Acta Medica et Biologica
Vol. 39, No. 1, 11-20, 1991

Histopathological Changes in the Lung with Low-Dose Asbestos Exposure

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Received December 14, 1990

Summary. **This study aims to evaluate the morphological changes in asbestos-exposed lung and to correlate the changes with the counts of asbestos bodies in the lung as observed under the microscope. Forty cases were selected and subdivided into 4 groups by asbestos body counts as follows: Group 1 (10 cases) showed 100-1,000 asbestos bodies per gram of wet tissue in the lung treated with 40% KOH method; Group 2 (11 cases) showed 40-99 asbestos bodies; Group 3 (13 cases) showed 10-39 asbestos bodies; and Group 4 (6 cases) showed no asbestos bodies. The airway was divided, on the basis of their structural features, into 3 regions, i.e., small bronchi, bronchioles and alveolar ducts and the lesions occurring in those regions were graded into 4 ranks according to the severity of the fibrosis. The author found that the severity of the fibrosis paralleled the asbestos body counts (74.1% of the examined portions of the airway were associated with fibrosis in Group 1, 49.2% in Group 2, 41.9% in Group 3 and 14.8% in Group 4), and this also applied to every region of the airways. The small airways (bronchioles and alveolar ducts) tended to show more severe fibrosis as compared with larger ones, and in parallel with asbestos body counts moderate and severe fibrotic changes seemed to be accelerated more conspicuously in those small airways. The relationship between asbestos body counts and anthracosis was also examined. The small airways showed more severe anthracosis, which increased with the asbestos body counts. Subjects engaged in blue-collar jobs were frequently involved in Group 1. Occupations varied in Group 2 and 3. Fibrosis tended to be more severe in the cases of blue-collar jobs.**

INTRODUCTION

It has been established that asbestos exposure exerts an injurious influence on human health, leading to various kinds of diseases. Asbestosis,[1] malignant mesothelioma[2] and pulmonary carcinoma[3] are well known as asbestos related diseases. Not only such respiratory diseases, but also malignancy in the digestive tract[4,5] and in the hematopoietic system including multiple myeloma, macroglobulinemia, chronic lymphocytic leukemia[7] and several autoimmune diseases[8] have been reported in the context of asbestos exposure. Some authors have demonstrated that asbestos bodies exist in extrapulmonary organs,[9,10] and others have reported that fibrosis occurred in various organs.[11] Recently, the harmful effects of asbestos exposure are becoming a serious social problem, and appropriate countermeasures should be considered immediately.

On the other hand, the pathological diagnosis for asbestosis has generally been made on the basis of the presence of asbestos bodies in the pulmonary tissue. Furthermore, interstitial pneumonia and honeycomb lung are characteristic of asbestosis.[12,13] Histopathological studies in patients with asbestosis have indicated that the severity of interstitial fibrosis correlates with asbestos body counts.[14,15] However, these papers have dealt with cases in which the asbestos body counts were as high as 1,000-10,000 per gram of wet pulmonary tissue. In this study, the relationship between asbestos body counts and the severity of fibrosis will be discussed in cases in which asbestos body counts are less than 1,000.

MATERIALS AND METHODS

A quantitative study of asbestos bodies in the lung from 1,674 autopsied cases performed during the past 30 years at Niigata University has been reported elsewhere by Zhang.[16] The present author selected 40 cases from his study, and divided them into 4 groups with regard to their asbestos body counts. Namely,

the lungs showing 100-1,000 asbestos bodies per gram of wet tissue were put into Group 1, those with 40-99 asbestos bodies per gram of wet tissue into Group 2, those with 10-39 asbestos bodies per gram of wet tissue into Group 3, and those with no asbestos bodies into Group 4. With regard to the evaluation, cases with certain lesions were excluded, including carcinoma, tuberculosis and acute interstitial pneumonia caused or related to other disorders. The tissue sections were obtained from every lobe of both lungs.

The airway was divided into 3 regions depending on structural features. The author defined those portions with a number of goblet cells among the columnal epitheliums, bronchial glands, muscles and cartilages as small bronchi. Those portions which lacked cartilage and contained few or no goblet cells among the cuboidal epitheliums were defined as bronchioles. Alveolar ducts were identified only if they could be confirmed to connect to respiratory bronchioles.

The lesions in the airway were graded into 4 ranks with regard to the severity of fibrosis, according to the classification of Report of the Pneumoconiosis Committee, as follows. Grade 0: No fibrosis is associated with the airway walls (Fig. 1). Grade 1: Fibrosis involves the airway walls with or without extension into the septa of the immediately adjacent layer of alveoli (Fig. 2). Grade 2: Fibrosis in the airway walls as in Grade 1 further involves alveolar ducts or two or more distant layers of alveol, though there still remains a zone of nonfibrotic alveolar septa between adjacent bronchioles (Fig. 3). Grade 3: Fibrosis appears as in Grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, forming fibrotic septa; some alveoli may be obliterated completely. Regarding the severity of anthracosis, the changes were also graded into 3 levels: mild, moderate and severe.

