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ASBESTOSIS AND CARCINOMA OF THE LUNG

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THE INCREASING INCIDENCE of pulmonary carcinoma has stimulated considerable interest in the search for possible causative agents, especially those of the inhalant type. There now exists considerable data to support the contention that pulmonary asbestosis has a definite role in the development of neoplastic change in the respiratory system. In general, the question as to whether specific pneumoconiosis predisposes to carcinoma of the lung is of considerable medicolegal importance, and in spite of extensive experimental and clinical research, none of the agents studied have been clearly implicated except uranium in the case of the Schneeberg miners in Germany. Bridge and Henry² formulated the following specific conditions as necessary for the acceptance of industrially acquired cancer: (1) the rate of incidence in the occupation under review should exceed that in the general population to a significant extent, and (2) in the occupation concerned, there would be sufficient association of the worker with a substance proved experimentally to have carcinogenic properties. Although there is a statistically proved high incidence of pulmonary carcinoma in asbestosis, it is readily apparent that these postulates have not as yet been fulfilled. Indeed, it should be pointed out that a study by Jacob and Bohlig¹⁶ indicated that the incidence of carcinoma in asbestos workers in Dresden was not increased. In view of the fact that the role of asbestosis in the pathogenesis of carcinoma of the lung remains unproved, we felt it would be worthwhile to review the existing evidence and present clinical and pathological findings on

the cases we have seen. In the review of our own surgical and autopsy material we were able to find 6 cases of bronchogenic carcinoma associated with pulmonary asbestosis. Five additional cases were obtained from the files of the Armed Forces Institute of Pathology, Washington, D.C.

CASE REPORTS

Case 1. P.K.E. was a 58-year-old hod carrier who had worked with insulating material for 20 years. He was a heavy smoker. A routine chest roentgenogram at Virginia Mason Hospital, Seattle, Wash., showed an unsuspected lesion in the middle lobe of the right lung. Right pneumonectomy was carried out. A white, firm, slightly gelatinous, well-demarcated, 2x3-cm. tumor was found in the middle lobe. Another small firm area was at the apex. The lesion was an adenocarcinoma with growth along alveolar walls. The stroma was densely fibrous and contained numerous asbestos bodies (Fig. 1). Of particular interest was the finding of a separate focus of tumor in the apical scar, which also contained asbestos bodies (Fig. 2).

Case 2. J.W. was a 46-year-old ironworker admitted to Virginia Mason Hospital with mild congestive heart failure. He had been a heavy smoker for many years. A chest roentgenogram showed a right upper lobe lesion. An exploratory operation revealed a well-defined tumor in the posterior segment of the right upper lobe, extending through the interlobar fissure into the right lower lobe. Pneumonectomy was performed. A separate malignant tumor was found in the right apex. Both tumor nodules were surrounded by firm areas of fibrosis. Microscopically, the tumors were terminal bronchiolar carcinoma. There was marked pulmonary fibrosis, and typical asbestos bodies were found in areas of fibrosis.

Case 3. G.M.G. was a 55-year-old Negro shipyard worker admitted to Firland Sanatorium with hemoptysis and wheezing. A roentgenogram showed a lesion in the right upper lobe. Because of reduced pulmonary function, a right lobectomy only was done. He died the following day. The tumor measured 4x7 cm. and projected into the apical segmental bronchus. Microscopically, it was a

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We are indebted to the Armed Forces Institute of Pathology, Washington, D.C., for their permission to use 3 cases from their files and also to Dr. Alexander Breslow for 2 cases obtained from Firland Sanatorium, Seattle, Wash.

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squamous cell carcinoma with marked fibrosis of the surrounding tissues. Numerous asbestos bodies were present in alveolar spaces and in peribronchial fibrous tissue.

