Leslie Preger

SECTION 5
LUNG CANCER

Asbestos is one of many substances incriminated in lower respiratory tract carcinogenesis as shown in Table 2-11. In the assessment of the role of asbestos and other industrial agents in carcinogenesis, a multifactorial approach is necessary because these agents are not restricted to industrial workers congregated at work sites; these noxious agents may spread far from industrial areas. Lung cancer mortality is increased in patients with high ferruginous body counts without known asbestos exposure[1] other than that of urban living. Similarly, there is an excess lung cancer mortality in those living in the vicinity of arsenic-emitting smelters[10] or in heavily industrialized areas with much air pollution from benzo(a)pyrene and other polycyclic aromatic hydrocarbons.[8,9,15] The role of hydrocarbons contained in vehicular exhaust gases in respiratory tract carcinogenesis is controversial.[16]

Synergistic and multiplicative effects need to be considered. In male and female asbestos workers, cigarette smoking increases the lung cancer burden;[17,18] this is discussed more fully below (see Table 2-12).

A similar relation exists in uranium miners inhaling radon daughter products. An excess of alcohol predisposes to cancer of the larynx, oropharynx, and esophagus, all of which are more prevalent in asbestos workers.[20] Experimental[21] and epidemiological data[22] indicate that an excess of lung cancer is associated with a lower vitamin A intake.

The drug history of asbestos workers needs to be considered. Leukemia is said by some to be more common in asbestos workers (see references in Chapter 2, Section 6), and to this risk there is the additive one from the use of myleran (busulphan) in myeloid leukemia. This agent produces precancerous cytological changes in the lung and, in one reported patient, an apparent progression to bronchiolar cell carcinoma. Bronchogenic carcinoma is more common in patients with leukemia than in the general population. There is an excess of adenocarcinoma of the lung as well as histiocytic lymphoma following immunosuppressive therapy.[16]

Immunologic susceptibility may be responsible for some lung cancers in asbestos and other workers. Abnormally high levels of inducible aryl hydrocarbon hydroxylase activity in cultured lymphocytes is present in those who smoke[23] and in some lung cancer patients[24] but not in others.[25] This genetically regulated defect affects hydrocarbon metabolism and may be related to the

Table 2-11

Occupational Lung Carcinogens	References
Asbestos	1
Radon	2
Halo ethers	3
Mustard gas	4
Polycyclic hydrocarbons	6, 7
Chromates	8
Arsenic and arsenic trioxide	9, 10
Iron (hematite)	11
Printing ink	12
Vinyl chloride	13
Nickel	14

multiplicative effect of cigarette smoking and the risk of asbestos-induced lung cancer.[16] There is insufficient data accumulated to know if patients with easily inducible aryl hydrocarbon hydroxylase are susceptible to certain histological types of lung cancer. The inducibility of the enzyme system in cultured lymphocytes parallels that in lung tissue and may be a way of distinguishing asbestos workers at greatest risk of lung carcinogenesis. The increased incidence of certain antigens and antibodies in some patients with asbestos-related pulmonary fibrosis is described in Chapter 1 and Chapter 2, Section 2. The mechanism of transition of pulmonary fibrosis to lung cancer and the reason for the increased incidence of lung cancer in asbestos-induced pulmonary fibrosis

Table 2-12

Bronchogenic Carcinoma in:	Incidence per Million	Relative Risk Ratio
Nonsmokers (30% population)	8	1
General population	60	7
All smokers (70% population)	85	10
Heavy smokers (25% population)	130	15
Nonsmoking asbestos workers	8	1
Smoking asbestos workers	560	70

Modified from Higginson.[3] The percentage estimates of smoking population are Higginson's.
The incidence of lung cancer in nonsmoking asbestos workers is not greater than that in the general population (smokers and nonsmokers), but there are very few asbestos workers with lung exposure who do not smoke. There is insufficient data to be certain that there is no lung cancer excess as compared with nonsmokers in the general population.

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Table 2-13
Epidemiologic Data of Lung Cancer Risk in Asbestos Workers

Author	Exposure	Increased Incidence of Lung Cancer	Comments
Selikoff[38]	New York and New Jersey insulation workers using chrysotile and amosite	× 8.3	Follow-up more than 20 years since last exposure.
			Follow-up less than 20 years since last exposure.
			Follow-up more than 20 years since last exposure.
	U.S. and Canadian asbestos workers using chrysotile and amosite	× 3.1	
	Amosite asbestos workers	× 3.5	
		× 6.4	
	U.S. and Canadian insulation workers	Lapsed time since onset of exposure	Excess lung cancer appears as early as 10–14 years after first exposure; increased to 30–40 years after exposure.
		10–14 years × 2.4	
		15–19 years × 3.7	
		20–24 years × 3.3	
		25–29 years × 4.8	
		30–34 years × 7.1	
		35–39 years × 6.5	
		40–45 years × 5.9	
		45–49 years × 4.6	
		50+ × 4.5	
Edge[41]	Shipyard workers U.K.	× 2.4	
Fletcher[42]	Shipyard workers U.K.	× 2.5	
Lumsden[43]	Shipyard workers	No increased incidence detected	Compared registration of lung cancer in dockyard workers with age-related controls living in same geographical area but not employed in dockyards.
Enterline[44]	Asbestos production workers	× 1.7	Includes pleural mesothelioma. Is an average for all industries of exposure; with heavy exposure, increased incidence is 3.0
	Asbestos maintenance workers	× 2.5	

*Input 1 – million particles per cubic foot years is an index determined from the products of asbestos fibers in the air at the place of work and years of exposure.