Paraffin sections were produced from formalin fixed lungs. Hematoxylin-eosin stain, periodic acid Schiff reaction, silver impregnation, elastica van Gieson stain, Azan stain, iron stain and trichrome stain were used in order to evaluate the sections of each case.

RESULTS

Details of the 40 cases are listed in Table 1. Group 1 comprised 10 cases, their ages ranging from 41 to 71

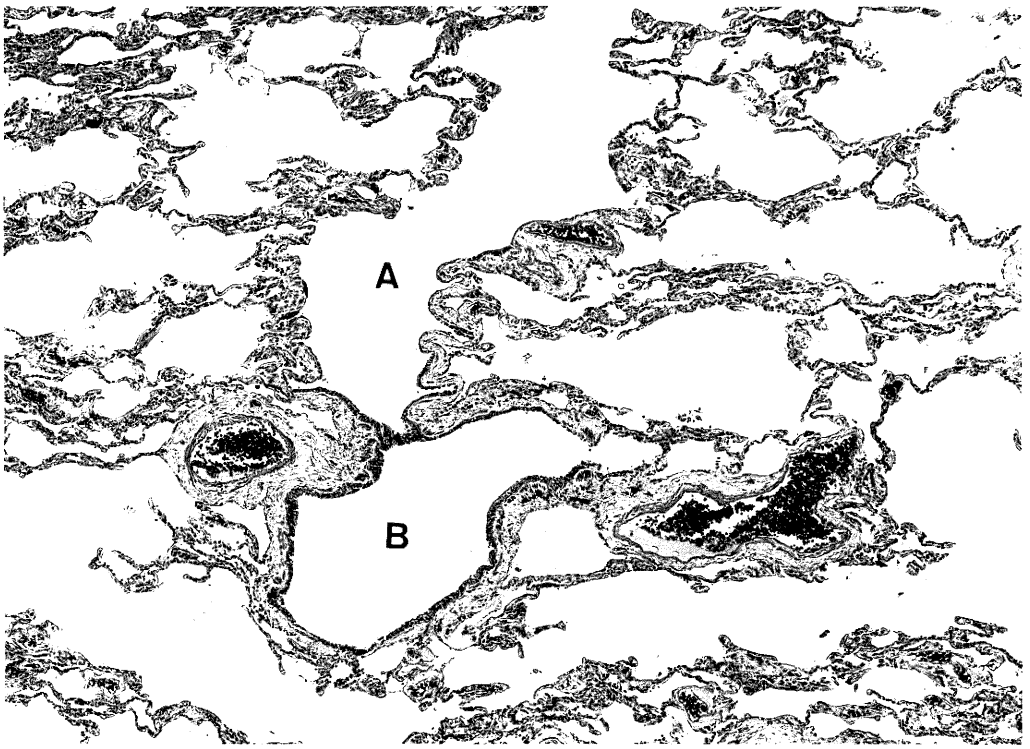

Fig. 1. Micrograph showing a bronchiole (B) and an alveolar duct (A) in the right lung of case No. 36. No fibrosis is associated with the airway walls. (×50, trichrome stain)