Case 4. H.M.G. was a 71-year-old retired bricklayer admitted to Firland Sanatorium with suspected tuberculosis. Symptoms included hemoptysis, cough, and wheezing. A large infiltrate was seen in the left upper lobe and a mottled appearance in the lower lobe by roentgenogram. Cultures were positive for tubercle bacilli. His condition deteriorated over a 3-month period, and he died. A polypoid, soft, white tumor in the left main bronchus was continuous with a mass in the apical-posterior segment of the left upper lobe. The tumor had infiltrated into the chest wall posteriorly. There was fibrocaseous tuberculosis of the right lung. Microscopically, the tumor was a poorly differentiated squamous cell carcinoma. There was moderately severe pulmonary fibrosis with numerous asbestos bodies present. There were numerous foci of caseation necrosis associated with the tuberculous granuloma formation.

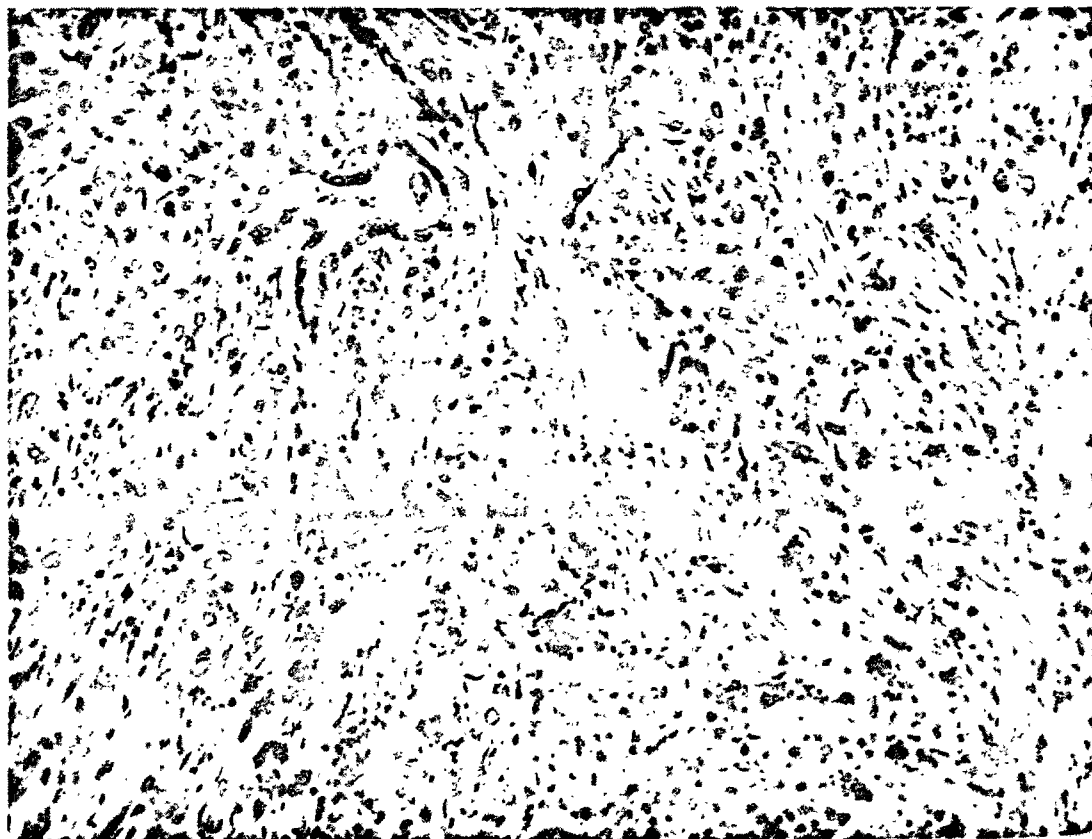


FIG. 1. Case 1. Microscopic section showing asbestos fibers intimately associated with cords of epidermoid carcinoma of the lung. ($\times 250$.)

Case 5. G.J.B. was a 64-year-old white male pipe insulator and coverer admitted to the Seattle Veterans Administration Hospital because of exertional dyspnea. He had been a heavy smoker for 10 years previously. A chest roentgenogram showed a mass in the right lung and atelectasis of the middle and lower lobes. A right lower lobectomy was carried out, and a firm infiltrating malignant tumor was found. Microscopically, this tumor was a moderately differentiated adenocarcinoma that had infiltrated the mucosa of the main bronchus entering this lobe. There was diffuse fibrosis of lung parenchyma, and numerous asbestos bodies were seen both in the tumor and in the areas of fibrosis.

