KAWASAKI MED. J. VOL. 14 : NO. 4, 159-169 (1988)

Intraluminal (Intra-alveolar) Diffuse Fibrosis of the Lung

Toshiaki MANABE, Takuya MORIYA and Keiko SUGIHARA

Department of Human Pathology II
Kawasaki Medical School, Kurashiki 701-01, Japan

Accepted for publication on February 1, 1989

ABSTRACT. The present communication describes the morphology, etiology and mechanisms of intraluminal (or intra-alveolar) diffuse fibrosis of the lungs. Pulmonary fibrosis is the end-stage of tissue injury in the lungs and is usually non-specific. The determination of its original cause is difficult, but intraluminal diffuse fibrosis with loose stroma is quite unique and characteristic. In addition to paraquat lungs, we herein show that radiation pneumonitis, infarction, and some forms of bronchiolitis obliterans may cause this type of fibrosis. It is speculated that intraluminal diffuse fibrosis is the result of severe alveolar epithelial damage occurring diffusely and continuously, followed by edema and organization of the alveoli.

Key words : pulmonary fibrosis — intra-alveolar fibrosis — paraquat lungs

Pulmonary fibrosis is the end-stage of tissue injury in the lungs. It is usually non-specific and determination of its original cause may be difficult. Whatever its cause, pulmonary fibrosis may be classified roughly into two types morphologically; interstitial and intra-alveolar (or intraluminal) fibrosis. Basset *et al.*[1] further divided intra-alveolar fibrosis into three morphological patterns; 1) intraluminal buds, which are connected to the alveolar walls by a narrow stalk and partially fill the air spaces, 2) obliterative changes, in which the alveolar spaces are completely obstructed by loose connective tissue, and 3) mural incorporation. Similarly, we[2,3] have divided it into four types; 1) intraluminal polypoid fibrosis (Masson bodies), 2) intraluminal diffuse fibrosis of complete type, 3) intraluminal diffuse fibrosis of incomplete type, and 4) hyaline membrane incorporation. The "intraluminal buds" of Basset *et al.* correspond to our intraluminal polypoid fibrosis and then "obliterative changes" to our intraluminal diffuse fibrosis of complete type. It should be noted that their "mural incorporation" represents an early stage or a mild form of intraluminal diffuse fibrosis. Therefore, we designated it as intraluminal diffuse fibrosis of incomplete type.[2] We favor the term intraluminal over intra-alveolar, since the fibrosing process may take place not only in the alveolar spaces but also in the alveolar duct spaces. In order to avoid any confusion in our discussion, however, the terms "intraluminal" and "intra-alveolar" will be used interchangeably. Hyaline membrane incorporation results from organization of the hyaline membrane. The structural changes of each fibrosing process defined by us are depicted in Fig. 1.

