ASBESTOS, AN EXTRINSIC FACTOR IN THE PATHOGENESIS OF BRONCHOGENIC CARCINOMA AND MESOTHELIOMA

WARD M. O'DONNELL, MD, RICHARD H. MANN, MD, AND JOHN L. GROSH, MD

In 55 asbestos textile workers who had pathologically proven asbestosis, 28 malignant neoplasms were found—23 bronchogenic carcinomas and 5 mesotheliomas of peritoneum or pleura. Of the 28 patients with neoplasms, 26 had been exposed to asbestos dust before 1936; the medium total occupational exposure was 20 years. The interval from initial exposure until the recognition of the neoplasms varied from 20 to 40 years. Thirteen of the individuals no longer were employed in the industry when evidence of the neoplasms appeared. The primary anatomical site of the carcinomas was in the lower lobes of the lungs in 22 patients and in one instance was multicentric in origin. In the morphologic classification of the neoplasms, 10 were the squamous cell variety; 7 were anaplastic; 5 were adenocarcinoma and one was bronchiolar. The frequent association of pulmonary asbestosis with bronchogenic carcinoma (42%) and mesothelioma (8%), as seen in this study, lends further support to the opinion that asbestos is a carcinogen in susceptible individuals after critical exposure in the textile phase of the industry.

THE CAUSAL ROLE OF ASBESTOS IN THE development of bronchogenic carcinoma and mesothelioma has been a subject of increasing concern during the past decade. Recent reports from South Africa,[12, 14] England[1, 4] and the United States[3, 5, 9] have incriminated the asbestos fiber as an etiologic agent which can induce neoplasia in exposed individuals. Current interest in this association has been stimulated by the Conference on Biological Effects of Asbestos, presented in New York, in October 1964.[11]

The 8-fold increase in world consumption of this mineral during the past generation, the increase in the number and variety of industrial products utilizing this material, the fact that the fiber itself is practically indestructible, all have lead to a more widespread exposure of our population to asbestos.

Evidence now is being presented to implicate the asbestos fiber as a modern urban hazard. Thomson reported finding asbestos bodies in lung smears in 26% of the routine autopsies performed in Cape Town[13] and in 27% of those performed in Miami.[11] In Pittsburgh Cauna[2] and others found 41% of the individuals autopsied to have asbestos bodies in lung smears. These observations suggest that asbestos fibers are widely encountered in our atmospheric environment today.

Occupational exposure due to the inhalation of finely divided asbestos fibers is limited in geography to those areas where the textile manufacturing phase of the industry exists or to those occupations where individuals handle the finished asbestos product. We have had the unusual opportunity to study this disease in patients who had been employed in an asbestos textile factory in a small community in Pennsylvania. This report will be concerned with patients studied by us in the Lancaster General Hospital and there will be a special effort to evaluate the relationship between asbestosis and neoplasia as seen in these workers. Part of this material had been presented as a preliminary report in a Symposium on Diseases caused by Environmental

From the Departments of Pathology and Medicine, Lancaster General Hospital, Lancaster, Pa.
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TABLE 1. Twenty-three Asbestos Workers Who Developed Bronchogenic Carcinoma

