PATHOLOGY OF CARCINOMA OF THE LUNG ASSOCIATED WITH ASBESTOS EXPOSURE

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Fifty cases of carcinoma of the lung in patients occupationally exposed to asbestos were compared with 50 matched control cases of carcinoma of the lung. The two series differed significantly only in the distribution of the tumors in relation to upper and lower lobes. Another statistically less striking difference was a somewhat more frequent severe pleural involvement in the exposed group. Position within a lobe, cell types, and metastatic incidence and pattern showed no significant difference between the two series. This essential similarity would appear to be in agreement with epidemiologic and experimental investigations indicating that asbestos is a co-carcinogen. It is weak in itself, but markedly augments the effect of another potent carcinogen which in the human population is probably cigarette smoke.

THE RELATIONSHIP OF EXPOSURE TO ASBESTOS with an increased incidence of carcinoma of the lung has been firmly established by epidemiologic studies.[2,6,14] Animal experimentation also has demonstrated an additive effect by asbestos in the production of lung cancer.[17] There have been a number of case reports and tangential references to one or another aspect of the morphology of asbestos-associated carcinoma in related discussions. However, a systematic study of the pathology of asbestos-associated lung cancer has not come to our attention. Moreover, such generalities as have been expressed often contradict each other, and the basis for their development is not clear. As for assisting in the elucidation of pathogenetic mechanisms in human asbestos-associated lung cancer, human anatomic study does not appear to have contributed anything of specific significance.

It was our desire, therefore, to determine, if we could, whether any qualitative or even quantitative anatomic differences existed between asbestos-associated cancer and that in the non-occupationally exposed population.

Although the incidence of carcinoma of the lung in individuals with asbestosis is high, estimates ranging from about 15 to 50% in series followed to death,[5] the collection of material seems to be more difficult than with the much less common asbestos-associated tumor mesothelioma which carcinoma exceeds by five or six times.[15] This is presumably because the occupational history does not seem as relevant in carcinoma and is not as diligently pursued, and even the presence of asbestos bodies in tissue sections is often overlooked. We were able to accumulate sufficient information and histologic material in 50 cases to permit, we believe, relevant study. Approximately a dozen cases with incomplete information were excluded. Coming as it did from different institutions and covering a considerable time span, there were inevitably variations in the quantity and precision of information, and in a number of cases significant areas of uncertainty, which will be indicated.

In pursuing any clinicopathologic investigation related to carcinoma of the lung, it is well known that in almost every phase of morphology, disparate, if not contradictory, statements can be found in the literature. Having reviewed the literature, it seemed to us that we could draw valid conclusions only by comparing the asbestos-associated cases with our own control series using the same gross and histologic criteria. We drew from our own

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TABLE 1. Material, Carcinoma of Lung

	Total cases	Autopsies	Lobectomies or pneumonectomies	Biopsies	Age (avg.)	Age range
Asbestos-associated	50	33	11	6*	60.3	43–77
Controls	50	33	11	6†	61.1	38–81

* Bronchoscopic–2; pleural–3; metastasis–1.
† Bronchoscopic–2; pleural–2; metastasis–2.

available material 50 cases in which there was no history of asbestos exposure or presence of asbestos bodies in lung sections. Table 1 presents the composition of our series. Matching of the type of specimen was carried out with only minimal deviations. Since all the subjects in the asbestos-associated series were males, the control series consisted only of males. No selection on any other basis was made. Cigarette smoking history was available in only a portion of the cases in both asbestos-associated and control series. While it may have been possible to obtain smoking histories in more of the cases, since much of the material came from patients who had died from 10 to 17 years before in various parts of the country it would have been impossible to obtain complete smoking histories. It was assumed, therefore, that cigarette smokers occurred with about the same frequency in our asbestos-associated group as among asbestos workers with carcinoma of the lung in general and in our control series as in the overall group of non-occupationally exposed cases of carcinoma of the lung. In view of the random nature of our control series and previous studies of smoking habits among asbestos workers, we do not believe that this assumption led to a significant error.

Table 2 indicates an essential inversion in the upper lobe: lower lobe ratio of lobe of occurrence in the two groups. The predominance of lower lobe tumors in asbestos-associated cases, as well as the predominance of upper lobe tumors in general, has been commented on by others. Hueper states that the ratio is 53:7,[5] but it was only approximately 3:2 in our study.