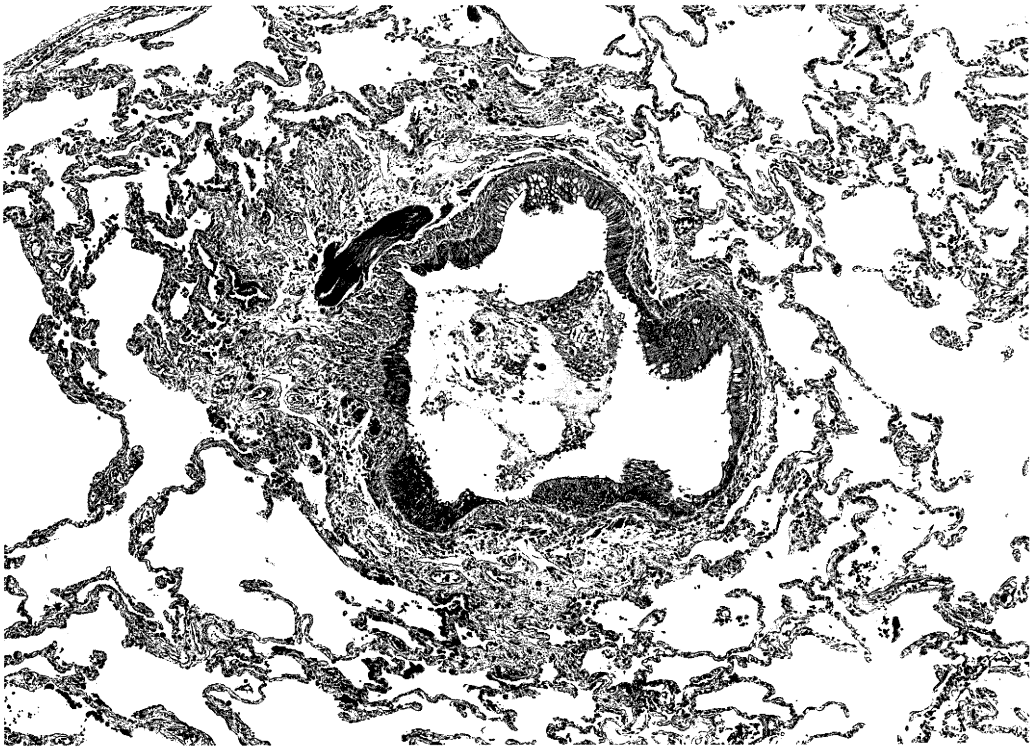

Fig. 2. Micrograph showing a small bronchus in the right lung of case No. 36. The airway wall shows fibrosis of Grade 1. (×50, trichrome stain)

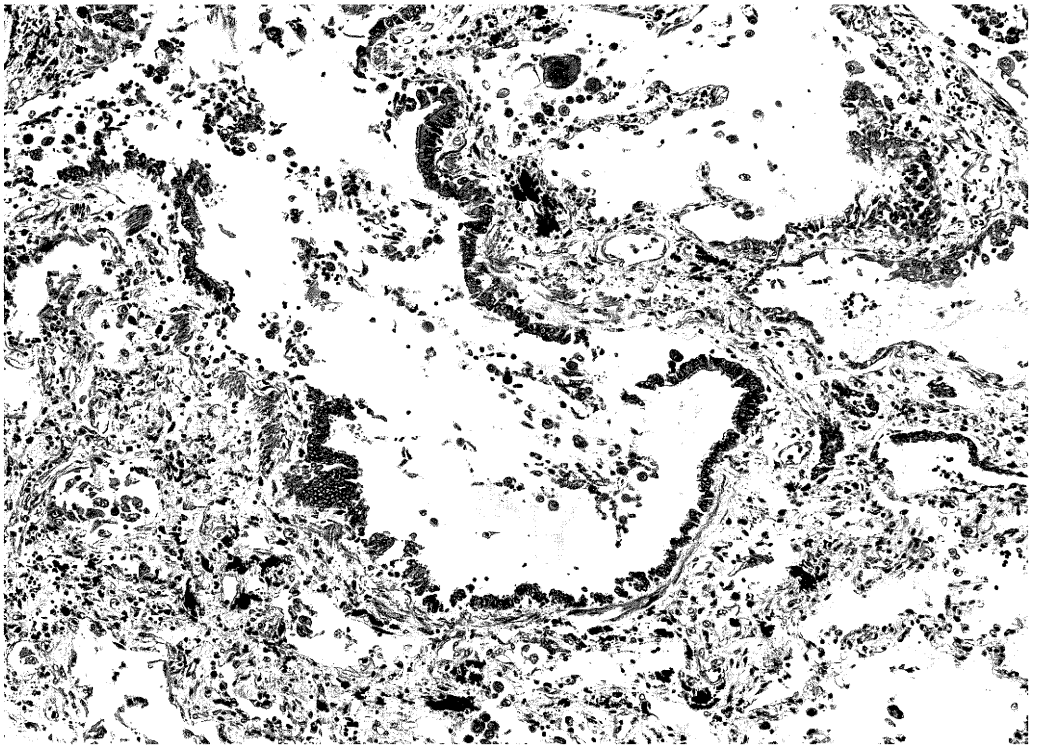

Fig. 3. Micrograph showing a bronchiole in the pulmonary tissue obtained from the autopsied case of a worker in asbestos spraying. Fibrosis involving the airway wall is judged as Grade 2. (×125, trichrome stain)

years (mean 62.4). The asbestos bodies counted up to 986 (mean 438.4). Group 2 had 11 cases, with ages varied from 40 to 79 (mean 59.5) and the average count of asbestos bodies being 58.2. Group 3 possessed 13 cases, the ages ranged from 55 to 83 (mean 67.6) and the asbestos bodies counted 18.3 in average. Group 4 had 6 cases with the ages from 58 to 87 (mean 67.1). All of the cases were male.