Name	Year of established morphologic diagnosis	Age	Years of exposure	Total exposure (yr.)	Interval from initial exposure to discovery of ca. (yr.)	Histopathologic classification of neoplasm	Anatomic location
W.P. 4033	1940	37	Worked prior to World War I	—	—	Anaplastic carcinoma	Lower lobe right lung
H.T. A-48-114	1948	60	1925–1948	23	23	Squamous cell carcinoma	Lower lobe left lung
L.F. A-50-140	1950	52	1925–1939	14	25	Squamous cell carcinoma	Lower lobe left lung
R.G. A-50-53	1950	53	1923–1950	27	27	Squamous cell carcinoma	Lower lobe right lung
H.B. A-52-165	1952	59	Worked prior to World War I	—	—	Anaplastic carcinoma	Lower lobe left lung
J.S. S-52-2097	1952	49	1924–1952	28	28	Squamous cell carcinoma	Lower lobe right lung
W.B. A-53-61	1953	69	1923–1953	30	30	Adenocarcinoma	Lower lobe right lung
J.T. A-53-96	1953	52	1929–1952	23	24	Squamous cell carcinoma	Lower lobe left lung
H.F. S-53-507	1953	41	1923–1953	30	30	Squamous cell carcinoma	Lower lobe right lung
P.B. O-A-54-48	1954	59	Worked prior to World War I	—	—	Adenocarcinoma	Lower lobe left lung
I.F. S-55-3600	1955	54	1919–1934	15	36	Squamous cell carcinoma	Lower lobe right lung
S.D. A-56-164	1956	55	1923–1924	1	33	Adenocarcinoma	Lower lobe right lung
C.N. A-56-76	1956	61	1914–1922	8	42	Squamous cell carcinoma	Lower lobe left lung
R.F. A-57-34	1957	55	1917–1918	1	40	Anaplastic carcinoma	Lower lobe right lung
H.M. O-A-57-169	1957	61	1935–1947	12	22	Adenocarcinoma	Lower lobe left lung
P.Y. A-58-61	1958	60	1914–1930	16	44	Squamous cell carcinoma	Lower lobe right lung
M.M. A-59-73	1959	53	1929–1959	30	30	Squamous cell carcinoma	Lower lobe right lung
H.S. S-59-1812	1959	52	1925–1927 1954–1959	11	34	Bronchiolar carcinoma	Lower lobe left lung
B.W. A-59-143	1959	60	1917–1938	21	42	Adenocarcinoma	Lower lobe left lung
H.F. A-61-116	1961	61	1933–1961	28	28	Anaplastic carcinoma	Lower lobe right lung
C.Y. A-61-183	1961	68	1941	.333	20	Anaplastic carcinoma	Lower lobe left lung
W.W. A-62-194	1962	61	1926–1942	16	36	Anaplastic carcinoma	Multicentric origin
M.D. A-62-154	1962	51	1935–1962	27	27	Anaplastic carcinoma	Right lung

Factors during the meeting of the American Association of Pathologists and Bacteriology in April 1957 in Washington, D.C.

MATERIAL

During a 25-year period covering 1940 to 1965 55 patients with pathological proven pulmonary asbestosis were seen in the Lancaster General Hospital. These observations were established at autopsy in 52 cases and in the remaining 3 patients by examination of lungs removed at surgery. Only those cases in which the diagnosis had been established by morphologic means were included in this study.

All except one of the patients previously had been employed in the same textile manufacturing plant. As can be seen in Table 1, these individuals had been employed for varying periods of time. Some individuals still were working in the industry when the symptoms developed which necessitated their hospitalization; other individuals were admitted years after they had stopped working in the asbestos plant. Most of the workers had been

TABLE 2. Five Asbestos Workers Who Developed Mesothelioma

Name	Year of established morphologic diagnosis	Age	Years of exposure	Total exposure (yr.)	Interval from initial exposure to discovery of ca. (yr.)	Histopathologic classification of neoplasm	Anatomic location
H.B. O-A-57-169	1957	44	1937–1957	20	20	Mesothelioma	Peritoneum
G.M. A-59-138	1959	60	—	—	—	Mesothelioma	Peritoneum
R.B. A-64-132	1964	49	1929–1963	34	34	Mesothelioma	Peritoneum and pleura
S.B. A-65-41	1965	53	1926–1946	20	39	Mesothelioma	Peritoneum
H.D. A-65-139	1965	51	1933–1935	1.58	32	Mesothelioma	Pleura

exposed to the hazards of asbestos dust during the first 4 decades of this century prior to the recognition of this type of pneumoconiosis.

The factory where the exposure occurred in this study had been in operation since shortly after the turn of the century. This industrial unit was concerned with carding, spinning and weaving of the fibrous rock known as asbestos. In the early years of operation there was no realization of the danger due to the inhalation of asbestos fibers. As a matter of record, the concentration of asbestos dust was of such intensity that several of the departments previously mentioned were referred to as "a dust hole" and it has been stated "that a man could not see beyond an arm's length" in the contaminated areas.

Pulmonary asbestosis is a pneumoconiosis of relatively recent origin. Merewether and Price[8] gave the first warning of the danger of asbestos dusts in 1930. Lynch and Smith[6] first suggested a causal relationship between asbestos and bronchogenic carcinoma in 1935. With the recognition of the danger due to environmental air pollution by asbestos dust, the industry instituted remedial measures. In the processing plant where our patients worked, effective industrial hygiene was accomplished between 1935 and 1940. Only one of the workers in this series began employment after 1940. It is possible that our observations may be of historical value since the same intensity of exposure no longer exists. Prospective studies are under way to test this premise.

