult. The presence of similar pleural changes on previous x-ray films makes the diagnosis of mesothelioma less likely; repeat chest x-ray films after several weeks are necessary when no previous chest x-ray are available. (c) The differential diagnosis between pleural mesothelioma (*primary* malignant tumor originating in the pleura) and secondary involvement of the pleura by a malignant tumor, either lung cancer or another primary malignant tumor with metastatic spread to the pleura, has been given much attention. In the case of lung cancer, sputum cytology and fiber optic bronchoscopy with bronchial biopsy, in addition to the radiologic appearance, contribute to the differential diagnosis. The proportion of cases which remain undecided is small. The possibility of a malignant primary tumor originating in another site, with metastatic spread to the pleura is investigated by the routine clinical work-up. Patients with no other detectable primary tumor but with clinical and radiologic features of mesothelioma have, with a high degree of probability, pleural mesothelioma. The absolute certainty of this differential diagnosis is reached only after postmortem examination.

In reviewing the experience accumulated over the last 20 years, it becomes obvious that pleural mesothelioma has been largely underdiagnosed in the past. This has been established in prospective cohort studies of asbestos-exposed workers (28)(33)(34)(38)(44)(47)(60); in many studies investigating diagnostic accuracy in series of reported mesothelioma cases (15); and in systematic reviews of all pathology material—as in Scotland where 80 undiagnosed cases were discovered (39).

In the 1967-1977 cohort study of 17,800 asbestos insulation workers in the United States and Canada, out of a total of 2,270 consecutive deaths, 60 were recorded on the death certificate as mesothelioma (31 pleural, 29 peritoneal). Review of medical records, including pathology reports, chest x-ray films, postmortem examinations (when available) and independent review of tissue specimens by experienced pathologists resulted in a diagnosis of mesothelioma in 175 cases (66 pleural, 109 peritoneal). The death certificate accuracy was 47% for pleural mesothelioma and 27% for peritoneal mesothelioma (Table VIII-32). In another cohort of 689 asbestos workers, 11 cases of mesothelioma (4 pleural, 7 peritoneal) were recorded on death certificates for the period 1959-1975. Review of medical records and pathology material resulted in a diagnosis of mesothelioma in 26 cases (14 pleural, 12 peritoneal), with the death certificate accuracy only 28% for pleural mesothelioma, and 58% for peritoneal mesothelioma (Table VIII-33).

In the majority of pleural mesothelioma cases it is possible to establish the diagnosis intravitam. The greater awareness of population groups with present or past exposure, of the Department of Health, Education and Welfare, of other governmental agencies, and of the medical community are expected to result in earlier diagnosis. This is a prerequisite for future meaningful attempts of therapy.

The requirement of postmortem examination for the definitive diagnosis is necessary for the complete assessment of mesothelioma incidence from an epidemiologic point of view, although it is expected that a higher index of suspicion will substantially reduce the difference between the number of cases diagnosed while alive and those in which the diagnosis is reached only after postmortem examination.

METHODS OF PREVENTION

The prevention of pleural mesothelioma is dependent on the reduction of exposure to asbestos fiber to the minimum possible level, since this adverse health effect has been specifically associated with low level and short-term exposure. In December 1976, NIOSH, based on a "Reexamination and Update of Information on the Health Effects of Occupational Exposure to Asbestos," recommended to the DHEW and OSHA that the standard be reduced to 0.1 fibers /cm^3. This was based on the lowest concentration at which asbestos fibers can be reliably identified by phase contract microscopy.

RESEARCH NEEDS

Critical problems where research is needed:

1. Determine mechanisms of carcinogenicity (mineral fibers; potential effect of other mineral fibers, such as zeolites, titanite fibers, etc.).
2. Define, to the extent that it is at all possible, the lowest level of asbestos exposure which may result in mesothelioma. This is of paramount importance for the acceptable standard.
3. Establish the role(s) of immune mechanisms in individual susceptibility for mesothelioma.
4. Determine mechanisms of carcinogenicity in peritoneal mesothelioma, including the significance of ingestion of fibers. This is important since water may be polluted with mineral fibers from various sources, and the risk of mesothelioma from such a situation has not yet been assessed.
5. Establish mesothelioma therapy.

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Table VIII-32

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

Accuracy of death certificate categories

Cause of death	*Expected*	*Death Certificate*		*Ascertained*	
		Number	*o/e*	*Number*	*o/e*
Cancer, all sites	319.90	888	2.77	994	3.10
Cancer, lung	105.97	403	3.80	485	4.57
Pleural mesothelioma	—	31	—	66	—
Peritoneal mesothelioma	—	29	—	109	—
Cancer, esophagus	7.01	16	2.28	18	2.56
Cancer, stomach	14.23	19	1.34	22	1.55
Cancer, colon	37.86	58	1.50	59	1.56
Cancer, pancreas	17.46	48	2.75	22	1.26
Cancer, liver	7.50	18	2.40	5	0.66
Cancer, brain	10.34	19	1.84	14	1.35
Asbestosis	—	108	—	162	—
Chronic obstructive lung disease	58.58	127	2.17	66	1.13

Death certificate accuracy: Cancer, 89%; lung cancer, 83%; G.I. cancer, 94%; pleural mesothelioma, 47%; peritoneal mesothelioma, 27%.

Table VIII-33

RELATION BETWEEN DIAGNOSIS OF CAUSE OF DEATH AS RECORDED ON THE DEATH CERTIFICATE AND AS ASCERTAINED BY REVIEW OF ALL AVAILABLE INFORMATION, IN 274 DEATHS AMONG 689 ASBESTOS WORKERS OBSERVED JANUARY 1, 1959 - DECEMBER 31, 1975

	Death certificate	*Ascertained*
Cancer, all sites	94	99
Cancer of lung	36	35
Pleural mesothelioma	4	14
Peritoneal mesothelioma	7	12
Mesothelioma — unspecified site	7	0
Cancer of esophagus, stomach, colon, and rectum	12	15
All other cancer	28	23
All respiratory disease	43	42
Asbestosis	26	35
Pneumoconiosis	8	0
All respiratory disease	9	7
All other causes	137	133

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