In regard to their occupations, Group 1 consisted of a construction worker, a factory worker, a welder, a steel-mill worker, a plumber, a miner and so on. Most of the members were blue-collar workers. Various

Table 1. Summary of examined cases

Group	Case	Age	Occupation	ABs	Primary disease	Smoking
1	1	50	Fisherman	114	Chronic pyelonephritis	−
	2	70	No occupation	698	Pulmonary abscess	−
	3	62	Construction worker	460	Pulmonary Ca (squamous)	+
	4	64	Factory worker	986	Pulmonary Ca (large cell)	+
	5	70	Welder	202	Gastric Ca	+
	6	41	Plumber	890	Gastric Ca	+
	7	67	*	204	Esophageal Ca	+
	8	67	Miner	316	Silicosis	+
	9	71	Steel-mill worker	396	Pulmonary Ca (adeno)	−
	10	65	Farmer	118	Mitral regurgitation	+
2	11	78	*	52	Pulmonary thrombosis	*
	12	47	Carpenter	52	Liver cirrhosis	+
	13	40	*	52	Acute myelocytic leukemia	*
	14	54	Farmer	80	Postoperative endocardistis	+
	15	46	Navvy	74	Diaphragmatic hernia	*
	16	65	Acupuncturist	90	Esophageal Ca	−
	17	79	No occupation	60	Ischemic colitis	*
	18	43	*	50	Behcet's disease	*
	19	65	No occupation	40	Ca of bileduct	+
	20	47	Judicial scrivener	46	Leukemia	*
	21	74	*	44	Rectal Ca	*
3	22	62	Director	12	Esophageal Ca	*
	23	63	Factory worker	38	Pulmonary Ca (small)	+
	24	70	Farmer	28	Pulmonary Ca (small)	*
	25	56	Public officer	14	Esophageal Ca	+
	26	55	*	34	Pelvic bone fructure	+
	27	55	No occupation	16	Acute myelocytic leukemia	+
	28	76	Artisan	18	Ca of gall bladder	+
	29	68	Office worker	10	Pulmonary Ca (squamous)	+
	30	59	Office worker	14	Gastric Ca	+
	31	65	Clerk	16	Renal cell Ca	+
	32	83	No occupation	10	Pulmonary Ca (adeno)	+
	33	70	*	18	Miliary tuberculosis	+
	34	83	No occupation	10	Gastric Ca	*
4	35	59	Carpenter	0	Urinary bladder Ca+Colon Ca	−
	36	70	No occupation	0	Pertonitis	+
	37	87	No occupation	0	Colon Ca	−
	38	70	No occupation	0	Gastric Ca	+
	39	66	Hardware shop dealer	0	Acute myocardial infarction	*
	40	58	Teacher	0	Pulmonary Ca (large cell)	+

Ca: carcinoma * : unknown

kinds of occupations were found in Group 2 such as a carpenter, a farmer, a navvy, a judicial scrivener, an acupuncturist and so on. Many white-collar jobs were observed in Groups 3 and 4 including a member of a directorate, a public officer, a clerk, a teacher and a hardware dealer.

Table 2 shows the number of airway regions of the tissue blocks examined in this study and the incidence of different grades of lesions for each group. As the table indicates, 25.9% of the examined portions of airways in Group 1, 50.8% in Group 2, and 58.1% in Group 3 were judged as Grade 0; this amounted to 85.2% in Group 4. The percentage of Grade 0 tended to decrease with the increase of asbestos body counts.

Fig. 4 schematically shows the incidence of fibrosis in the 3 regions of the airway in each group. In all 4 groups, small bronchi showed a higher percentage of Grade 0 than bronchioles and alveolar ducts. From the results of statistical analysis, differences could be recognized between Group 4 and Group 1, between Group 4 and Group 2, and between Group 4 and Group 3 ($p<0.001$ or 0.05) in the cases of bronchioles and alveolar ducts. On the other hand, in regard to the small bronchi, statistical differences could be recognized between Group 4 and Group 1, and between Group 4 and Group 2 ($p<0.001$), but not between Group 4 and Group 3.

The incidence of significant lesions with fibrosis was next examined, with the results shown in Table 3. In regard to the small bronchi, there were no airway regions to be classified into Grade 2 and Grade 3 (Grade 2+3) in both Group 3 and Group 4. There were also no airway regions to be classified into Grade 2+3 in Group 4 in regard to the alveolar ducts. The incidence of Grade 1 increased gradually from Group 4 towards Group 1 (14.6% in Group 4 and 29.7% in Group 1) in regard to the bronchioles. The same was the case in the alveolar ducts (22.5% to 32.0%). In contrast to Grade 1, the percentage of Grade 2+3 increased rapidly from Group 4 to Group

Table 2. The numbers of airway samples belonging to each group of asbestos body counts and each grade of fibrotic changes