RESULTS

In 55 patients who had asbestosis of the lungs 23 individuals had associated bronchogenic carcinoma and 5 had mesotheliomas (Tables 1 and 2). The remaining 27 patients died of pulmonary insufficiency with or without the syndrome of cor pulmonale or of some unrelated disease. Our observations in this report are confined to those individuals who had asbestosis complicated by neoplasm.

Sex and age: Twenty-five of the workers were males and 3 were females. The ages ranged from 37 to 69, with a median of 54 years.

Years of exposure: In Tables 1 and 2 the known years of exposure to asbestos dust are recorded for each worker. In 3 individuals the only known data on employment dates were that they had worked prior to World War I. The majority of our patients had been employed during the years 1920 to 1950; only one individual began working after 1940. (The occupational history of this man [C.Y., A-61-183] revealed a 4-month exposure during 1941. Since the lungs at necropsy were compatible with those seen in advanced classical asbestosis with many asbestos bodies in the parenchyma, we question the completeness of the exposure history which we were able to obtain.) The number of years of exposure in the remainder of the patients ranged from one to 34. The mean duration of exposure was 20 years in those individuals who developed neoplasm.

Interval from initial exposure to discovery of neoplasm: In the 25 patients for whom such information was available the time from which the workers first were exposed until the neoplasms were recognized clinically varied from 20 to 44 years. The period of latency averaged about 30 years.

Interval from cessation of exposure to asbestos dust and development of neoplasm: This period varied from zero to 39 years. Eleven of the workers still were employed in

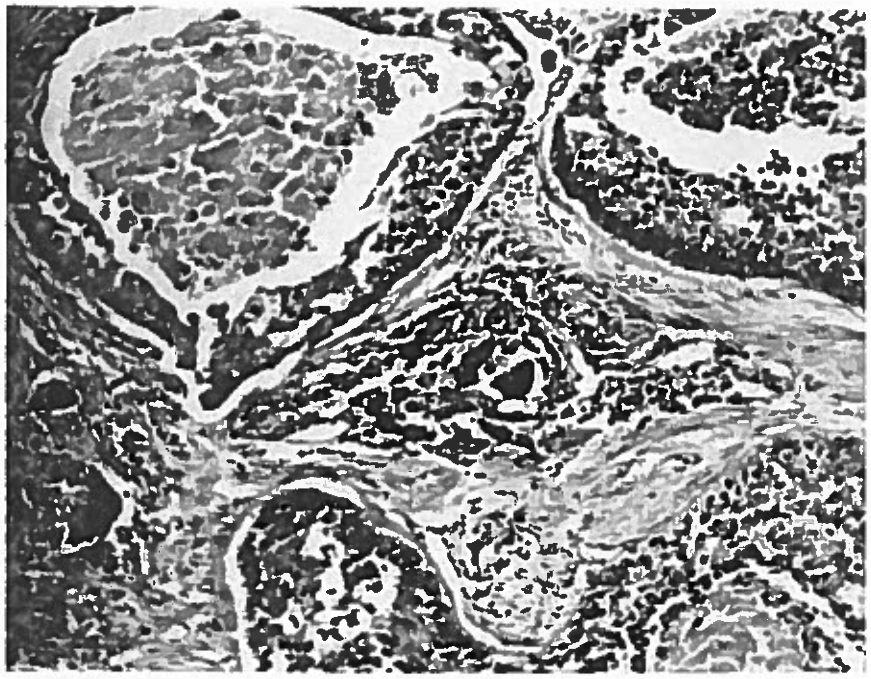

FIG. 1. Case I.F. S-55-3600. Section of lung showing asbestos bodies and nests of squamous cell carcinoma (×160).

the plant when the malignant complication was discovered. In those individuals no longer associated with the industry, 21 years was the average postemployment interval before the neoplasms were recognized.