Identification of such morphological patterns in any pulmonary fibrosis may

真鍋俊明，森谷卓也，杉原佳子

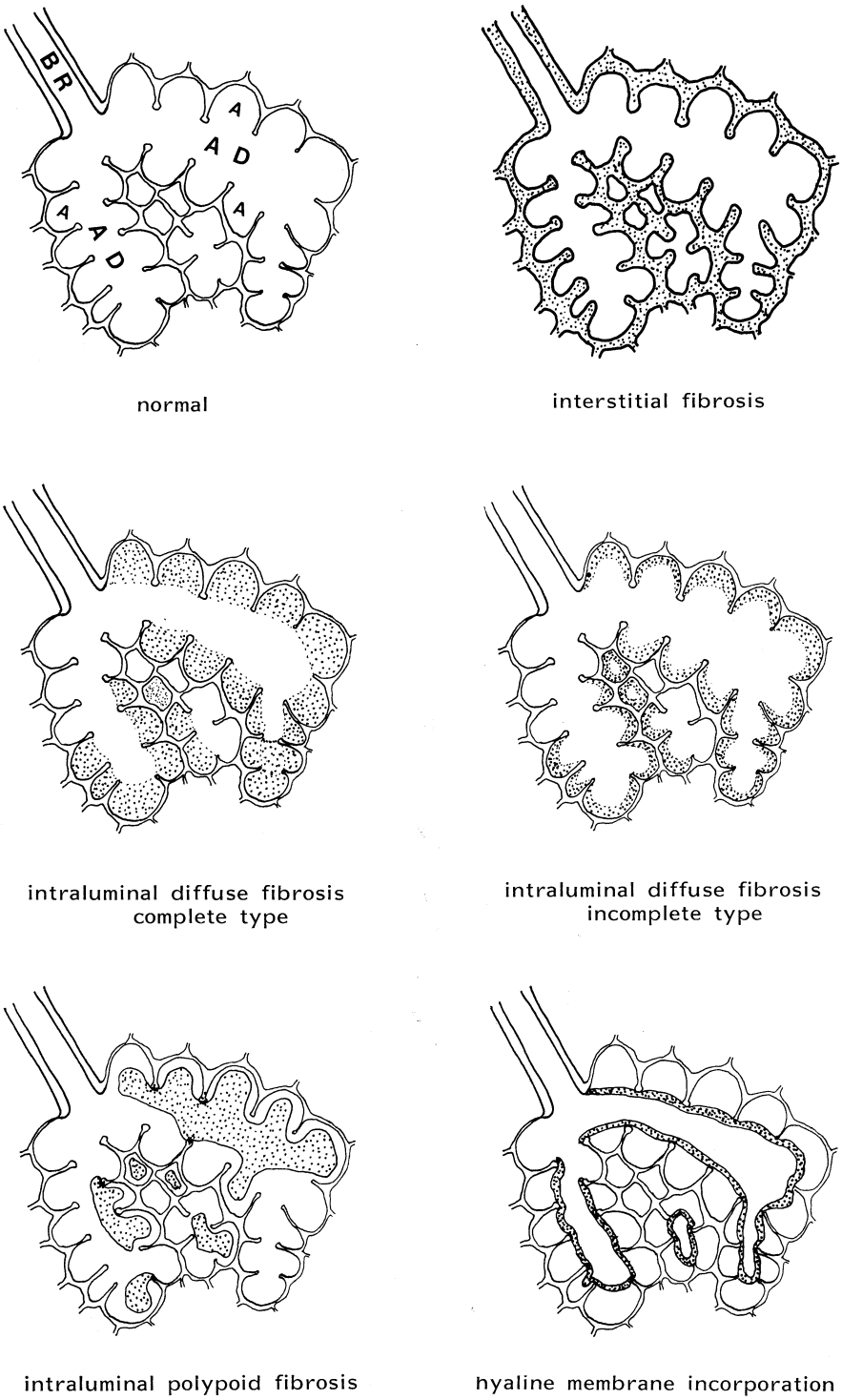


Fig. 1. Classification of pulmonary fibrosis.
BR: bronchiole, AD: alveolar duct, A: alveolus

be facilitated by the use of special staining techniques, such as elastica van Gieson and periodic acid-methenamine silver (PAM) stain, and these techniques are also helpful in speculating on the pathogenesis and/or etiology of these conditions. During the past few years, we have used this approach to examine fibrotic lesions of the lungs. In contrast to other patterns of fibrosis, that of intraluminal diffuse fibrosis with loose stroma is quite unique and most characteristically seen in paraquat lungs.

Herein, we wish to summarize our general ideas regarding (1) what intraluminal diffuse fibrosis looks like in paraquat lungs, (2) what other diseases this type of fibrosis may appear in, (3) what the difference is between intraluminal diffuse fibrosis and extensive intraluminal polypoid fibrosis and (4) what the possible mechanism of this fibrosing process is.

INTRALUMINAL DIFFUSE FIBROSIS IN PARAQUAT LUNGS

Intraluminal diffuse fibrosis, whether of complete or incomplete type, is commonly and characteristically seen in paraquat lungs.[4] In this type of fibrosis, the process begins with edema, which is soon replaced by myxoid tissue with a few cellular and vascular components in the alveolar spaces. Then, with time, the intra-alveolar material becomes more eosinophilic and appears as fibrous tissue often containing very few cells (Fig. 2).[2,5,6] The underlying alveolar wall architecture may be remarkably well preserved, even when extensive intra-alveolar fibrosis is present (Fig. 3). In paraquat lungs, however, this is not the only type of fibrosis. Other types of fibrosis including interstitial fibrosis as well as features of diffuse alveolar damage existing with or without intraluminal diffuse fibrosis have been observed.