	Small Bronchi	Bronchioles	Alveolar Ducts	Total
Group 1				
Examined number	99	286	125	510
Grade 0	51	60	21	132 (25.9%)
Grade 1	28	85	40	153 (30.0%)
Grade 2	15	92	39	146 (28.6%)
Grade 3	5	49	25	79 (15.5%)
Group 2				
Examined number	223	511	223	957
Grade 0	163	232	91	486 (50.8%)
Grade 1	42	131	89	262 (27.4%)
Grade 2	18	122	37	177 (18.5%)
Grade 3	0	26	6	32 (3.3%)
Group 3				
Examined number	158	404	114	676
Grade 0	144	175	74	393 (58.1%)
Grade 1	14	192	34	240 (35.5%)
Grade 2	0	34	6	40 (5.9%)
Grade 3	0	3	0	3 (0.4%)
Group 4				
Examined number	73	137	40	250
Grade 0	69	113	31	213 (85.2%)
Grade 1	4	20	9	33 (13.2%)
Grade 2	0	4	0	4 (1.6%)
Grade 3	0	0	0	0 (0%)

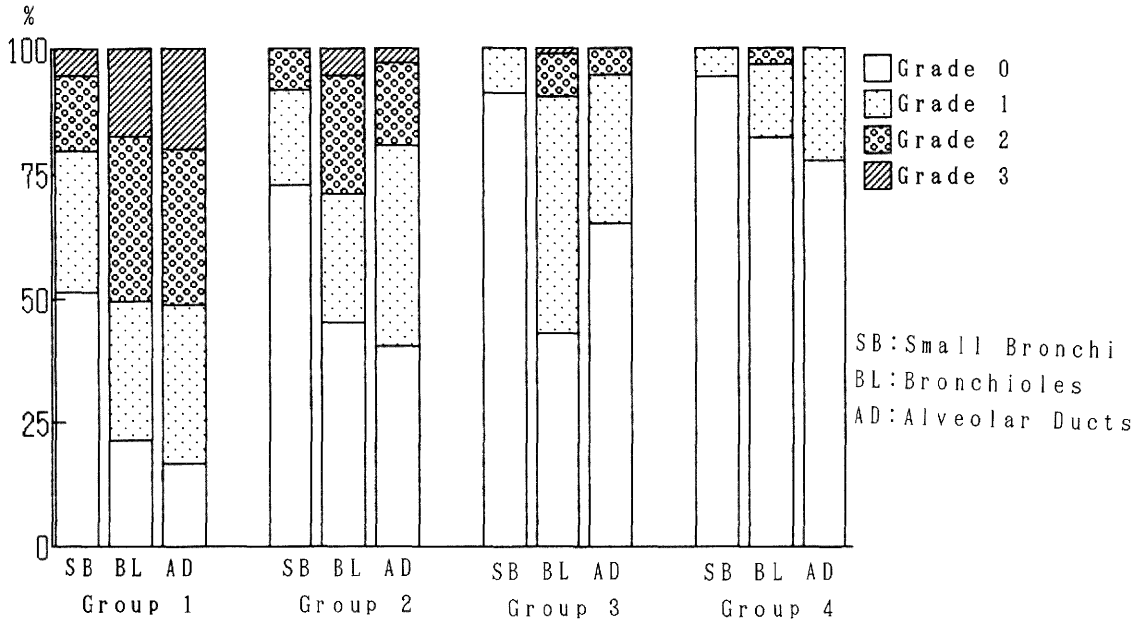

Fig. 4. Severity of fibrosis in different regions of the airway as grouped according to asbestos body counts.

Table 3. Incidence of different grades of fibrotic lesions in different groups of asbestos body counts

Region	Grade	Group			
		1	2	3	4
Small bronchil	1	28.3%	18.8%	8.9%	5.5%
	2+3	20.2%	8.1	0	0
Bronchioles	1	29.7%	25.6%	47.5%	14.6%
	2+3	49.3%	29.9%	9.2%	2.9%
Alveolar Ducts	1	32.0%	39.9%	29.8%	22.5%
	2+3	51.2%	19.3%	5.3%	0

1. In regard to the bronchioles, only 2.9% of the airway regions showed Grade 2+3 in Group 4, while this amounted to 49.3% in Group 1. Furthermore, it amounted to 51.2% in Group 1 in regard to the alveolar ducts.

Fig. 5 shows the results of investigation of the severity of anthracosis in each Group. In all 4 groups, the small bronchi showed a lesser percentage than the bronchioles and alveolar ducts as concerns moderate and severe anthracosis. Almost all airway regions in Group 4 were judged to show mild anthracosis. Moderate and severe lesions increased along with the asbestos body counts in every region of the airway. By statistic analysis, in regard to small bronchi, significant differences were demonstrated between Group 4 and Group 2, and between Group 4 and Group 1 ($p<0.01$) but not between Group 4 and Group 3. On the other hand, the difference in severity of anthracosis was significant also between Group 4 and Group 3 in the bronchioles and alveolar ducts ($p<0.001$ or 0.05).