Case 6. H.R.H. was a 69-year-old white man admitted to the Seattle Veterans Administration Hospital with symptoms of increasing shortness of breath and chronic pulmonary disease. He had worked in an asbestos plant for 48 years. He had been told he had asbestosis 15 years prior to his admission to the hospital. He had smoked cigarettes for 20 years. A biopsy of a skin nodule revealed metastatic anaplastic



FIG. 2. Case 1. Microscopic section showing asbestos bodies. ($\times 450$.)

carcinoma. Autopsy revealed a primary carcinoma arising in the lung and infiltrating the chest wall and lymph nodes. Numerous asbestos bodies were present in the adjacent tissue.

Case 7. E.J.H. was a 65-year-old white man who was admitted to the hospital with a primary carcinoma of the neck. He had worked as an asbestos insulator on the USS *Albatross* (SSN-581) the past year and had been in an asbestos plant for 15 years. He had been experiencing dyspnea with exertion and had been admitted to the hospital for pulmonary fibrosis. Numerous asbestos bodies were present in the lung area.

Case 8. P.K. was a 68-year-old white man who presented with a primary carcinoma of the lung and had been taken on admission to the hospital.

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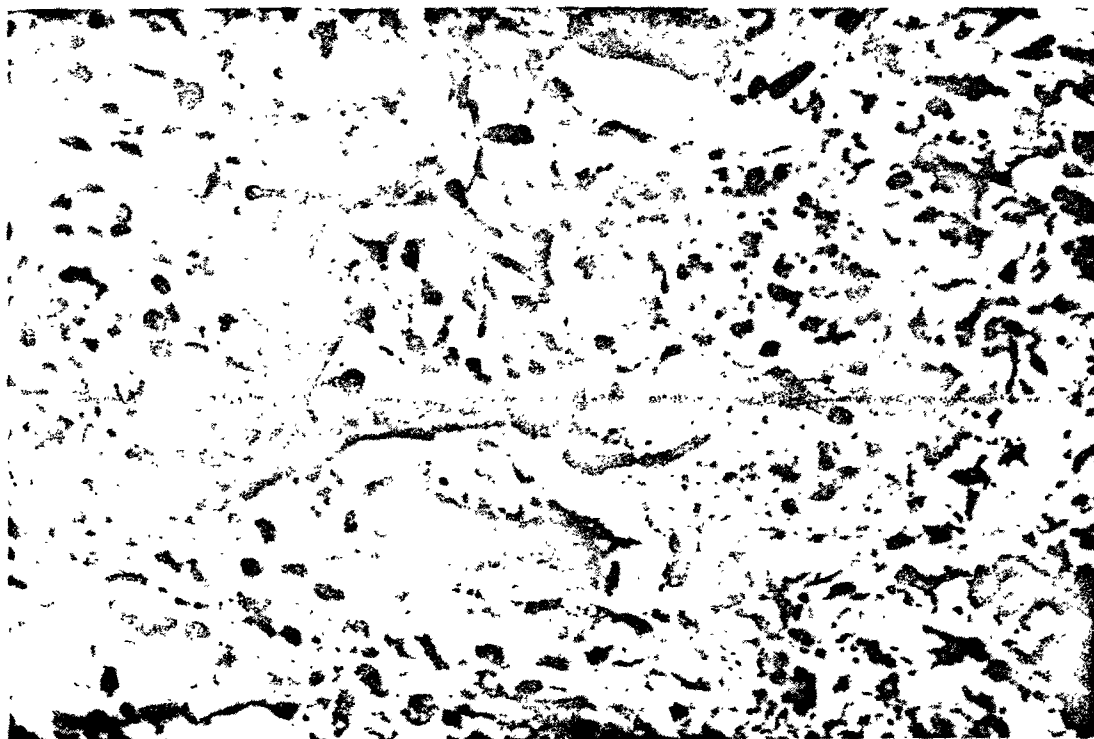