It has been stated that asbestos-associated tumors tend to be peripheral.[18,19] There has been a difference in statistics regarding lung cancer in general in this respect, presumably in part because of variation in mode of study (x-ray, surgical specimen, autopsy)[3,4] and, in part, as a result of definition of terms.[10,18] Defining as central only those tumors that arise in lobar or main stem bronchi, we found a similar predominance of peripheral tumors in both series (Table 2).

Classification according to histology or cell type is quite difficult with the less-differentiated tumors of the lung. Atypical, inhomogeneous tumors are not rare,[1,11,12] and observer variability has been a serious problem. Even with attempted standardization of terminology, especially by the World Health Organization,[7] variability has not been eliminated. We employed a simplification of the WHO system since further subdivisions reduced the number to an inconclusive few in each category. In Table 3, lack of a critical difference between the two series is obvious. Although squamous cell carcinoma is less frequent in both groups than in many reported series, and adenocarcinomas somewhat more common, there is such variation in published statistics as to defy comparison.[18] Certain surveys have employed panels of pathologists with expertise, who come to at least majority agreement in individual cases. The present authors, in effect, employed a similar procedure between themselves. Since the asbestos-associated cases had been studied individually by one of us (M.K.) as received, we could not carry out a truly "blind" study by both authors. However, the second author (J.C.) saw

TABLE 2. Location of Tumor

	Distribution by lobe					Position in lobe				
	U	L	M	Two lobes	No data	Central	Peripheral	Both	Diffuse	No data
Asbestos-associated	13	19	4	3	11	16	22	2	3	7
Controls	29	12	1	1	7	17	28	0	4	1

TABLE 3. Cell Types of Tumor

	Squamous	Anaplastic small cell	Adeno-carcinoma	Anaplastic large cell	Combined	Unclassified
Asbestos-associated	11	11	11	6	8	3
Controls	12	14	9	8	7	0

the cases without knowing the antecedents. Initial disagreement occurred in some 10% of cases, most often in the distinction between poorly differentiated squamous cell and undifferentiated large cell types. One aspect about which there is considerable agreement is the overwhelming predominance of adenocarcinomas in non-smokers,[8] and the shift to squamous and especially anaplastic small cell tumors in smokers.[20] Some observers have claimed a large proportion of adenocarcinomas in asbestos-exposed cases in contradistinction to other environmentally induced tumors.[18,19] While it is true that there was a considerable proportion of adenocarcinomas in our own asbestos-associated cases, a very similar proportion was present also in our control series.

The only major disagreement between our control series and those of others is in the smaller number of squamous cell cancers relative to the number of adenocarcinomas. Observer proclivity must play a strong role in categorization. The advantages of a parallel series system seem evident here. Where disagreement with us by others might exist, we believe it would be in the assignment of certain cases to the large cell undifferentiated tumors which they would perhaps call poorly differentiated squamous cell carcinomas. This would somewhat increase the squamous cell group but would not diminish the adenocarcinomas.

There was no representation of rarer subgroups in our series. Several tumors of bronchiolo-alveolar type were classified under adenocarcinoma.

Table 4 includes several diverse features thought to be of interest. There were five cases in the asbestos-associated group and only one in the control group showing extensive pleural spread of tumor. This may be a significant difference.

Fibrosis of the parenchyma ws also graded. This was a relatively subjective evaluation. The finding of much more frequent and higher grades of fibrosis in the asbestos-associated cases would seem not only consistent with the clinical antecedents but a measure of the validity of our concept of comparison. It may be noted that a moderate number of control cases had mild, and a few had more advanced, fibrosis. This is to be expected in a population consisting largely of cigarette smokers and in an age group with a certain incidence of chronic pulmonary disease such as emphysema, chronic bronchitis, bronchiectasis, etc., as well as arteriosclerotic heart disease. Almost two thirds of the control cases had evidence of chronic pulmonary disease of these types.

Finally, a comparison was attempted between the number of asbestos bodies and the degree of fibrosis in the 44 cases where sufficient lung tissue permitted comparison (Table 5). It might be pointed out, however, that the number of sections available varied from case to case, and the site of origin in the lung of the tissue blocks was generally unknown. The symbolic representation of the quantity of asbestos bodies from + to ++++ was the average in a section approximately 2 cm^2. The presence of one to five ferruginous bodies consistent with asbestos bodies was designated + and when the number exceeded 50 the designation was ++++. It is seen that there was

TABLE 4. Other Features

		0	+	++	+++	++++	Unknown
Involvement of plaura by tumor	Asbestos-associated	21	12	2	2	3	10
	controls	29	9	5	1		6
Fibrosis of parenchyma	Asbestos-associated	1	10	12	17	4	6
	controls	23	14	4	2		7
Chronic lung disease	Asbestos-associated		44				6
	controls	12	31				7

no apparent correlation between the number of asbestos bodies and fibrosis in the areas examined.