Percentages of Grade 0 and Grade 2+3 were checked and plotted in each case. Fig. 6 shows the results of all cases in the present study. Cases of the slightest fibrosis were chosen from Group 1; they were cases No. 1, No. 6, and No. 10 which represented a higher percentage of Grade 0 and lesser percentage of Grade 2+3 in comparison with other cases. The occupations of cases No. 1 and No. 10 were a fisherman and a farmer, and were the cases with a lower asbestos body count in Group 1. In contrast, the occupation of No. 6 was a plumber, and the asbestos body count was 890, a large amount even for Group 1. As far as the cases which had more than 200 asbestos bodies were concerned, less than 20% of the portions of the airways were judged as Grade 0 except No. 6. The severity of fibrosis varied in Group 2 and 3. Occupations of the subjects were as previously described and among them, a judicial scrivener, a director, a clerk, and office workers tended to show low percentages of Grade 2+3. In contrast, a carpenter, a navvy, and a factory worker tended to show more severe fibrotic changes. In Group 4, all cases had a very low percentage of Grade 2+3, and the percent-

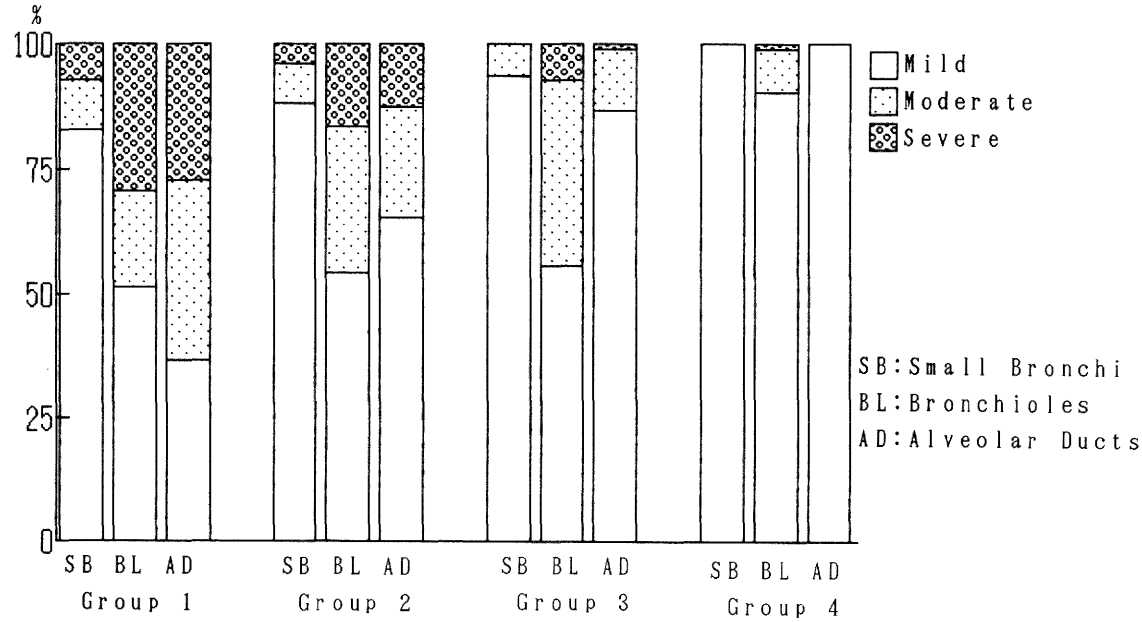

Fig. 5. Severity of anthracosis in different regions of the airway as grouped according to asbestos body counts.