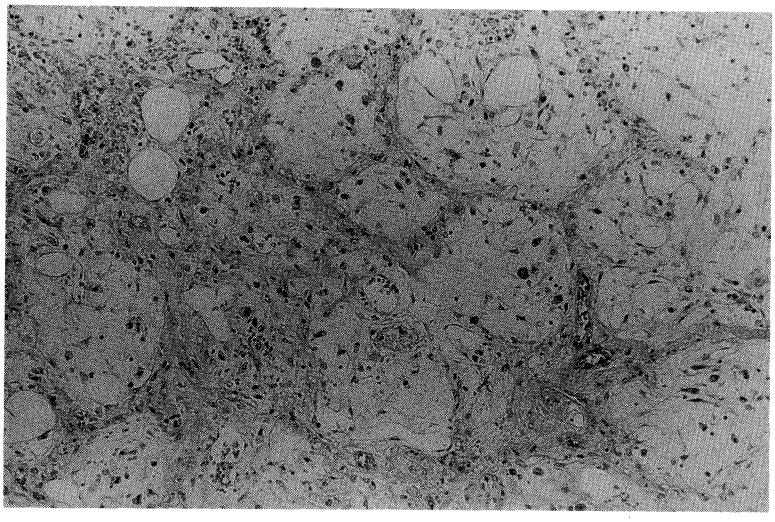


Fig. 2. Intraluminal diffuse fibrosis in paraquat lung.
(H-E, ×200)

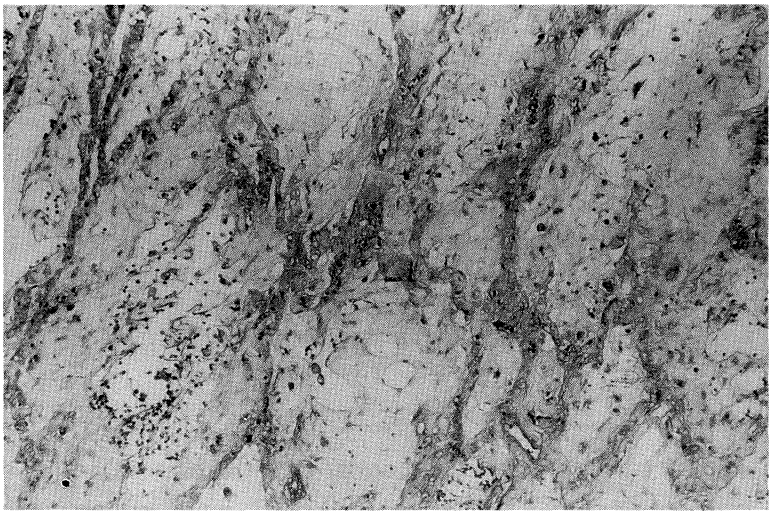


Fig. 3. Intraluminal diffuse fibrosis in paraquat lung. Note that the original framework of the alveolar walls is well preserved. (Pap's reticulin stain, ×360)

INTRALUMINAL DIFFUSE FIBROSIS IN LUNG DISEASES OTHER THAN PARAQUAT LUNG

Is intraluminal diffuse fibrosis really specific to paraquat poisoning? Do other lung injuries show exactly the same or quite similar morphological changes? To answer these questions, lung tissues from 941 autopsies, performed in the Department of Pathology of the Kawasaki Medical School Hospital between the beginning of 1983 and the end of 1987, were histologically examined. Excluding cases of paraquat intoxication, we encountered several cases with a

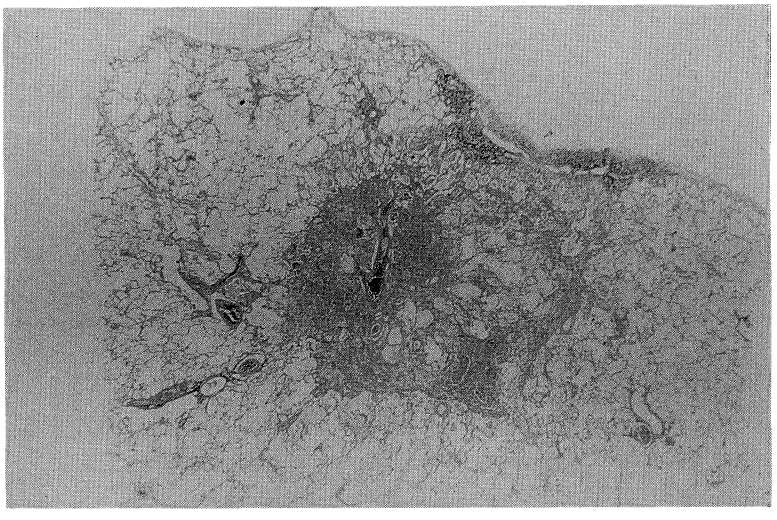


Fig. 4. A section of anemic infarction of the lung under scanning magnification. (H-E, ×4)

similar fibrotic pattern. The majority of these cases were already in the late stage with dense fibrosis and were usually located in subpleural areas. In a few cases, lesions composed of alveoli filled with loose and myxoid stroma were present within the lung parenchyma. Specific causes, including pulmonary infarction, radiation pneumonia, and a type of bronchiolitis obliterans, could be identified in some of these cases. A similar fibrotic pattern was seen in a patient who died with bronchopneumonia and the nephrotic syndrome, but no apparent cause was found.