TABLE 5. Asbestos Bodies and Fibrosis

	Asbestos bodies				
Fibrosis	+	++	+++	++++	Unknown
0		1			
+	3	3	3	1	
++	4	3	1	3	
+++	5	6	2	5	
++++	1	1	0	2	
Unknown	2	1			3

DISCUSSION

As indicated in the introduction, the data and material presented have had certain deficiencies inherent in most retrospective studies, especially of material of diverse origin and varying quality. These and the limited number of cases restricted the scope and detail

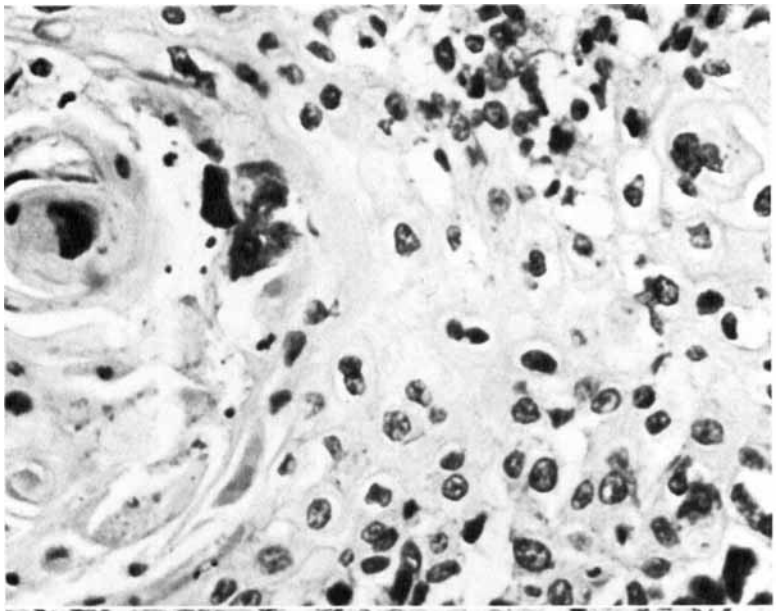

FIG. 1. Well-differentiated squamous cell carcinoma. Keratinization is present at the left (H and E, ×450).

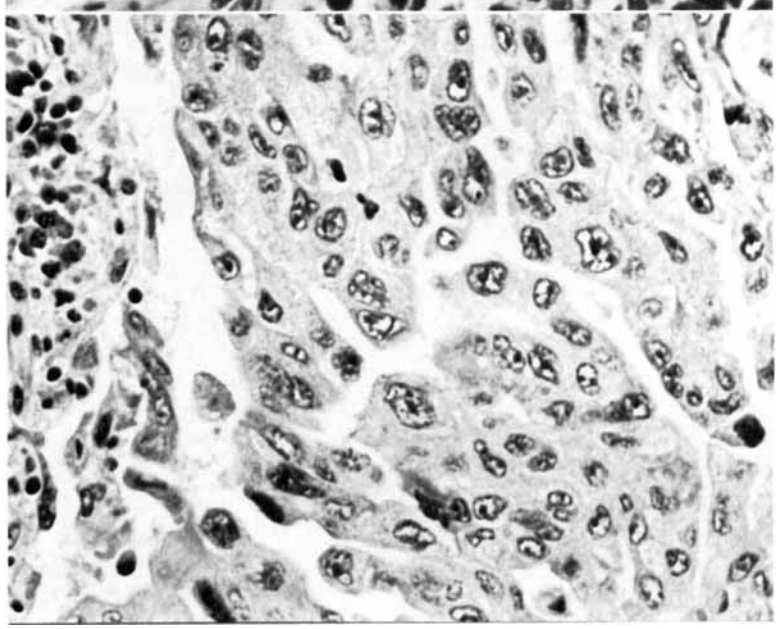

FIG. 2. Poorly differentiated squamous cell carcinoma. No keratinization or intercellular bridges are seen (H and E, ×450).