[b]The value of × 1.4 increased incidence of lung cancer in "nonsmoking" asbestos workers is at variance with most series in which no detectable excess burden of lung cancer is found in nonsmoking asbestos workers. The "nonsmoking" status is an assumption attributed to those who died from lung cancer and was based on smoking habits of current workers. The assumption may be unjustifiable.

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are less clear. Adenocarcinoma and alveolar cell carcinoma are seen in patients with systematic sclerosis (scleroderma),[25] and sarcoidosis patients with impaired cellular immunity are prone to lung cancer;[26] both these diseases characterized by pulmonary fibrosis. Subclinical immune defects have been found in familial sporadic cases of lung adenocarcinoma,[27,28] and some patients with asbestosis tend to have impaired cellular immunity and histocompatibility antigens[29,30] that may affect subsequent carcinogenesis. There a reduction in T-cell immunocompetence in patients with pulmonary asbestosis. It is suggested that these factors may play a part in fibrogenesis and carcinogenesis. In a pilot study of asbestos workers,[30] HLA W27 antigen was three times more common than among controls. Those with HLA W27 antigen appeared to have more severe pulmonary fibrosis, and a shorter and more recent period of exposure to asbestos. More recent reports have not confirmed this finding (see Chapter 2, Section 2). The influence of race has not been investigated in asbestos-related cancers; there is an increased incidence of lung cancer in black men and Mexican Americans irrespective of asbestos exposure.[31,32] In a survey of counties with known natural asbestos deposits, which were matched with those without known deposits, no great hazard to the general population of counties with asbestos deposits was noted.[33] Table 2-13 presents a survey of epidemiologic data on lung cancer risk in asbestos workers.

CELL TYPE OF ASBESTOS-RELATED LUNG TUMOR

A peripheral lower lobe adenocarcinoma is typical of an asbestos-related lung tumor (see Fig. 2-78). Based on U.K. workers with certified asbestosis who died of cancer of the lung, an analysis by Whitwell et al.[45] of 88 male cases in which there was adequate tumor tissue yielded the data listed in Table 2-14. One patient with alveolar cell carcinoma was included in the adenocarcinoma group. The female group was small, 9 patients, and in females, histological cell types in controls differ from that of men, but 3 of 9 patients had adenocarcinoma and a further 3 of 9 had oat cell carcinoma. A preponderance of adenocarcinoma is present in some, but not all, other series (see Table 2-1 and Fig. 2-79).

Accepting an incidence of about 35 percent adenocarcinoma in the asbestos-related groups, what is the percentage of this cell type in unselected controls? For autopsy material, Whitwell et al. state 27 percent.[45] Much depends on the source of pathological material. Bronchial biopsy specimens



Fig. 2-78. *Bronchogenic cancer in an asbestos worker. Note the typical lower lobe and peripheral location. Tissue type was adenocarcinoma, which predominates in asbestos workers, even in those with a smoking history. The subaxillary, noncalcified parietal pleural plaques act as biological markers of prior asbestos exposure (horizontal arrows).*

Table 2-14

Histological Type	%
Adenocarcinoma	34.1
Oat	26.1
Squamous	21.6
Other	18.2

Table 2-15

Author	Number of Patients with Asbestos Exposure and Lung Cancer	% Adenocarcinoma
Heuper[37]	104	19
Hourihane[38]	17	35
Kannerstein[38]	50	22
Warren[39]	30	43



Fig. 2-79. Upper lobe adenocarcinoma demonstrated on tomography. The adjacent pleural plaques are enclosed by an oval arrow. This patient had small parietal pleural plaques. Occupational exposure to asbestos was 30 years previously.

Table 2-16

Cell Type	% Bronchial Biopsy Series	% Operative Series	% Necropsy Series
Adenocarcinoma	2	9	27
Oat	34	13	37
Squamous	41	57	17
Others	23	20	19

obtained with a rigid bronchoscope reflect the high incidence of oat cell and squamous tumors in the larger, more accessible proximal airways. Transbronchial lung biopsy with a fiberoptic bronchoscope with fluoroscopic visualization samples peripheral masses. A high proportion of squamous cell and a low proportion of oat cell and adenocarcinomas are seen in surgical series, since squamous cell carcinomas are more likely to be resectable, and adenocarcinoma and oat cell are frequently inoperable. Conversely, a higher percentage of adenocarcinoma is present in autopsy series, since autopsies are more frequently done when the diagnosis is in question. This is more common in peripheral adenocarcinoma, which may be inoperable when first seen, compared with more central carcinoma, e.g., squamous or an oat cell types, where a cytological or histological diagnosis is more easily made. The experience of Whitwell et al.[45] along these lines is summarized in Table 2-16. The percentage is expressed to the nearest percent and is based on 1841 male lung cancer patients seen from 1950 to 1960 at an acute general Liverpool hospital. These patients did not show lung parenchymal evidence of asbestosis, but in this area, about 10 percent of males have pleural plaques at autopsy. Thus the observed adenocarcinoma (2 percent in biopsy series, 9 percent in operative series, and 27 percent in necropsy material) probably includes some asbestos-related tumors. A reasonable estimate of frequency of adenocarcinoma in an unselected population is therefore about 15 to 20 percent of all lung tumors, while in asbestos workers it is about double.