Fig. 4 shows an area of anemic infarction under scanning magnification. The alveolar spaces are filled with loose avascular connective tissue (Fig. 5a), but the alveolar framework is well preserved (Fig. 5b). Intra-alveolar fibrosis becomes dense in older infarct lesions (Fig. 6). Such is the case in the end-

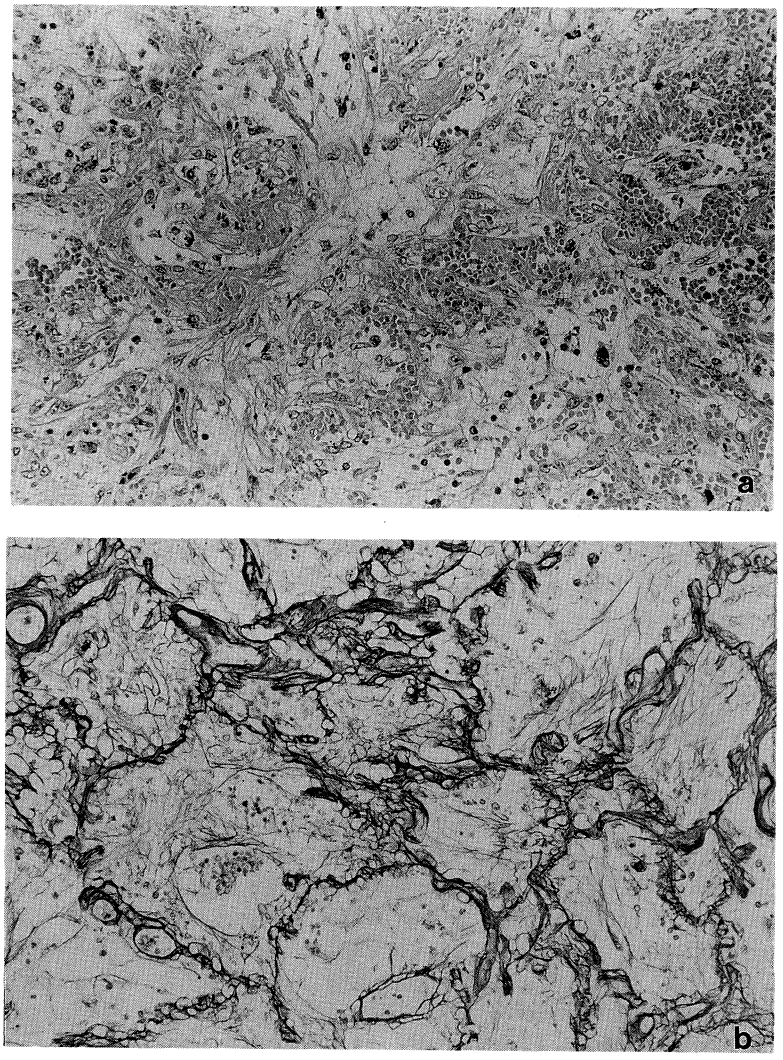


Fig. 5. Intraluminal diffuse fibrosis in pulmonary infarction.
(a. H-E, ×400, b. Pap's reticulin stain, ×350)

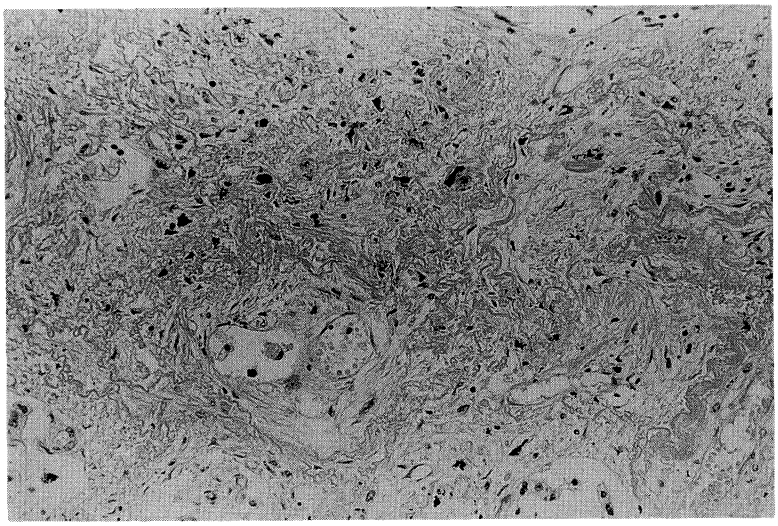


Fig. 6. An older lesion of pulmonary infarction (H-E, ×400)