Smoking histories: In 5 of the patients a definite history was recorded of smoking more than one pack of cigarettes daily. Unfortunately, detailed smoking histories were not available from the clinical records for the remaining individuals. In those for whom there was no history of smoking we had no way of knowing whether they smoked, had smoked and stopped or had never smoked.

Histopathologic classifications of neoplasms: In the pathologic presentation the 23 lung carcinomas were classified as follows: Squamous cell—10; anaplastic—7; adenocarcinoma—5; bronchiolar—one. In 22 patients the origin of the carcinoma was found in the lower lobes of the lungs. In the remaining patient (W.W., A-62-194) the origin was considered to be multicentric.

The mesotheliomas found in our patients have been reported elsewhere.[7] In 3 individuals the serosal cell tumors originated in the peritoneum and were confined to the abdominal cavity. In the fourth patient the mesothelioma developed independently and perhaps simultaneously in both peritoneum and pleura. In the fifth case the neoplasm was localized to the pleura. The pertinent data are recorded in Tables 1 and 2.

COMMENT

It had not been our intent in this report to determine the so-called "incidence of lung cancer or mesotheliomas" in asbestos workers. We recognized that our patients were selected from a segment of the asbestos-exposed population whose hospital admissions were based on symptoms and signs related to advanced pneumoconiosis or complicating neoplasm. Furthermore, we realized that this was a retrospective study and that the concentration of asbestos dust which existed during the years of exposure of our patients is no longer a hazard of the same degree. Lastly, the asbestos worker has the same nonoccupational liability to develop lung cancer as does the general population.

We had the opportunity to determine the association of neoplasia and asbestosis in hospitalized patients in terminal illness. These individuals had been long-term regularly employed asbestos workers in the same plant in the textile phase of the industry and we were able to obtain fairly complete exposure histories. The individuals lived and died in a stable community and we had pathologic confirmation of our findings. We think the above

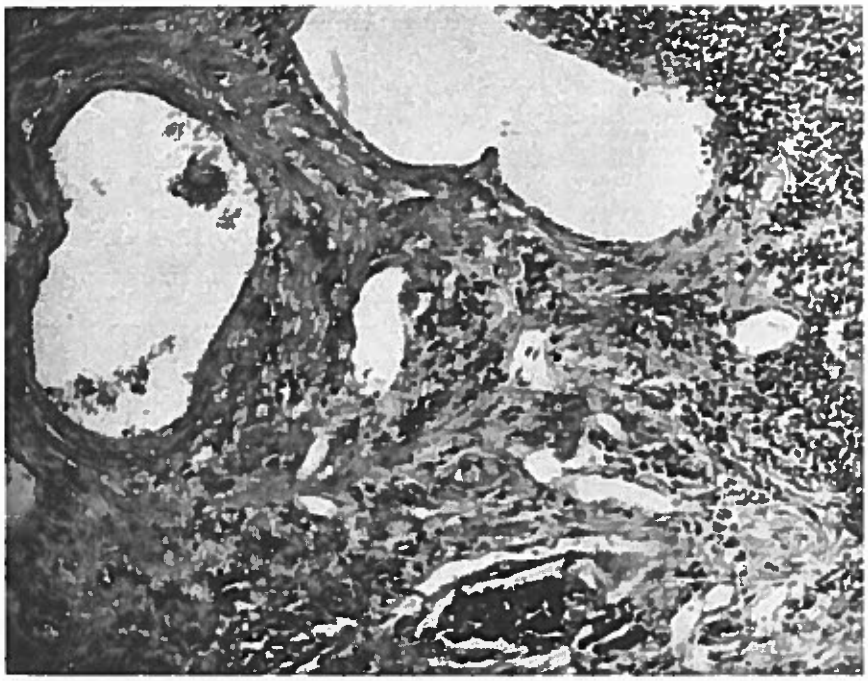

FIG. 2. Section of lung from the same case, showing replacement fibrosis of the parenchyma and several asbestos bodies (×160).

facts made this a worthwhile study of the association of bronchogenic carcinoma and mesothelioma in asbestosis.

The high incidence of associated neoplasm (50%) in our material is not necessarily at variance with the observations of Selikoff[10] and others who found a 20% association of cancer of the lungs and pleura in insulation workers handling the finished product. The degree of exposure was far more intense in our group. In England in the Annual Report of the Chief Inspector of Factories[1] for the year 1947, there was a lower percentage (13%) of the association of lung cancer and asbestosis.