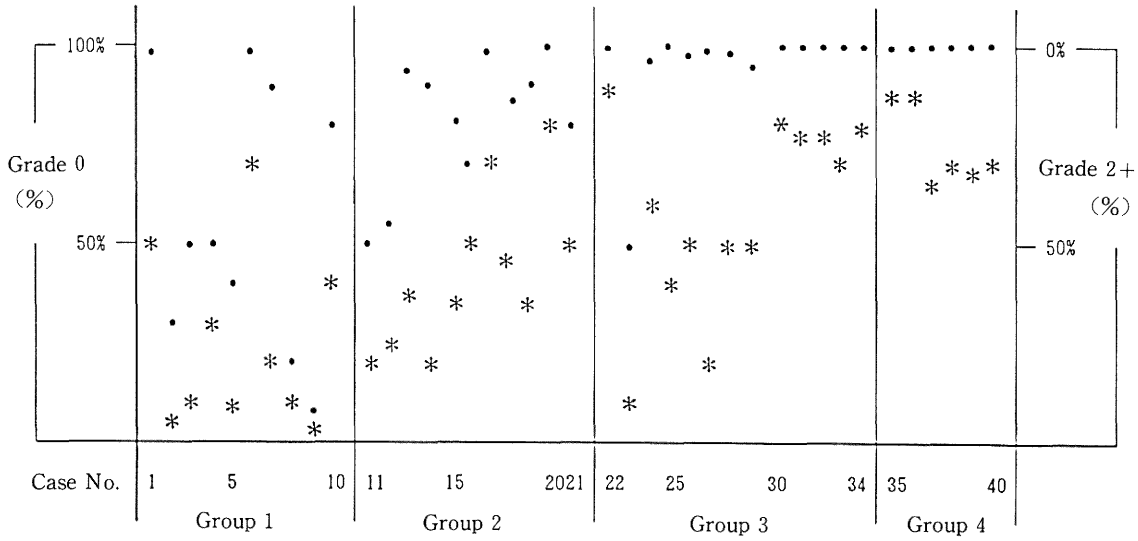

Fig. 6. Severity of fibrosis in examined cases as grouped according to asbestos body counts. The asterisks (*) indicate incidences of Grade 0 and the dots (•), those of Grade 2+3.

age of Grade 0 was very high in comparison with other groups.

DISCUSSION

Using microscopy for tissue sections, asbestos bodies could be observed only in the cases in which asbestos body counts in their lungs were rather high. Out of all cases in this study, asbestos bodies were relatively easy to be observed in cases No. 4 and 6. In these cases—especially in case No. 4—the airway wall showed marked fibrosis often accompanied by anthracosis. Asbestos bodies could be observed in the thickened airway wall (Fig. 7). These findings, on the other hand, indicate that the presence of asbestos bodies is diagnostically helpful only when the subject was exposed to a large amount of asbestos. It can also be said that an asbestos-exposed lung is difficult to be diagnosed as such only by the demonstration of

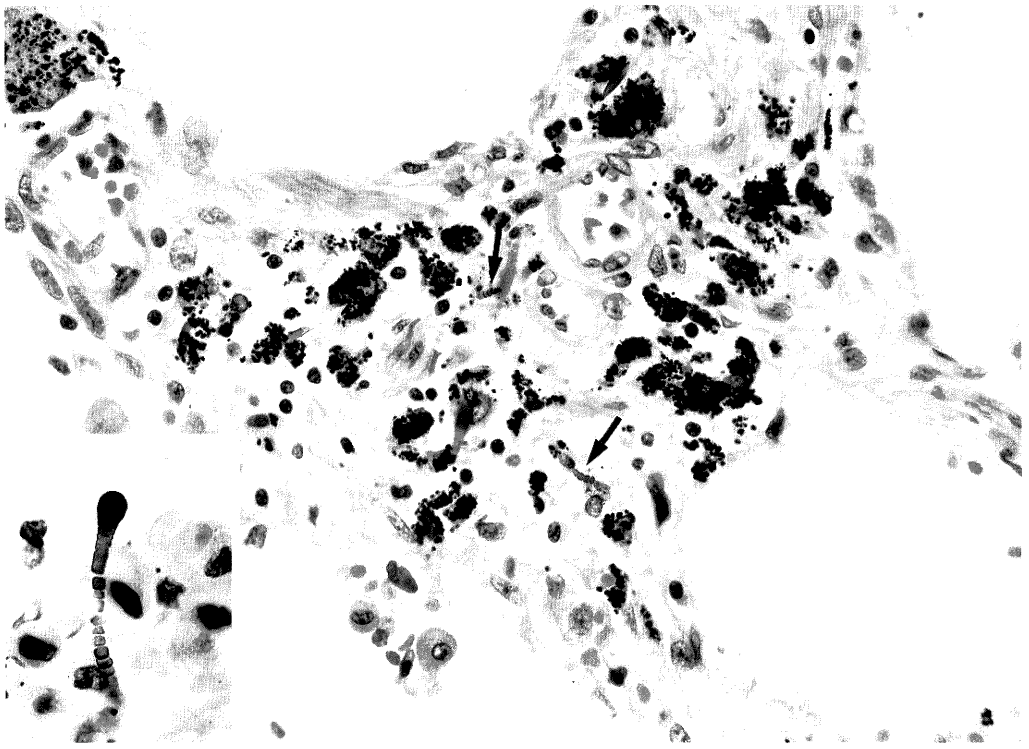

Fig. 7. Closer view of a region from the pulmonary tissue identical with that shown in Fig. 3. Asbestos bodies are present in the fibrous thickening airway wall (arrows). (×500 H.E.). Inset shows an asbestos body with a typical banded structure.

asbestos bodies. The reason for this is that there have previously been many cases which were proved asbestos exposed lungs by quantitative analysis of the tissue, and yet could not be demonstrated as such in histological sections. Therefore, the present author tried to examine those lungs to determine whether some correlations might be found between asbestos body counts and histopathological changes, especially fibrosis.