stage pulmonary infarction seen in Fig. 7a, where collapsed alveolar walls are associated with an increase in elastic fibers (Fig. 7b). In Fig. 8, intra-alveolar diffuse fibrosis with loose stroma can be seen in the region adjacent to an area where radiation was used to treat squamous cell carcinoma of the lung. Since no other causes could be identified clinically and pathologically, we regarded this fibrosis as a feature of radiation pneumonitis. As shown in Fig. 9a and b, similar fibrotic changes were present in bronchiolitis obliterans or bronchiolitis obliterans-organizing pneumonia. However, in addition to the presence of fibrosis in the alveolar spaces, the alveolar ducts and respiratory bronchioles were completely filled with loose connective tissue. Although this type of fibrosis is typically seen in these diseases in pure form, it may often be combined with other types of fibrosis, such as hyaline membrane incorporation and/or intraluminal polypoid fibrosis, and may sometimes be superimposed on these other types or vice versa.

SIMULATORS OF INTRALUMINAL DIFFUSE FIBROSIS

There are some fibrotic lesions which almost completely obliterate the alveolar spaces and mimic the fibrosing pattern of intraluminal diffuse fibrosis. For example, when intraluminal polypoid fibrosis is severe enough to largely obliterate the lumen, it resembles intraluminal diffuse fibrosis. In such situation, however, slender slits are usually discernible between intraluminal fibrotic masses and the original alveolar walls. When these slits are not clearly discernible, immunohistochemical study with anti-epithelial membrane antigen (EMA) antibodies is helpful. These antibodies generally clearly show the alveolar walls to be lined with EMA-positive epithelial cells, thereby making the pattern of polypoid fibrosis evident. Occasionally, such slender slits become filled with loose and/or edematous stroma as stated earlier. These changes seem to suggest that first polypoid fibrosis occurs due to organization of intraluminal exudate