LOCATION OF ASBESTOS-RELATED LUNG TUMORS

A peripheral location in one of the lower lobes is typical (see Table 2-17 and Fig. 2-80). In a large autopsy series without special attention to the history of evidence of asbestos exposure and regardless of cell type, the incidence of lower lobe tumors is about 24 percent. Kannerstein and Churg[38] did not find a

Table 2-17

Author	% Lower Lobe Cancer
Whitwell[45]	78
Kammerstein[78]	55
Hueper[46]	87
Control group	24

greater proportion of peripheral location or pleural involvement in their asbestos-associated group as compared with controls.

The tendency to a lower lobe and peripheral location may be explained by the effect of gravity on asbestos fibers and the fact that respiratory mechanics ensure a greater degree of ventilation in the lower zones. It is these areas that contained the highest concentration of ferruginous bodies in earlier series, although more recently uniform distribution has been reported, and the more severe fibrotic disease. The peripheral predilection is explicable if asbestos dust acts as a cocarcinogen with cigarette smoke or other atmosphere pollutants and so exerts its carcinogenic effect at the place of deposition.

RELATION OF LUNG CANCER AND PULMONARY FIBROSIS

Lung carcinoma is about twice as common in asbestos workers with moderate or severe pulmonary fibrosis as in asbestos workers with only mild fibrosis or otherwise normal lungs[45] (see Figs. 2-81 and 2-82). In addition, the proportion of adenocarcinoma increases with moderate and severe pulmonary fibrosis. Whitwell et al.'s[45] data are summarized in Table 2-18. Additional data relates ferruginous body counts in the lung with tumor type and position[49] (see Table 2-19). The ferruginous body counts were per gram of wet lung tissue; all the patients had low asbestos exposure. The apparent increase in proportion of adenocarcinoma with increasing ferruginous body counts is, however, not statistically significant, since the total number of patients was only 30. This is not surprising, because in asbestosis there is a relation between asbestos load in the lung and mild fibrosis, but in severe fibrosis there is no correlation with a further increase in asbestos fiber concentration. It is in the more severely fibrotic lungs that the excess of adenocarcinoma develops. In systemic sclerosis in which, like asbestosis, lower lobe pulmonary fibrosis is frequent, adenocarcinoma, together with alveolar and bronchiolar carcinoma, occurs relatively frequently.[25,50] In sarcoidosis, lung cancer has been reported to occur three times more frequently than in the general population.[26] In this disease,



Fig. 2-80. *Peripheral adenocarcinoma hidden by diaphragm in PA view (A) and better seen in lateral and LAO views (B and C). Hilar involvement (A), fibrosis, and plaques (C) are indicated by arrows. This is a 71-year-old male who smoked, with occupational exposure to asbestos.*



Fig. 2-81. *Alveolar cell carcinoma (oat carcinoma) developing in an area of pulmonary fibrosis. In June 1972, the multiple densities were thought to be focal areas of fibrosis. In December 1972, the malignant nature of one of the densities is apparent. The interstitial fibrotic change in the remainder of the lung is more apparent in later, more heavily exposed film.*



Fig. 2-82. *Alveolar cell carcinoma in a fibrotic lung in an ex-asbestos worker. An unsuccessful attempt at brush biopsy was made. Penetration of peripheral bronchi in fibrotic lungs is difficult. Percutaneous needle biopsy may be a wiser choice.*

Table 2-18

Cell Type	Normal Lung or Mild Asbestosis	Moderate or Severe Asbestosis
Adenocarcinoma	25%	38%
Oat	25%	28%
Squamous	29%	19%
Other	21%	15%

Table 2-19

Ferruginous Body Count	Adenocarcinoma	Lower Lobe Location
Low	33%	14%
High	58%	33%

pulmonary fibrosis is characteristic. The sequence of events may be different however since in sarcoidosis the increased lung cancer burden may be related to an immunologic deficiency.[26] Furthermore, since many of the patients are treated with steroids, ease of inducibility of aryl hydrocarbon hydroxylase may be relevant because steroids increase levels of this enzyme (see Chapter 2, Section 2).

RELATION OF LUNG CANCER AND PLEURAL PLAQUES

There is a 2.5-fold increase of bronchial carcinoma in shipbuilders with plaques but no radiographic evidence of pulmonary fibrosis compared with controls from a neighboring area whose x-rays were strictly normal but who may have had some degree of asbestos exposure.[51] The significance of this very recent report is difficult to assess. One inference is that patients with plaques should be followed for detection of lung cancer; but in some urban areas, about 10 percent of persons coming to autopsy will have pleural plaques, no clear-cut history of asbestos exposure, and the cause or death attributed to some disease unrelated to asbestos exposure.