FIG. 2. Case 1. Microscopic section from separate focus of the tumor in apical scar showing several asbestos bodies. ($\times 450$.)

carcinoma. Autopsy revealed an anaplastic carcinoma, arising in the right upper lobe bronchus and infiltrating the major portion of that lobe. Metastases were evident in the hilar lymph nodes, liver, and adrenal glands. Asbestos bodies were seen within the tumor and in the adjacent fibrous lung tissue.

Case 7. E.J.H. was a 65-year-old white man who was admitted to the hospital with a primary complaint of swelling of the right side of the neck of 1 week's duration. He had worked as an asbestos insulator in the Bremerton Naval Shipyard, Bremerton, Wash., during the past year and prior to that had worked in an asbestos manufacturing plant for 53 years. He had smoked 1 package of cigarettes per day for 40 years. He had progressive dyspnea with rapidly decreasing respiratory function and died 3 weeks after his admission to the hospital. Autopsy revealed severe pulmonary fibrosis with a squamous carcinoma infiltrating the right upper lobe. Asbestos bodies were prominent within the tumor-bearing area.

Case 8. P.K. was a 62-year-old white man who presented with symptoms of general disability and weight loss. A roentgenogram taken on admission to the hospital revealed

an area of increased density in the right upper lobe and emphysema. A hilar mass was evident on the right. At thoracotomy, a tumor involving the right upper lobe was found. However, the tumor had, by direct extension, involved the chest wall and was considered inoperable. The patient died 3 days post-operatively in respiratory failure. The tumor was for the most part an undifferentiated carcinoma with areas of mucus-producing adenocarcinoma. Asbestos bodies were identified in both the tumor and the areas of pulmonary fibrosis.

Case 9. G.S. was a 68-year-old white man who had worked for many years with asbestos and Fiberglas as an insulation worker. His chief complaints were productive cough, exertional dyspnea, and weight loss. A roentgenogram of the chest revealed interstitial pneumonitis in the right upper lobe. The patient showed progressive pulmonary difficulty with cyanosis and died 10 days after admission to the hospital. At autopsy, the left lung revealed multiple firm nodules up to 1.5 cm. in diameter, and the right lung contained a firm but honeycombed area in the right apex. Sections showed a bronchiolar carcinoma with multiple foci throughout both lungs and the hilar lymph nodes. Asbestos bodies were

identified in the tumor and in areas of pulmonary fibrosis.

Case 10. W.C.D. was a 60-year-old white man who was admitted to the Seattle Veterans Administration Hospital because of extreme dyspnea, anorexia, and chest pain that had been progressive during the past year. He had worked as an asbestos handler for 40 years. He had noticed hemoptysis 3 months prior to admission. A chest roentgenogram revealed densities in both lower lobes compatible with asbestosis. A needle biopsy of the liver revealed metastatic anaplastic carcinoma. Roentgenograms revealed osteolytic lesions of the vertebrae and skull and Paget's disease of the left innominate bone. He was given X-ray therapy to the lungs. The patient died on the third hospital day after progressive dyspnea. Autopsy revealed a malignant tumor apparently arising in the right lower lobe bronchus and infiltrating the entire right lower lobe. A 3.5-cm. tumor nodule was seen beneath the pleura of the left lower lobe. The remaining lung parenchyma was replaced by dense fibrous tissue. On microscopic section the tumor revealed undifferentiated carcinoma with foci of necrosis. Asbestos bodies were identified in the tumor-bearing area.

Case 11. G.B. was a 64-year-old white man who was admitted to the hospital with complaints of dyspnea on exertion for 3½ years. He had been exposed to asbestos and magnesium for the previous 30 years. A roentgenogram revealed a circumscribed density in

the posterior right lower lobe, with diffuse emphysema. A right lower lobectomy showed a firm but gelatinous tumor lying beneath the pleura. Microscopic examination revealed a mucous adenocarcinoma characteristic of bronchiolar carcinoma. Large club-shaped asbestos bodies were noted throughout the tumor and in the adjacent fibrotic pulmonary tissue.