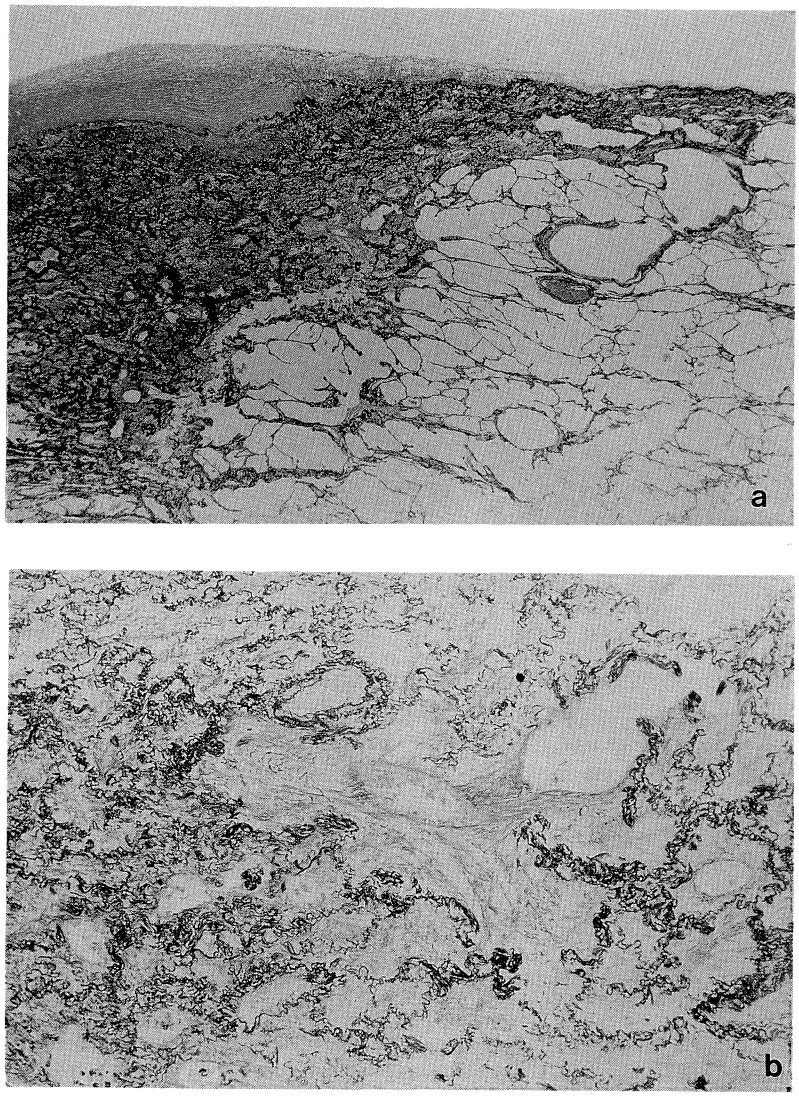


Fig. 7. Healed lesion of pulmonary infarction.
a. A wedge-shaped subpleural fibrosis is characteristic of pulmonary infarction. Intraluminal diffuse fibrosis and elastosis of the alveolar walls are apparent even at this magnification. (elastica van Gieson, ×20)
b. Diffuse fibrosis also occupies the alveolar duct space. Elastosis is prominent. (elastica van Gieson, ×250)

through partially damaged sites of the epithelial lining, especially at the alveolar mouth (alveolar duct wall). Then the remaining alveolar epithelia are severely damaged and diffuse fibrosis ensues in between the polypoid fibrotic areas and the alveolar walls. Under such conditions, intraluminal fibrosis is not morphologically homogeneous. Instead, it is composed of a variety of fibrotic regions in different fibrosing stages in the same alveoli. Basset *et al.*[1] described luminal obliteration in cases of drug-induced pneumonitis; chronic organizing pneumonitis

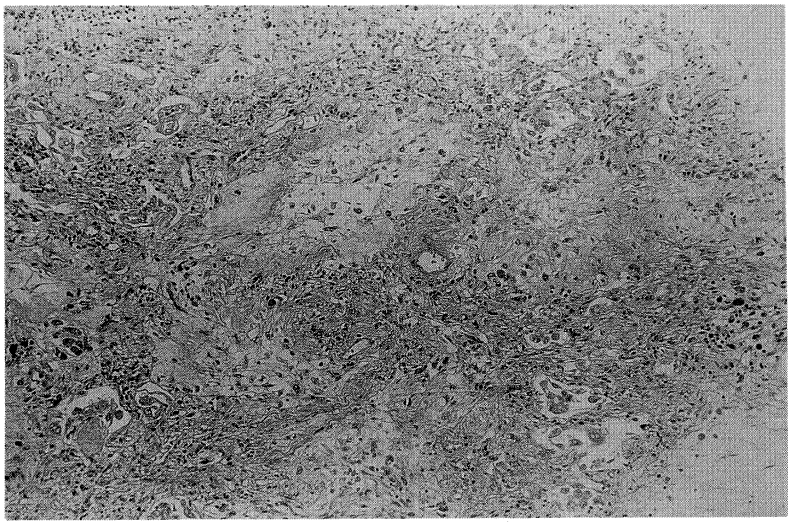
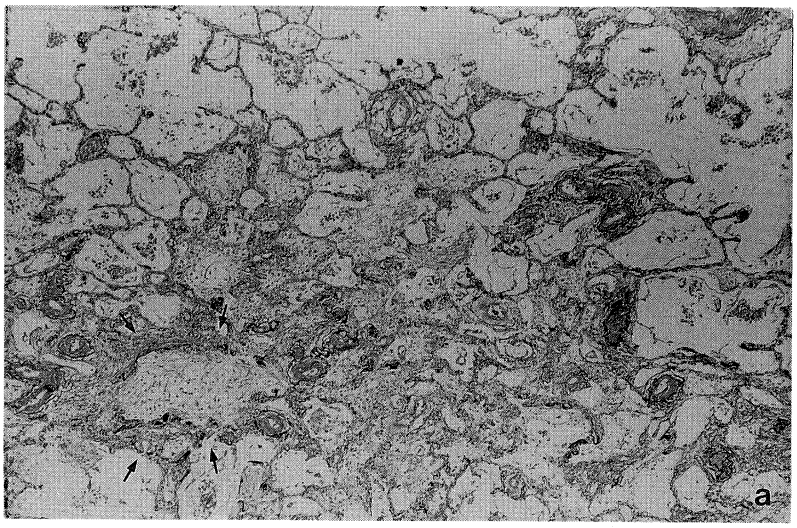