RELATION OF SMOKING AND LUNG CANCER IN ASBESTOS WORKERS

Lung cancer in male asbestos workers is mainly confined to those who have smoked cigarettes (see Fig. 2-83). If there is a risk of lung cancer in nonsmoking asbestos workers, the increase over the control population of nonsmoking workers not exposed to asbestos is slight or none (see Table 2-12). Hammond[52] reports a 5.3-fold increased risk of lung cancer in asbestos insulation workers who smoke cigarettes compared with age-specific U.S. mortality per white males, disregarding smoking. The number of nonsmoking insulation asbestos workers was too small to be statistically significant. These insulation workers had been exposed to both chrysotile and amosite but not to crocidolite. The effect of smoking could be additive or multiplicative to the risk of carcinogenesis from asbestos. Studying a group of asbestos textile workers who had been exposed to chrysotile, amosite, and crocidolite, Newhouse's data suggests a multiplicative rather than an additive effect.[39] Death from lung cancer was 2.5 times greater for male asbestos workers who smoked than for a group of male smokers without asbestos exposure; for women the rate was 11

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Fig. 2-83. *Hilar oat cell carcinoma in an asbestos worker who was a heavy smoker. Apex contains old tuberculous foci with scarring and calcifications. Faint parietal pleural ringlike densities are present (horizontal arrows). Cigarette smoking tends to produce oat cell carcinoma proximally and adenocarcinoma distally. By absorbing carcinogenic pollutants in cigarette smoke, asbestos fibers may affect carcinogenesis at the site of fiber deposition in the airways.*

times the rate in a control group. The difference between incidence of lung cancer death for smoking asbestos workers and other smokers only became significant for those with severe asbestos exposure. It thus appears that there is no proof that asbestos exposure in the absence of a smoking history is carcinogenic to the lungs. In accepting this concept, two series that appear contradictory must be mentioned. First, in Finland, miners of anthophyllite who smoke have a 17-fold burden of lung cancer in comparison to nonsmoking nonasbestos workers, compared to nonsmoking anthophyllite miners, there is a 40 percent excess of lung cancer. A possible explanation to explain the 40 percent burden, when compared to the insignificant excess burden in other series of nonsmoking asbestos workers, is that anthophyllite is relatively insoluble in human lungs as compared to the chrysotile.[38] Second, Quebec chrysotile

miners and millers who developed lung cancer have a higher proportion of nonsmokers and light smokers than do controls in general population. The reason is unclear, but the burden of excess lung cancers in Canadian chrysotile workers only becomes apparent with heavy exposure.

Mesothelioma-related death is described in Chapter 2, Section 4. One may note, however, that for death due to mesothelioma, the rate is 50-fold greater for those exposed to crocidolite during production of filter pads for military gas masks in World War II compared to that associated with chrysotile production.[54]

It is probable that the type of tumor induced by an inhaled carcinogen may depend on which part of the respiratory tract is affected.[55] With cigarette smoke, which contains a higher proportion of carcinogens while it is in the proximal airways, squamous and oat cell cancers are produced proximally and adenocarcinomas peripherally. When the multiplicative effect of asbestos dust is added, the cocarcinogen reaches the distal airways, and peripheral adenocarcinomas become common.[45]

RELATION OF INTENSITY AND DURATION OF EXPOSURE TO LUNG CANCER

Accepting the increased risk of bronchial carcinoma associated with asbestos use, how is this related to intensity and duration of exposure? The data show increasing risk with intensity and duration of exposure. The various study groups are not comparable in that not only are there fiber differences but, in addition, age at first exposure and period of follow-up vary. Also, the comparison group is derived variously from national mortality data and mortality data from nonexposed groups in the same geographical area, and matching for age, sex, and smoking habits is nonuniform. Tables 2-20A to 2-20D present data from the various study groups.

The lung cancer excess manifests itself with a dust exposure index of more than 200 mpcc-years. The dust exposure index reflects two components, duration and intensity of exposure. These may be examined separately (Table 2-20B).

The almost quadrupling of the lung cancer mortality when the follow-up is extended from 15 to 25 years is seen in Table 2-20B. A similar trend is seen in U.S. asbestos workers (Table 2-20C).

There is no great difference in mortality based on age at which asbestos exposure began (Table 2-20D).

Table 2-20A
Quebec Chrysotile Miners (Male)

Death from Lung Cancer per 1000 Men	Dust Exposure Index (million particles per cubic foot - years
10.3	10
13.1	10–100
13.4	100–200
15.5	200–600
21.4	600–800
32.1	800 +

Data from McDonald[36]

Table 2-20B
British Male Asbestos Textile Workers

	Deaths from Lung Cancer: Ratio of Deaths from Lung Cancer: Observed to Expected: 15 Years After First Exposure	25 Years After First Exposure
Low intensity of exposure and short duration less than 2 years	2.5	0.5
Low intensity of exposure and long duration more than 2 years	4.3	1.6
Severe intensity of exposure and short duration less than 2 years	4.0	1.4
Severe intensity of exposure and long duration more than 2 years	6.3	1.0

Data from Seidman[37]