The results are summarized as follows: fibrosis gradually developed in parallel to asbestos body counts in the lung. This rule could be applied to each region of the airway. Bronchioles and alveolar ducts showed more severe fibrosis than small bronchi, and if the asbestos body counts increased, fibrosis was accelerated-especially in bronchioles and alveolar ducts. Fibrosis in Grade 2+3 developed with the increment of asbestos body counts, especially in bronchioles and alveolar ducts. These findings indicate that the severity of fibrosis correlates with asbestos body counts, and that fibrosis, especially moderate and severe changes, tends to develop from the small airway as bronchioles and alveolar ducts. An exceptional case was No. 6 in which the asbestos bodies were of a large amount, whereas, fibrosis was relatively slight among the cases in this study. This discrepancy seems to be accounted for by that the subject had been exposed to asbestos but likely died of gastric cancer before pulmonary fibrosis developed. This case was the youngest (41 yr.) among the subjects studied and showed very few pathological changes in both lungs, except for gastric cancer metastasis.

The relationship between asbestos body counts and the severity of anthracosis in every group was also examined. Anthracosis gradually grew in parallel to the asbestos body counts and small airway showed more severe anthracosis.

Recently, social consciousness toward environmental sanitation has increased, and the use of asbestos has come to be regulated strictly. Health management and countermeasures have been considered, especially in occupational exposure to asbestos. Working conditions have been improved by social control and management, and workers in high risk occupations are expected to live a longer life than

before.

From the 1960's until very recent years, asbestos consumption had continued to grow. Japan was the leading country in the world in asbestos consumption even after the world's attentions had been directed to the danger of asbestos. It took many years until the outcome of the consumption is manifests itself in the occurrence of asbestos associated diseases, as almost all subjects affected by asbestos will remain clinically silent for a certain latent period. The influences of asbestos on the human body will be apparent in the near future, a fact which could not be observed before because of shorter life spans of the workers. Occasions to encounter such cases will undoubtedly increase. Several surveys have been made about the latent period, i.e., from the beginning of asbestos exposure to the onset of asbestos related disease. Some researchers have reported that this is more than ten years or even 20-40 years.[17] When an asbestos associated disease is suspected from clinical symptoms or laboratory data, the subjects have often retired from the occupations or changed their employment. Therefore, it is important to review detailed information of any of their occupations even if they currently seem unrelated to asbestos exposure. The present cases actually included several subjects who were not associated with asbestos manufacture directly but had conceivably been exposed to asbestos in their places of work. Some other cases showed almost the same asbestos body counts as the cases of blue-collar jobs although the occupations seemed unrelated to asbestos exposure. In these cases, at least two possibilities are suspected. One is that the subjects had previously been employed in other occupations associated with asbestos exposure, even for a short period. Another possibility is exposure due to the environment, for example, from car brakes on heavily traveled roads or falling from buildings. This means that the possibility of asbestos exposure exists anywhere, and can not be anticipated. Especially in the latter case, no one can avoid passive asbestos exposure. On the other hand, some papers reported that a case was suspected as occupational exposure when asbestos body counts in the lung were more than 100[18] or more than 40.[19]

Pleural plaques have been considered one of the morphological hallmarks of asbestos exposure, and lesions occur in low concentration exposure. Forty cases in this study were reexamined for the presence of this lesion by protocol, but in no cases was a description of such a pathological state available. Two reasons may be considered concerning this negative result. One is that some subjects might have died before the plaques became evident, because the interval between the time of initial exposure and the development of plaques is believed to be more than 10 years. The other possibility is that little attention was directed to such a pathological change if it was not pronounced. Pleural plaques are not especially noteworthy for pathologists except those who at autopsy, have already been aware of the change being associated with asbestos exposure.

Correlation between the severity of fibrosis and the asbestos body counts in the lung was evaluated in this study. However, it is difficult to regard the histopathological change as specific for the asbestos-exposed lung. It is also difficult to regard asbestos exposure as the sole factor causing pulmonary fibrosis, because if the working environment has a high potential for asbestos exposure, it is often reasonable to suspect that other factors causing fibrosis might exist there. Actually, it is now well recognized that some kinds of mineral matters induce pulmonary fibrosis. Although there might be some other causable factors, it can be concluded that significant fibrosis is proved in the asbestos-exposed lung even if asbestos bodies are not numerous enough to be demonstrated using microscopy in tissue sections. If the histopathological change can be diagnosed in the patient's lung, or if it is suspected by clinical status or laboratory data, it is necessary to consider the possibility of low concentration asbestos exposure. Therefore, detailed history taking, especially with regard to occupations and working environments of the patient, and thorough following up by periodic examinations including auscultation, respiratory function test, and chest X-ray, will be useful for the diagnosis of asbestosis and the decision of appropriate countermeasures.

Acknowledgments. The author thanks Professor Yoshihisa Ohnishi for his critical reading of the manuscript and helpful comments, and Dr. Hisashi Watanabe for his advice. The author also wish to thank Mr. Tomiyoshi Hasagawa and Mr. Susumu Momozaki at the 2nd. Department of Pathology, Niigata University medical School, for their excellent technical assistance.

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