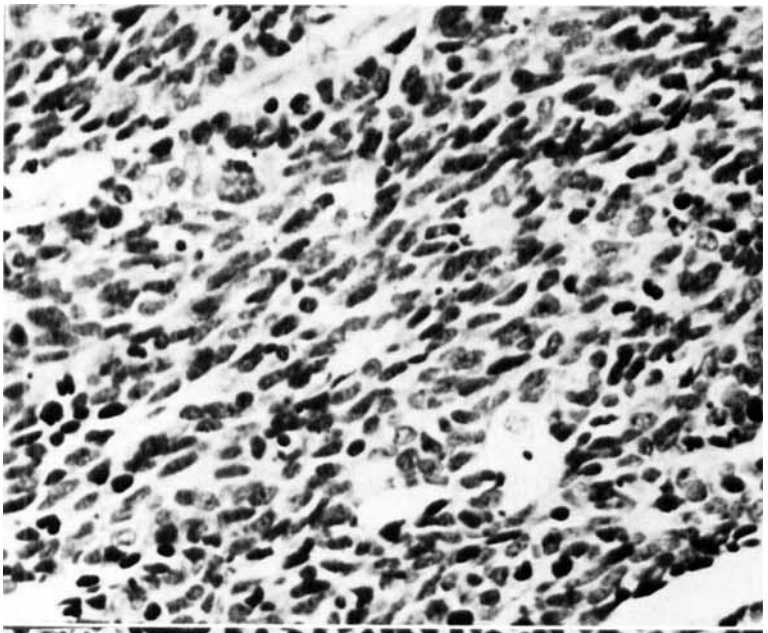

FIG. 3. Small cell anaplastic carcinoma of the "oat cell" type (H and E, ×450).

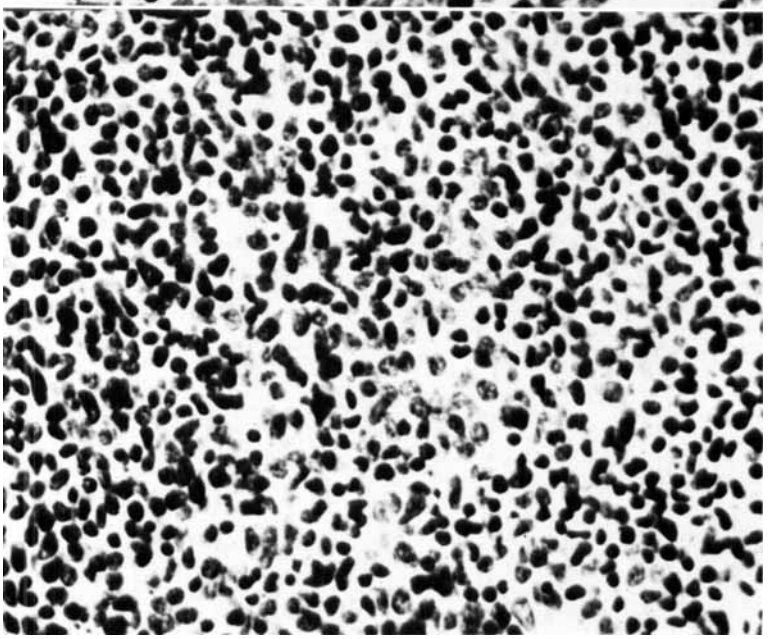

FIG. 4. Small cell anaplastic carcinoma of the round cell type (H and E, ×450).

that would have been desirable. Therefore, it is possible that subtle differences between the study and control series may have been undetected and certainly an attempt to demonstrate developmental dynamics was ruled out. Nevertheless, within these limitations, the lack of major differences between the two series is evident. The outstanding difference is the predominance of lower lobe tumors in the asbestos-associated group. The other difference—the somewhat greater tendency to pleural involvement in the asbestos-associated series—is of a lower order of magnitude.

If our conclusion is correct: that no modal morphological difference exists between carcinoma of the lung, with and without asbestos association, may we then conclude that no basic biologic difference exists? Perhaps not with finality. It would seem reasonable, a least, to consider the character of the tissue reaction to be essentially the same in both series. In view of the much greater incidence of

carcinoma of the lung in those occupationally exposed to asbestos, the simplest assumption would be that asbestos is a powerful carcinogen and the lung responds to it as it responds to other environmental carcinogens. However, Selikoff et al.[16] have shown that occupational exposure to asbestos did *not* greatly augment the incidence of lung cancer, if indeed at all, among non-cigarette smokers. The explosive increase, amounting to 8.05 times, occurred among cigarette-smoking asbestos workers. Furthermore, the risk of carcinoma of the lung in the latter group was 92 times that among non-smokers who were not exposed to asbestos!