Table 2-20C
Deaths from Lung Cancer in U.S. Male Asbestos Insulation Workers

Observed to expected ratio deaths from 20 years from first exposure	1.9
Observed to expected ratio more than 20 years from first exposure	4.5

Data from Weiss[37]

Table 2-20D
Deaths from Lung Cancer in U.S. Male Asbestos Insulation Workers

Age at Onset of Exposure	Observed to Expected Ratio of Death
< 25	5.6
25–30	4.3
35–44	4.3
45 +	3.1

Data from Webster.[37]

FIBER TYPE IN RELATION TO LUNG CARCINOGENESIS

Crocidolite is the most potent initiator of mesothelioma. So far, however, a definite statement on the importance of fiber size in the production of bronchogenic carcinoma cannot be made.[56] This situation is unlike that regarding mesothelioma, in which studies of cohorts of workers exposed to a certain type of fiber (e.g., fine fiber Western Australian crocidolite) have enabled the formulation a statement relating risk of mesothelioma induction with fiber length and diameter (see Chapter 2, Section 4). The morphology of fibers from a single source varies with processing; currently used chrysotile is finer than that used previously. Transvaal crocidolite and amosite contain a larger portion of large fibers, which are less likely to penetrate deeply into the lungs than those obtained from the NW Cape Province of South Africa. Despite this, one may deduce from data published by McDonald,[36] Webster,[37] and Meurman[38] that crocidolite and amosite are more carcinogenic than anthophyllite and chrysotile. This opinion is based on recent epidemiologic surveys, and the author has not read any confirmatory experimental data.

Lung cancer follows inhalation of asbestos fibers by experimental animals, but the data do not correlate well with clinical experience. Carcinogenicity data are given in Table 2-21. Squamous cell and adeno (alveolar cell) carcinoma were produced, always in a peripheral location and in areas of severe fibrosis. Adenocarcinomas were slightly more common than squamous cell carcinomas.[57]

The relation between the aerodynamic qualities inherent in various fiber shapes and the consequent degree of airway penetration and retention within the lung is discussed in Chapter 2, Section 2.

Table 2-24
Cancers in Rats Following Asbestos Inhalation

Fiber	Percent of Animals Developing Cancer
Chrysotile	59
Anthophyllite	50
Amosite	43
Crocidolite	22

CHEMICAL FACTORS AND TRACE AGENTS IN CARCINOGENESIS

The discrepancy between the high incidence of lung cancer in asbestos workers who smoke compared with those who do not suggest that bronchogenic carcinoma induction in humans is not directly related to fiber shape nor to pulmonary fibrosis and mesothelioma), or to the metals that are an integral part of asbestos fibers, or to trace elements such as chromium, lead, and nickel which are known to be carcinogenic in other circumstances. The implication is that the carcinogenic effect may be due to asbestos fibers concentrating on their surface carcinogenic hydrocarbons, or other substances found in cigarette smoke that have entered the lung by other means.[58] The trace metals may play an indirect role.[59] These trace metals may be eluted from asbestos trapped in the lung and may inhibit metabolism of carcinogenic benzpyrene, so that it remains biologically active in the lung for a longer period. This hypothesis, suggesting that the fibers are inert carriers of the cancer-potentiating trace metals, is unproven; in the case of Canadian chrysotile, carcinogenicity is correlated to content of iron, chromium, and nickel.

Asbestos fibers contain various oils in small amounts. There is no evidence that the small amounts present are carcinogenic. Previously, oil in jute bags used for transport and storage of asbestos fibers was found to be absorbed onto the fiber surface, and since this oil is weakly carcinogenic, jute bag use has been discontinued in the asbestos industry. Polyethylene bags were substituted primarily to reduce the release of fibers to the environment. Unfortunately, antioxidants incorporated into polyethylene may be converted by asbestos into carcinogenic quinones. The problem of the precise mechanism of asbestos carcinogenesis is far from a solution, and current work is centered on effect of asbestos on DNA and RNA synthesis.

RADIOLOGY

The radiological technique and assessment of pulmonary neoplasia is described in many current texts and is omitted here in favor of a discussion of the problems encountered in the assessment of lung cancer associated with asbestos exposure. The early detection of lung cancer may be difficult, even when one is on the alert. Two problems confront the radiologist. Identification of a tumor may be difficult if it develops in an area of severe pulmonary fibrosis and if it lies near a large or dense pleural plaque.