RESULTS

Eleven cases in which asbestosis and carcinoma of the lung coexisted have been reviewed. Five cases were obtained from the Armed Forces Institute of Pathology, Washington, D.C.; among 20 cases of asbestosis on file at the Institute, an incidence of 25%. Two cases were included from the files of the Seattle Veterans Administration Hospital, Seattle, Wash.; among 6 cases of asbestosis, an incidence of 33.3%. Two cases were obtained from Firland Sanatorium, Seattle, Wash.; from a total of 6 proved cases of asbestosis, an incidence of 33%. The remaining 2 cases were from the Virginia Mason Hospital, Seattle, Wash.

Table 1 summarizes the major findings of interest in this series of patients. The mean age of the patients at the time the diagnosis of carcinoma of the lung was established was 62 years. There were 10 white patients and 1 Negro patient, all of whom were men. The

TABLE 1
CASE HISTORIES OF 11 MALE PATIENTS WITH ASBESTOSIS AND LUNG CANCER

Case no.	Pt. init.	Pt. age, yr.	Pt. race	Durat. expos., yr.	Smoking history	Occupation	Site ca.	Type ca.
1	P.K.E.	58	W	20	2 pk./day 20 yr.	Hod carrier	Rt. mid. lobe	Adenoca.
2	J.W.	46	W	?	2 pk./day ? yr.	Ironworker	Rt. upp. lobe	Term. bronchiolar
3	G.M.G.	55	N	?	?	Shipyard worker	Rt. upp. lobe	Squam. cell
4	H.M.G.	71	W	40	1 pk./day ? yr.	Ret. bricklayer	Lt. upp. lobe	Squam. cell
5	G.J.B.	64	W	30	2 pk./day 10 yr.; stopped 8 yr. prior to death	Pipe insulator	Rt. low. lobe	Adenoca.
6	H.R.H.	69	W	48	1 pk./day 20 yr.	33 yr. in asbestos mfg. & 16 yr. as asbestos insulator	Rt. upp. lobe	Small cell
7	E.J.H.	65	W	40	1 pk./day 40 yr.	53 yr. in asbestos mfg.	Rt. upp. lobe	Well-diff. squam. cell
8	P.K.	62	W	None known	None	Carpenter	Rt. upp. lobe	Undiff.
9	G.S.	68	W	?	30 yr.	Insulation worker; worked with Fiberglas many yr.	Rt. upp. lobe	Term. bronchiolar
10	W.C.D.	60	W	40	1½ pk./day 46 yr.	Asbestos handler	Rt. low. lobe	Undiff.
11	G.B.	64	W	30	?	Occupat. expos. to asbestos & magnesium	Rt. low. lobe	Term. bronchiolar

mean duration of patients was 30 years. The tumor occurred most often in the lower lobe (6 cases of cigarette carcinoma). There was no evidence of carcinoma of the most common type, adenocarcinoma, lung cancer.

Asbestos is a mineral of a group of silicate minerals with a fibrillar structure. It is found in a variety of industries engaged in the manufacturing of asbestos-insulating materials (millboard, wall paper, etc.). The principal symptom consists of inhalation.

Some regard asbestosis as a form of pneumoconiosis, but it is accompanied by symptoms which should be considered as clinical manifestations of the development of a disease characterized by fibrosis, so-called asbestosis. The degree of asbestosis and degree of fibrosis, Lynch¹⁹ provide a pathogenesis of asbestosis into 4 stages. In stage 1, 3 to 15 years after exposure, symptoms for asbestosis are considerable individuality, some individuals rapidly while others without evidence. Symptoms of the disease are cough with expectoration, weight loss, palpitation, etc. Characteristic changes can be seen on roentgenogram.