It would appear then that it is as a co-carcinogen, in combination with cigarette smoking, that asbestos has an effect. A parallel phenomenon would seem to be that described by Saccomanno et al. who conclude that cigarette

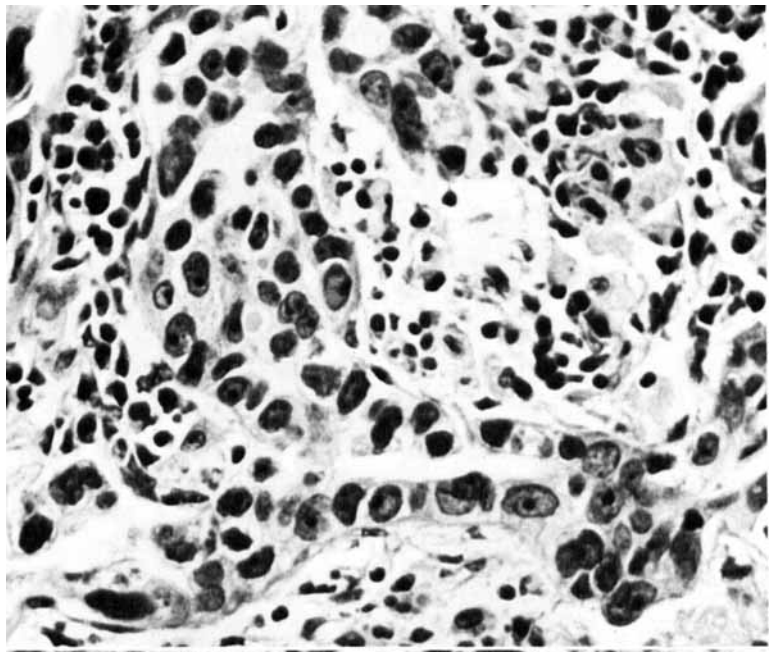

FIG. 5. Poorly differentiated adenocarcinoma (H and E, ×450).

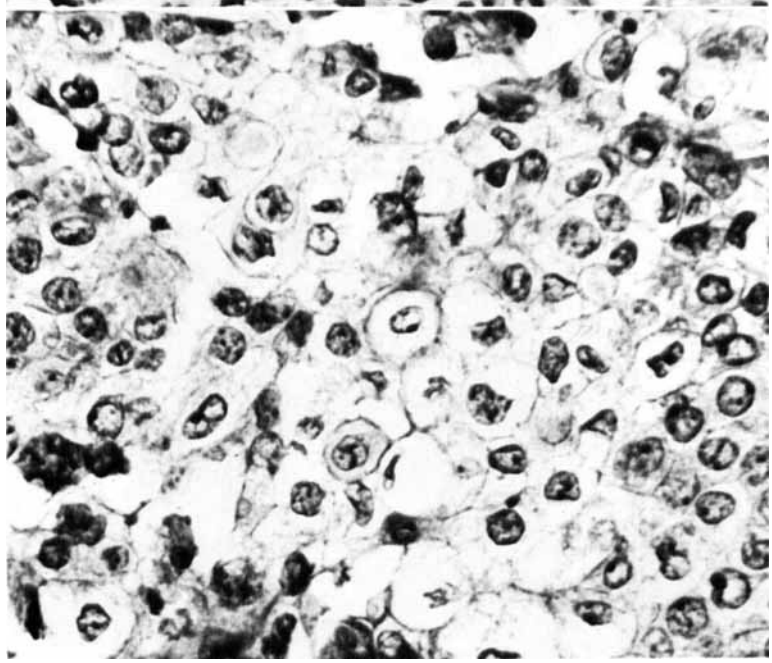

FIG. 6. Large cell carcinoma with copious, rather pale cytoplasm (H and E, ×450).