Fig. 8. Intraluminal diffuse fibrosis in radiation pneumonitis. Squamous cell carcinoma is not seen in this photograph. (H-E, ×300)

of unknown cause (which is equivalent to bronchiolitis obliterans and organizing pneumonia), hypersensitivity pneumonitis, chronic eosinophilic pneumonia, collagen-vascular diseases, idiopathic pulmonary fibrosis, sarcoidosis, and histiocytosis X. In our opinion, the luminal obliteration they described in these diseases is slightly different from the intraluminal diffuse fibrosis we have described here. In fact, the obliterative changes seen in Figs. 4-6 of their report seem to represent an extensive polypoid fibrosis.

A POSSIBLE MECHANISM OF THE FIBROSING PROCESS IN INTRALUMINAL DIFFUSE FIBROSIS

With regard to pulmonary fibrosis, Copland *et al.*[4] postulated four mechanisms; 1) organization of intra-alveolar (fibrinous) exudate, 2) fibrosis after primary damage to alveolar epithelium, 3) chronic lymphedema, and 4) fibrosis after presumed primary damage to alveolar capillaries. They considered the intra-alveolar fibrosis seen in paraquat lungs as a tissue reaction pattern reflecting a purely alveolar epithelial injury, and believed that this stage may be transitory and may depend on the severity of the insult. The results of our recent immunohistochemical study of paraquat lung[7] were in good agreement with this view. Therefore, we feel that intraluminal diffuse fibrosis is, in fact, the result of severe alveolar epithelial damage which has occurred diffusely and continuously in certain alveoli and has caused edematous alveolar exudate which is organized in time. The original alveolar framework is preserved. The same mechanism may be operative. Sudden ischemic attack, radiation, and toxic fumes can severely damage the epithelium diffusely and therefore cause intraluminal diffuse fibrosis. Fig. 10 depicts a structural remodeling of alveoli in both focal alveolar and diffuse alveolar damage.



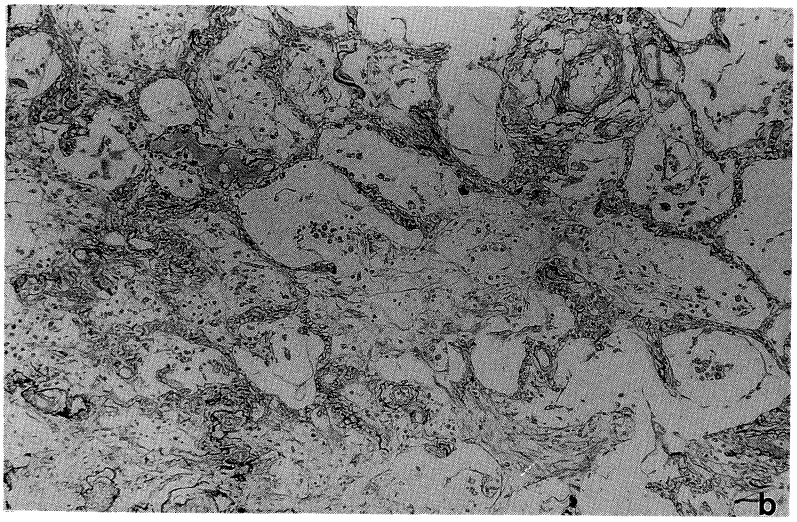
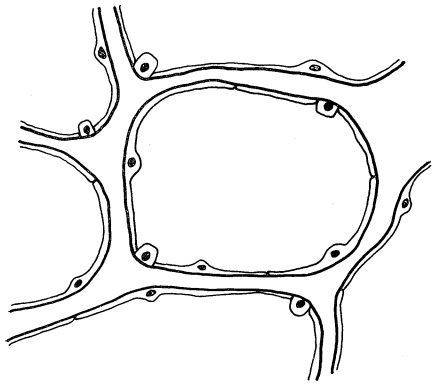