Detection of Lung Cancer in Fibrotic Lungs

The presence of pulmonary fibrosis of any etiology, not just from asbestos, should indicate the need for periodic assessment to identify an early scar carcinoma. If the interstitial fibrosis is slight, no great difficulties should ensue; in areas of severe or conglomerate fibrosis the development of an additional homogenous opacity may be undetected until the tumor is large. Figure 2-84 illustrates a patient with a working lifetime exposure to asbestos as an asbestos scraper in a boiler factory. Despite the presence of hemoptysis as a warning sign, a right lung neoplasm was not detected until it had reached a large size. Hemoptysis is not a sign of uncomplicated pulmonary fibrosis, and its occurrence, or a change in symptoms such as increasing cough or dyspnea, should initiate a search for an occult lung malignancy as well as exclusion of other causes such as bronchiectasis, mitral stenosis, infarcts, and infections. Similarly, an effusion is unusual in uncomplicated pulmonary fibrosis; rheumatoid lung in men is an exception. The presence of an effusion should initiate a search for an associated malignancy. The older techniques of tomography and bronchography have their limitations. Conventional tomography may reveal a homogeneous localized density in an area of diffuse fibrosis, but on two occasions the author was content to assume erroneously that these were areas of nodular fibrosis when, in fact, they eventually proved to be adenocarcinoma (see Fig. 2-81 and Fig. 2-85). Bronchography may reveal distorted bronchi due to pulmonary fibrosis, and any additional distortion due to neoplasia may be undetected. Many asbestos-related lung cancers are peripheral, and the bronchographic signs of bronchial tumor encasement and occlusion may not be present. Peripheral bronchi may be untilled with contrast material as a result of distortion by fibrosis.

It should be stressed that the fibrosis of asbestosis is usually diffuse and not nodular as it is in silicosis. Large fibrotic nodules (Progressive Massive Fibrosis) and necrobiotic nodules are very rare in asbestosis and exclusion of malig-



Fig. 2-84. Adenocarcinoma at right hilus in boilermaker. A, Roentgenogram in 1957 shows pleural thickening in the posterior right upper lobe. B and C, Laminagrams in 1967 and 1973 show progressive enlargement of the hilar mass and obliteration of the bronchus to the right upper lobe. Biopsy specimen was obtained by bronchoscopy.

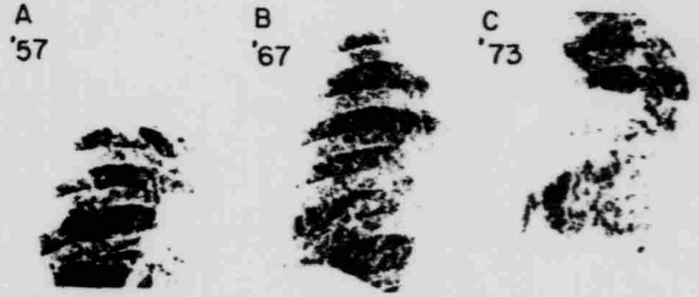


Fig. 2-85. Adenocarcinoma. Part A (1957) shows tuberculous infection in right upper lobe. In Part B (1967) there is a residual fibrothorax with some parenchymal fibrosis. In Part C (1973) a large infiltrative adenocarcinoma is seen. The patient had been a boilermaker with heavy asbestos exposure. He is alive and well 4 years later after cobalt therapy, the tumor being unresectable.

nancy is necessary. There is a tendency for the masses of progressive massive fibrosis to be bilateral and migrate slowly by fibrotic retraction towards the hila. If only one mass migrates, the possibility that the controlateral mass is a malignant tumor needs consideration.

Pleural Plaques Obscuring or Simulating Lung Cancer

On occasions, the author has found CT (computed tomography) useful in making the diagnosis of a parenchymal mass, separate from an adjacent large pleural plaque when this was not apparent from plain radiographs and conventional tomograms (see Figs. 2-86 to 2-88). Prior to the introduction of CT, the author has missed the diagnosis of lung cancer when its image was masked by an adjacent plaque.

Rarely, some plaques are quite rounded and not of the typical flat shape. They are usually noncalcified, unlike the flatter plaques. In addition, these rounded plaques occur more frequently near the diaphragms, arising from either the diaphragmatic parietal pleura or the parietal pleura near the costophrenic angle (see Fig. 2-89). Their uncalcified nature and lower zone of location make them quite indistinguishable from an asbestos-related tumor, which also typically occurs in the lower zone and peripheral in position. Computed tomography may have a potential in their assessment, but their differentiation from a circumscribed mesothelioma (a rare type most are diffuse) would still be difficult.

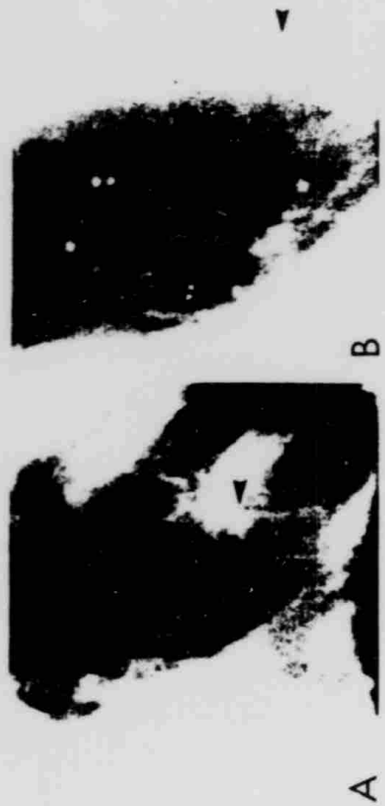




Fig. 2-87. *Poorly differentiated squamous cell carcinoma (horizontal arrow) that was initially not differentiated from adjacent plaques (vertical arrows). Part A is 5 months before B and C. C is a tomogram. Note the dense diaphragmatic and pleural plaques. The patient is a 75-year-old male smoker and ex-shipyard worker.*