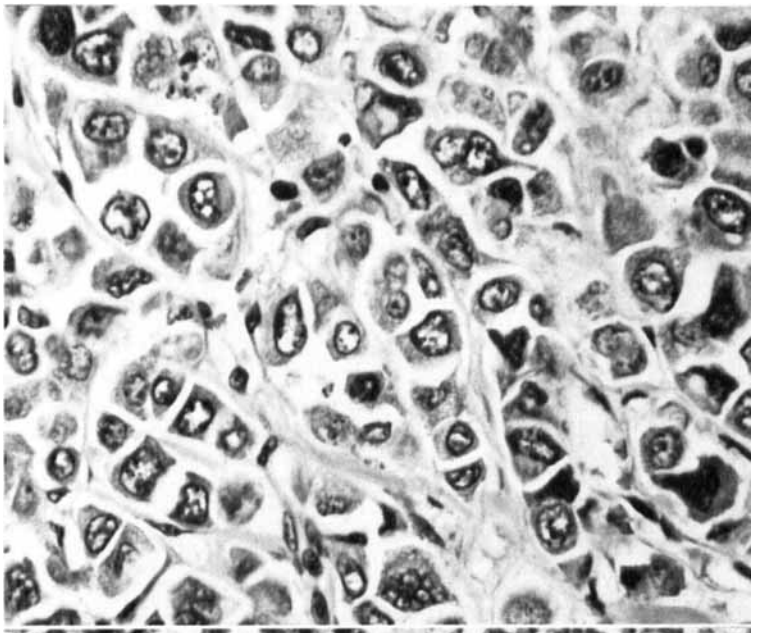

FIG. 7. Large cell carcinoma of polygonal cell type (H and E, ×450).

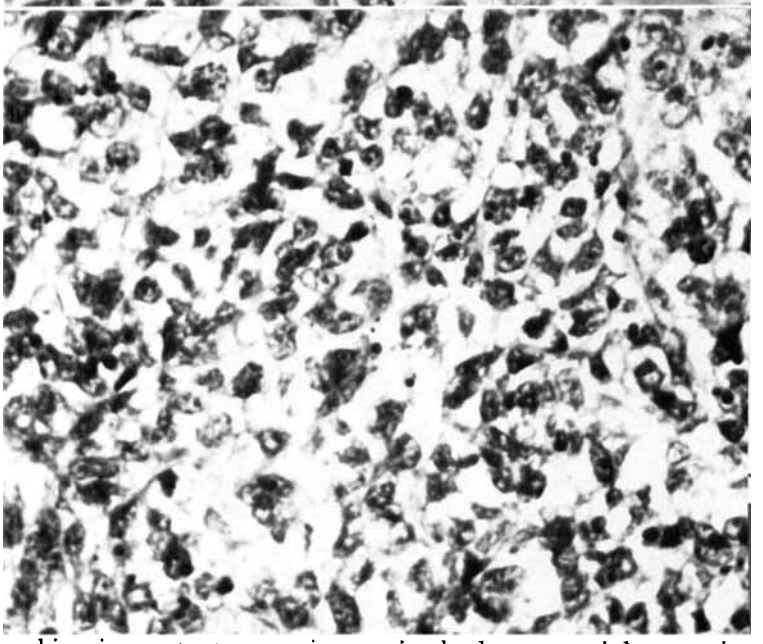

FIG. 8. Large cell carcinoma with vacuolated cytoplasm. Cells are somewhat smaller than in other large cell types illustrated (H and E, ×450).

smoking is a potent co-carcinogen in the lung cancer of uranium miners.[13]

An experimental demonstration of similar character is that of Smith et al.[17] who have proven that chrysotile asbestos injected intratracheally in hamsters will not produce lung tumors but when it is administered with the powerful carcinogen benzo(a)pyrene will produce more and larger tumors than does benzo(a)pyrene alone.

Kuschner,[9] in a discussion of the genesis of lung cancer, dwells on the thesis of multifactorial causation. He suggests that cigarette smoke, a combination of specific carcinogenic substances and of irritant chemicals, sufficient in itself to produce cancer can potentiate or be potentiated by other environmental agents.

We suggest that this concept may be applied to our human morphological data. The resemblance in the two series examined may be viewed not merely as a consequence of a limited versatility of tissue response, but rather as an indication of a basically identical causal complex, in which cigarette smoking is

by far the most potent factor, or combination of factors. Asbestos can then be regarded as an instrumentality by which the tobacco effect is enhanced. The synergistic mechanism has not been elucidated by our study. We are not able to accept fibrogenesis as an intermediate essential causal phase, partly because we do not see any evidence of a quantitative relationship between severity of asbestosis and lung cancer, and partly because of the absence of an increased incidence of pulmonary carcinoma in other fibrosing pneumoconioses.

Hypotheses of carcinogenesis relating to asbestos as a transport vehicle because of its high surface adsorptive properties, as a cause of injury resulting from fiber shape or chemical constitution far exceed the intended scope or attainment of this report. We may go as far as to suggest that the two differences indicated—lower lobe localization and increased pleural involvement by tumor—may result from structural alterations in the lungs preceding neoplasia. To go beyond this would be compounding speculation.

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