The pathogenesis of asbestosis is found in the deposition of the lung and in the formation of nodules.^{8, 13} The asbestos fiber, 10 to 20 microns in diameter, encased in a sheath of organic compound. The fibers may be of giant cells. The deposition of

er lobe, with diffuse tumor lying beneath examination revealed carcinoma characteristic of large club-shaped alveoli throughout the lung and fibrotic pulmonary

mean duration of exposure to asbestos in 7 patients was 33 years. Carcinoma of the lung occurred most frequently in the right upper lobe in 3 cases. Five patients had a history of cigarette smoking for 20 years or longer. There was no predominant cell type of carcinoma of the lung in our series. Death was most commonly attributed to bronchopneumonia, lung abscess, and cor pulmonale.

DISCUSSION

Asbestos is a magnesium silicate that is one of a group of silicate minerals of crystalline fibrous structure.²³ Industrially, the material is found in asbestos mining and in many industries engaged in the processing and manufacturing of asbestos products. These include insulating materials, fire resistant cloths, ropes, millboard, wallboard, mortar, and other products. The principal hazard in these industries consists of inhalation of the asbestos dust.

Some regard pulmonary asbestosis as a form of pneumoconiosis not necessarily accompanied by symptoms, whereas others feel the term should be reserved for cases in which clinical manifestations are present.²⁵ The development of pulmonary lesions that are characterized by fibrosis and the formation of the so-called asbestos body depends upon the duration and degree of exposure to asbestos dust.⁵ Lynch¹⁹ provided a careful description of the pathogenesis of the disease and classified it into 4 stages. The lesions may appear after 3 to 15 years' exposure but may not produce symptoms for many years.¹³ There is considerable individual variation in susceptibility, some individuals developing the disease rapidly while others may be exposed for years without evidence of pulmonary involvement. Symptoms of the disease consist of dyspnea, cough with expectoration, pallor, cyanosis, palpitation, weight loss, and chest pain.^{26, 27} Characteristic changes of pneumoconiosis may be seen on roentgenographic examination.

The pathognomonic asbestos bodies are found in the interstitial connective tissue of the lung and in peribronchial and hilar lymph nodes.^{6, 13} They consist of a central translucent fiber, 10 to 100 μ in length and 1 to 12 μ in diameter, enclosed in a golden-brown encrusted sheath composed of an iron protein compound. The ends are usually bulbous. The fibers may be surrounded by macrophages or giant cells. The fibrosis that accompanies the deposition of asbestos fibers tends to pro-

gress even after exposure to inhalation has been discontinued.

The exact nature of the association between asbestosis and pulmonary carcinoma has been difficult to unravel. Since the first report by Lynch and Smith,²¹ many observations have been made concerning this relationship,^{4, 6-8, 10-14} with the use of several different approaches to the problem.

It has been shown in a series of studies that there is a statistically proved higher incidence of carcinoma of the lung in patients with asbestosis than in the general population. One such study, the results of which are given in the Annual Report of the Chief Inspector of Factories for the Year 1947 in Great Britain, established that carcinoma of the lung occurs in 13% of cases of asbestosis in contrast to the 2 to 6% incidence in the general population.⁹

Doll,⁴ in similar studies, arrived at the conclusion that the risk of developing carcinoma of the lung was higher in individuals exposed for a long period of time to asbestos inhalation. Nordmann,²³ who published data on 6 cases, went even further to state that carcinoma of the lung is an occupational disease among people engaged in asbestos work. This opinion was also expressed by Hornig.¹²

The second point of interest concerns the multifocal development of cancer in these cases pointed out by Nordmann,²³ Gloyne,⁸ and Hueper.¹³ This feature has often characterized the malignant tumors found in asbestosis and has also been noted in 2 of the cases presented in this report.

Finally, the age-time exposure relationship has supported the idea of a causal relationship. The longer the exposure to asbestos, the greater the risk of developing a malignant tumor; and the younger the individual when first exposed to asbestos dust, the earlier is the development of the pulmonary carcinoma. However, this relationship is not invariably found.