Fig. 2-88. *(A) Barely visible parenchymal density in the right upper lobe of a nonsmoking insulator. Note larger subaxillary plaques. (B) Tomogram (photographic enlargement). Bronchoscopy and cytological examination showed no abnormality. The probability of an asbestos-related lung tumor seems probable. Prior film from 3 years earlier was eventually located, however, and no change had occurred.*

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Fig. 2-89. *Rounded peripheral plaque merging with diaphragmatic pleural surface. Calcification is present within the depth of the diaphragm. The rounded shape did not alter significantly in various projections. Differentiation from lung tumor was impossible until prior films showing constant size became available. The linear density projected through the lesion might otherwise suggest a scar or alveolar cell carcinoma.*

Rounded pleural plaques may develop quite rapidly, over a period of about a year, and simulate peripheral lung masses (see Fig. 2-90). The problem is compounded if the patient has a history of asbestos exposure. These plaques were known to prior generations of physicians. They occurred as fibrin balls in patients with therapeutic pneumothoraces for antituberculous therapy. These fibrin balls became adherent to the parietal pleura and occasionally remained as localized densities on the chest radiograph when the lung was allowed to reexpand.[60] The author has noted a similar radiographic appearance following a transthoracic incision for repair of a hiatus hernia (Fig. 2-90).

An additional problem may occur when several plaques are present. A false impression of multiple tumors may be obtained, and a fruitless, time-consuming (and expensive) search for a primary tumor may ensue. Here again, computed axial tomography may have an important but yet unproven role.

Computed Tomography

Accuracy of detection of peripheral tumors is greater with CT than with conventional radiographic techniques.[61] For central lesions or hilar deposits from peripheral masses, differentiation from normal mediastinal structures may

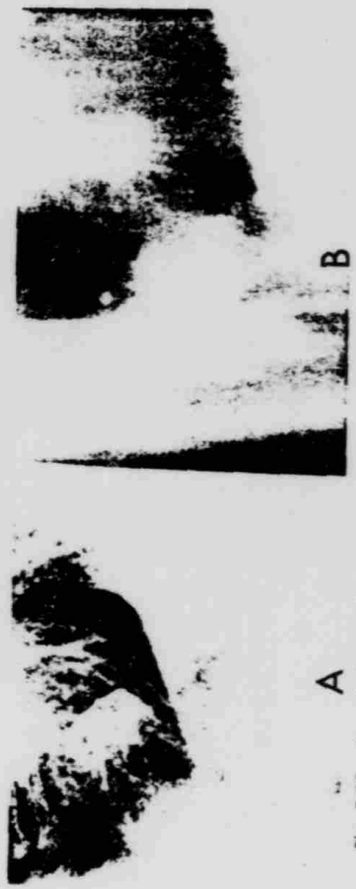


Fig. 2-90. *Rounded parietal pleural plaques. This patient had a transthoracic incision for repair of a hiatus hernia. Nine months later, a density was noted in the costovertebral angle (see lateral radiograph (A) and steep oblique tomogram (B). It was erroneously diagnosed as a peripheral lung or pleural neoplasm. Exploration revealed a dense parietal pleural plaque. The patient had no occupational asbestos exposure.*

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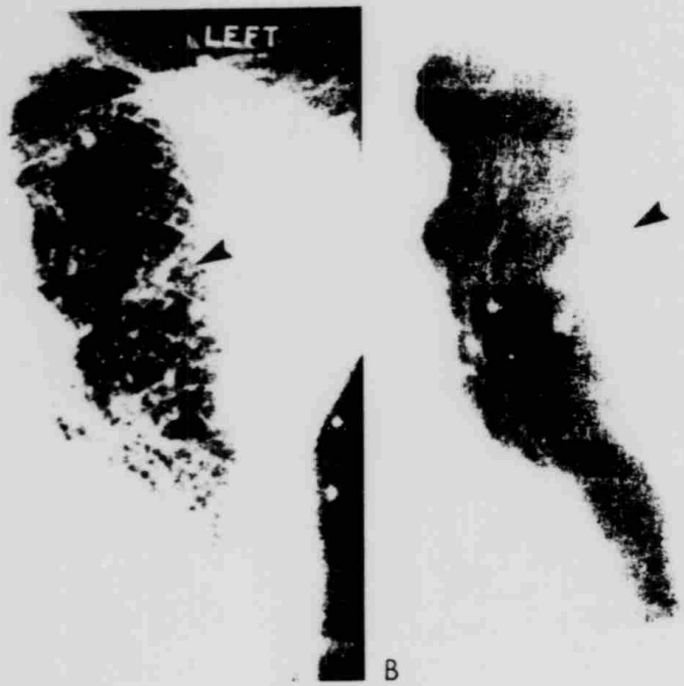