For years we have been impressed by the anatomical site of the origin of cancer associated with asbestosis. In each of our cases of bronchogenic carcinoma, with but one exception, the primary lesion was in a lower lobe of the lungs. In one patient the neoplasm was multicentric in origin in the lung parenchyma. In contrast, approximately 60% of cryptogenic lung cancers arise in the upper lobes of the lungs. We have related this unique finding in lung cancer with asbestosis to the fact that the greatest concentration of the fiber and resulting fibrosis is most marked in the lower lobes of the lungs. Cordova et al.[3] did not share our experience since 7 of the 11 cases of asbestos carcinoma reviewed by them originated in the upper lobes.

The 5 mesotheliomas were seen after 1956. There were fifteen bronchogenic carcinomas in our material before the first mesothelioma was recognized. Mesotheliomas have accounted for 5 of the last 15 malignant neoplasms associated with asbestosis seen since 1956. We have no explanation for this recently acquired complication of asbestosis, nor can we account for its absence until 1957. As a matter of fact, we first became aware of this complication in a report from the North Western Cape Province of South Africa, in which Wagner, Sleggs and Marchand[14] described 33 cases of pleural mesotheliomas in relation to asbestosis. Our first 2 cases (1957, 1959) were found upon review of our material.

Three of the mesotheliomas in our series were confined to the peritoneum. In the fourth case, the mesotheliomas involved the serosal coverings of both peritoneum and pleura and in the last patient the tumor was limited to the pleura. A plausible explanation for the development of peritoneal mesothelioma is that a chemical carcinogen is released in the lungs and gains access to the serosa of the abdominal cavity through the lymphatics of the diaphragm.

Selikoff et al.[10] found 10 mesotheliomas among American insulation workers—4 in the pleura and 6 in the peritoneum. There is no indication in their report that any of the pa-

tients had simultaneous involvement of both pleura and peritoneum. The same investigators thought Chrysotile type asbestos fibers used primarily in the American asbestos industry to be carcinogenic, as well as the Crocidolite type asbestos referred to in the South African and British literature.[10] We concur with the above opinion. The plant involved in this study used the Chrysotile type of asbestos fiber almost exclusively. The neoplastic hazard results from exposure to asbestos in general rather than to any one particular type fiber.

In our patients the interval from initial exposure until the neoplasms were diagnosed ranged from 20 to 40 years. This is in accord with the knowledge that an extrinsic factor which serves as the causal agent in neoplasia must be operative for a long period of time. In our study, a year of exposure was sufficient time for 2 individuals to inhale adequate numbers of fibers to develop subsequently asbestosis and neoplasm. Thirteen of the patients had stopped working in the mill with an average postemployment of 21 years elapsing before the neoplasms were clinically evident. The inhaled fiber is a life-long indestructible material in the lung and the fibrosis and carcinogenic change is a reaction of its presence. The exposed worker must live with his personal pulmonary contaminant long after he has ceased to be employed in the industry.

We were not able to correlate the origin of the bronchogenic carcinomas or mesotheliomas with the extent or severity of the pulmonary asbestosis. In some instances in which neoplasm occurred there were few asbestos bodies in the lung sections and fibrosis was minimal. Contrariwise, in patients who did not have a neoplasm but died of pulmonary insufficiency or unrelated disease there were many examples of advanced fibrosis of the lungs with asbestos bodies in practically every microscopic field. The individual who develops a malignant process must possess a susceptibility to the specific carcinogenic activity present and survive long enough to develop a malignant neoplasm.

Since there is no constant relationship between the severity of asbestosis and the liability to neoplasia, the lesser degrees of exposure seen in workers handling the finished asbestos product, those exposed intermittently in the building trade and the residents of cities, takes on added significance. It is even possible that less protracted and intense exposure to the fiber, as occurs in the modern textile plant, still may play a carcinogenic role in susceptible workers even though the classical type of pulmonary asbestosis may disappear. This is a problem for cancer epidemiology in the future.

At the present time, however, we believe that bronchogenic carcinoma and mesotheliomas are endemic occupational diseases, as seen in the asbestos textile worker, since the frequent association (50%) of these neoplasms with asbestosis can be explained only by a causal relationship.

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