As shown in the cases presented, 4 of the individuals had no known history of direct exposure to asbestos dust, and the diagnosis of asbestosis was made based entirely on the histological findings of pulmonary fibrosis associated with the presence of asbestos bodies. There are no documented cases in the literature to our knowledge of cases of asbestosis associated with carcinoma of the lung in which the patient had not been exposed at one time or another directly to asbestos dust, either in

asbestosis and carcinoma have been reported. Pathology, Washington, cases of asbestosis on incidence of 25% from the files of the Washington State Hospital. Cases of asbestosis, an cases were obtained in, Seattle, Wash.: cases of asbestosis, an including 2 cases were Hospital, Seattle.

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the mines, in the crude processing of the fibers, or in other phases of the manufacturing.^{8, 10, 11} However, it is well known that asbestos is now being utilized to a greater degree in the manufacture of products that apparently bear no direct relationship to asbestos, such as in insulating material, rope, wallboard, mortar with cement, and plaster of paris. If we accept the cases presented as asbestosis, then these individuals, even though known exposure is lacking in the history, have been exposed to asbestos dust in some form and for prolonged periods of time to induce changes compatible with asbestosis and the subsequent development of pulmonary carcinoma. The fact that no known exposure existed in 4 cases indicates that the disease can occur without prolonged exposure to known sources. The average time lapse from the initial exposure to asbestos dust to the development of asbestosis is 9 years according to Egbert and Geiger,⁵ although this figure varies according to different authors, and much shorter exposure times with development of asbestosis have been recorded. In individuals who have developed carcinoma of the lung, the asbestos exposure time averages 15 years, with a range of 3 to 27 years.^{13, 14} and with latent periods of from 15 to 22 years between the initial exposure to the asbestos dust and the development of a malignant tumor.³

There have been cases, however, in which an unusually short exposure time was recorded. In a case cited by Owen,²⁴ pulmonary carcinoma developed in an individual exposed to asbestos dust for only 12 months, approximately 20 years after the exposure.

The majority of the lung carcinomas associated with asbestosis recorded have been of the squamous cell type. In our series, bronchiolar carcinoma and undifferentiated carcinoma were present in equal numbers.

Localization of the tumor in these cases is of some interest. Carcinoma of the lung usually occurs more frequently in the upper lobes, whereas in asbestosis, approximately 80% of

the cases reported occurred in lower lobe where the pneumoconiosis is most severe. Our cases showed a majority of the malignant tumors occurring in the upper lobes (Table 1).

Other agents that are believed to be related to cancer of the lung are uranium, chromium and possibly nickel. In the case of asbestos although experimental proof is lacking, there appears to be sufficient clinical pathological evidence to make it highly probable that this is a carcinogenic agent.²⁰ It must be admitted that the carcinogenic stimulus is a weak one, and the mode of action is still obscure. Particle size is apparently of importance in the production of asbestosis. Those fibers less than 20 μ in length have no apparent deleterious effect.¹⁵ The fibrotic reaction in the lung is produced by both physical and chemical changes secondary to the asbestos fiber.^{8, 17} The fibrosis is a progressive phenomenon, with progression after exposure has ceased.¹² Multifocal areas of metaplasia of the bronchiolar epithelium have been described in the areas of fibrosis and the suggestion made that these represent early stages in carcinogenesis.²⁰ The silicate portion of the fiber is apparently not responsible for this activity. Carcinoma of the lung occurs in only 1.3% of cases of silicosis in contrast to 13% in cases of asbestosis.^{4, 14, 15} It has even been suggested that silicosis may be a deterrent or even offer protection against carcinoma of the lung.

SUMMARY

Eleven cases of asbestosis associated with carcinoma of the lung are presented. A known exposure to asbestos dust was obtained in 7 of these cases. In at least 2 cases, evidence is described for multifocal origin of the tumor. Typical asbestos bodies were identified in the tumor-bearing area of the lung in each case. The possible relationship of asbestos bodies as a carcinogen in the production of cancer of the lung is discussed.

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