Fig. 2-91. *A and B, P-A and tomographic views of left upper lobe carcinoma in an ex-smoker (oblique arrows). Fibrosis is seen in lower lung fields. (See facing page for C and D.) C, CT scan. Homogeneous density due to carcinoma in the left lung. D, Subpleural metastasis in right lung.*

be made if there is much mediastinal fat which, because of its lower attenuation coefficient, will enhance the visibility of denser structures. The author has not seen a critical analysis of the value of CT in the detection of central malignancy. The use of intravenous contrast material will enhance the aortic density and should make for easier assessment of central tumors or mediastinal spread, but again no critical assessment has been documented. There is a growing tendency with some clinicians to perform fiberoptic bronchoscopy and bronchial washings on patients with severe asbestos-related pulmonary fibrosis. In some instances, class III-V cells are found, despite the absence of any discernible masses on conventional radiographic examinations. In these circumstances, CT is extremely helpful in suggesting areas of the lung that may



be subsequently examined by conventional tomography to gain additional data so that an intelligent decision concerning thoracotomy may be made. Aspiration needle biopsy of lung masses is made easier with CT. Currently, with conventional techniques, a combination of fluoroscopy and triangulation is used; with CT, accurate measurements along the X and Y axes may be made either directly from the CRT image if a graticule is available or from the Polaroid or film image by utilization of the appropriate minification factor.

Although metastasis of bronchogenic carcinoma to the opposite lung is rare (Fig. 2-91), and even rarer to the ipsilateral lung, it is expected that the ability of CT to identify subpleural deposits,[51] the common site for such metastases, will shorten the time spent on investigations, diminish the number of resections without hope of cure, and hasten the introduction of palliative radiation and chemotherapy when appropriate. Similarly, CT identifies small pleural effusions more readily than do conventional techniques but at greater expense. Metastases may be detectable in the bony thorax by CT; the appropriate window width and height for bone must be utilized. The author has not

read a critical comparison of CT to isotopic methods. Central bronchogenic carcinomas commonly invade the pericardium to produce an effusion: this too is detectable by CT. Identification of calcification is made easy by CT, provided the appropriate window width and height is used. CT will show more widespread plaques than will conventional radiography, especially when sections are made to include the upper abdomen, since plaques may grow through diaphragm and extend on its undersurface. Mediastinal plaques become more evident on CT examination.

Radiographic Differentiation of Peripheral Cancer and Mesothelioma

Radiographic differentiation of an asbestos-related peripheral primary lung cancer from a circumscribed mesothelioma is impossible with current radiological methods. Both may be accompanied by pleural effusion. Fortunately, circumscribed mesotheliomata are rare. The differentiation is important, since a peripheral primary lung cancer may be resectable, while no methods of treatment are currently known to produce much prolongation of life in patients with mesothelioma.[62] More frequent is the problem associated with the presence of pseudotumors in mesothelioma masses. These pseudotumors are rounded masses of necrotic and pseudomucinous material of a slightly different tissue density than the adjacent mesothelioma mass. The difference is often apparent with conventional tomography. The radiographic problem is then to appreciate that the appearance is not due to a peripheral primary lung cancer with diffuse peripheral involvement but rather to a pseudotumor in a mesothelioma. A third problem in the differentiation of lung cancer from mesothelioma arises when a lobulated pleural mass, extending over a wide area, with or without accompanying effusion, is present. This is a common finding in metastatic pleural disease from an extrathoracic primary cause, and it is not rare with an anaplastic, rapidly developing peripheral lung cancer. A mesothelioma may have an identical appearance; however, most mesotheliomata produce a diffuse peel-like appearance, enveloping the lung, rather than a diffuse polycyclic contour.

In all cases of suspected lung cancer in those previously exposed to asbestos, a careful search for other stigmata such as pulmonary fibrosis, pleural plaques, and pleural effusion should be made. The presence of pulmonary fibrosis may indicate the need for lung function assessment prior to thoracotomy. An accompanying effusion must not be considered a "benign" asbestos effusion, even if the lung tumor is small. The author has seen no reports, or had personal experience, of a pleural effusion accompanying a lung tumor that resolved during the observed biological life of the tumor.

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SECTION 6
EXTRATHORACIC EFFECTS OF ASBESTOS

The extrathoracic effects of asbestos are summarized in Table 2-22.

ASBESTOS WARTS

In the past, asbestos warts were common in persons who handled asbestos fibers and textile. They occurred on the knuckles, fingertips, and forearms. Asbestos fibers, especially amphiboles rather than chrysotile, are responsible. The warts are tender and may persist for years unless the asbestos fiber is removed. They are rare today because manual handling of fibers is no longer done.[1]

GASTROINTESTINAL CANCER

Some disorders such as ulcerative colitis, familial polyposis, and to a lesser extent, regional enteritis predispose to the development of gastrointestinal malignancy. Exogenous effects such as diet and constipation also play a part. Asbestos may be an additional exogenous factor. Epidemiologic studies of cohorts of asbestos workers have shown an increased risk for gastrointestinal cancer. Data from recent series are summarized in Table 2-23. It may be that the true incidence of gastrointestinal cancer is understated, since some cancer patients will die from unrelated causes.

With the exception of the Finnish group exposed to anthophyllite, an excess of gastrointestinal malignancies is indicated in the other series. To gain further detailed information, the American Cancer Society has underway a prospective study of 16,000 asbestos workers.[11] The study will follow the workers for many years, and in the event of development of colon or rectal cancer, the surgical or autopsy specimens will be examined for the presence of asbestos fibers in the bowel epithelium and wall at the site of the lesion and in adjacent areas.

There are occasional observations of an excess of pancreatic, kidney,