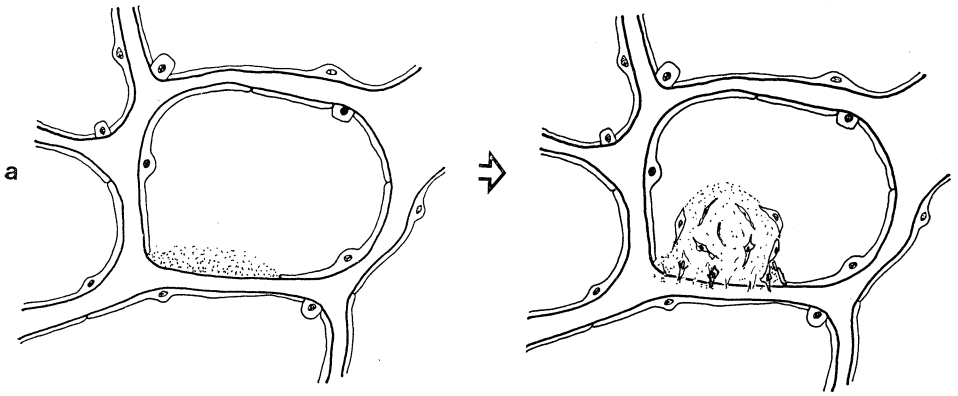
Fig. 9. Bronchiolitis obliterans-organizing pneumonia with intraluminal diffuse fibrosis (elastica van Gieson stain).

a. The respiratory bronchioles (arrows), alveolar ducts and alveolar walls are filled with loose fibrous tissue. (×50)

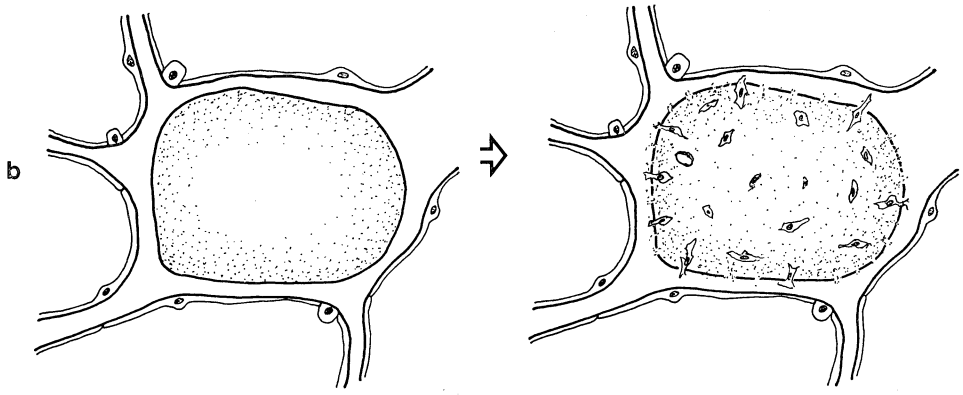
b. Intraluminal diffuse fibrosis of alveoli is seen in the left field of this photograph. The alveolar ducts are also filled with fibrous tissue but adjacent alveoli in the central field have been spared. (×250)



normal



a



b

Fig. 10. Pathogenesis of intraluminal fibrosis.
a. Intraluminal polypoid fibrosis
b. Intraluminal diffuse fibrosis

REFERENCES

1) Basset, F., Ferrans, V.J., Soler, P., Takemura, T., Fukuda, Y. and Crystal, R.G.: Intraluminal fibrosis in interstitial lung disorders. Am. J. Pathol. **122** : 443-461, 1986
2) Moriya, T., Hara, H. and Manabe, T.: Intra-alveolar fibrosis in the paraquat lung. —A histopathological analysis of 29 autopsy cases— Resp. Res. **7** : 359-365, 1988 (In Japanese)
3) Sugihara, K., Hara, H. and Manabe, T.: Microscopic and immunohistochemical study of alveolar damage. Resp. Res. **7** : 1178-1185, 1988 (In Japanese)
4) Copland, G.M., Kolin, A. and Shulman, H.S.: Fatal pulmonary intra-alveolar fibrosis after paraquat ingestion. N. Engl. J. Med. **291** : 290-292, 1974
5) Fukuda, Y., Ferrans, V.J., Schoenberger, C.I., Rennard, S.I. and Crystal, R.G.: Patterns of pulmonary structural remodeling after experimental paraquat toxicity: The morphogenesis of intra-alveolar fibrosis. Am. J. Pathol. **118** : 452-475, 1985
6) Hara, H., Moriya, T. and Manabe, T.: Immunohistochemical study of alveolar epithelium in paraquat poisoning. Nihon Kyobushikkan Gakkaishi **26** : 499-506, 1988
7) Hara, H., Manabe, T. and Hayashi, T.: Immunohistochemical study of fibrosing process in paraquat lung. Virchows Arch. [A] (in press)