# *Intraluminal Fibrosis in Interstitial Lung Disorders*

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**The histopathologic and ultrastructural features of intraluminal organizing and fibrotic changes were studied in open lung biopsies and autopsy specimens from 373 patients with interstitial lung disorders, including hypersensitivity pneumonitis (n=44), idiopathic pulmonary fibrosis (n=92), collagen-vascular diseases (n=20), chronic eosinophilic pneumonia (n=10), pulmonary histiocytosis X (n-90), pulmonary sarcoidosis (n=62), pneumoconioses (n=25), Legionnaire's disease (n=5), drug- and toxin-induced pneumonitis (n=4), radiation-induced pneumonitis (n=2), lymphangioleiomyomatosis (n=11), and chronic organizing pneumonia of unknown cause (n=8). Three patterns of intraluminal organization and fibrosis were recognized: 1) intraluminal buds, which partially filled the alveoli, alveolar ducts and/or distal bronchioles; 2) obliterative changes, in which loose connective tissue masses obliterated the lumens of alveoli, alveolar ducts or distal bronchioles, and 3) mural incorporation of previously intraluminal connective tissue masses, which fused with alveolar, alveolar ductal, or bronchiolar structures and frequently became reepithelialized. All three patterns had common morphologic features, suggesting that, regardless of their severity, they resulted from a common pathogenetic mechanism, ie, the migration of activated connective tissue cells, through defects in the epithelial lining and its basement membrane, from the interstitial into the intraluminal compartment. Intraluminal buds were observed most frequently in hypersensitivity pneumonitis, chronic eosinophilic pneumonia, and organizing pneumonia of unknown cause. Mural incorporation and, to a lesser extent, obliterative changes were observed in most interstitial disorders and were very prominent in idiopathic pulmonary fibrosis. Mural incorporation and obliterative changes play an important role in pulmonary remodeling, especially when several adjacent alveoli and/or other air spaces are involved. Under these circumstances, intraluminal organization can mediate the fusion of adjacent alveolar structures by intraluminal connective tissue. (Am J Pathol 1986, 122:443–461)**

FIBROTIC CHANGES in the interstitial lung diseases are classically conceptualized as fibrous thickening of the pulmonary interstitium, ie, those portions of the alveolar walls bounded by the alveolar epithelial and endothelial basement membranes.[1–5] In this context, the terms "fibrotic lung disease" and "interstitial lung disease" are often used synonymously. Because of the emphasis on the interstitial nature of these disorders, relatively little attention has been given to the fact that intraluminal organizing processes also may play an important role in their pathogenesis. These intraluminal phenomena take different forms and can involve alveoli, alveolar ducts, and, usually to a lesser extent, terminal or respiratory bronchioles. The final outcome of these intraluminal changes is variable. In certain circumstances, intraluminal organizing processes can be regressive.[6–8] In others, intraluminal fibrous scarring develops and may be followed either by incorporation of the fibrous tissue into the alveolar wall, resulting in fibrous thickening of the alveolar septa, or by filling and obliteration of the alveolar lumens.[4,9–11]

The distinction between interstitial and intraluminal fibrosis is of importance in understanding the pathogenesis of interstitial lung diseases, because the mechanisms leading to an accumulation of mesenchymal cells and their products within alveolar walls and within alveolar lumen appear to vary and to have diverse consequences in different diseases. To evaluate this problem in detail, we have made light- and electron-microscopic studies of the characteristics, frequency, and evolution of intraluminal changes in a series of open lung biopsies and autopsy specimens from 373

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individuals with a variety of chronic and acute pulmonary disorders.

## Materials and Methods

Samples of human lung were collected in two different institutions: INSERM U 82, Faculté Xavier Bichat in Paris, France, and the Pulmonary Branch of the National Heart, Lung and Blood Institute in Bethesda, Maryland. A great majority (n=366) of these samples were taken at open lung biopsy, performed for diagnostic purposes. A few (n=7) were taken at necropsy, as soon as possible after death, from patients who died of interstitial pulmonary disorders in intensive care units.

Both categories of samples were prepared similarly: one part was fixed for light microscopy in 10% formalin or Bouin's solution, and another was used for electron-microscopic study. Paraffin sections were stained with hematoxylin and eosin, periodic acid–silver methenamine (PAM),[12] Verhoeff, Masson, and Giemsa stains. For electron-microscopic study, a thin slice was fixed for 1 hour in 2.5% glutaraldehyde, buffered with 0.1 M cacodylate or 0.1 M phosphate, pH 7.4, at 4 C. Selected pieces were cut into small cubes, refixed for 20 minutes in freshly prepared fixative, rinsed overnight in buffer, postfixed in 1% osmium tetroxide, dehydrated in graded ethanols and propylene oxide, and embedded in Epon 812 or Polybed 812. One micron-thick sections were stained with alkaline toluidine blue and used to select appropriate areas for ultrathin sections, which were stained with uranyl acetate and lead citrate and, on some occasions, with the Kajikawa stain for elastic fibers.[13]

Tissues from a total of 373 patients were used for this study. Of these, 252 were studied by transmission electron microscopy. The clinical and pathologic diagnoses in these patients included idiopathic pulmonary fibrosis (n=92), hypersensitivity pneumonitis (n=44), sarcoidosis (n=62), histiocytosis X (n=90), interstitial lung disease associated with collagen-vascular disease (n=20), Legionnaire's disease (n=5); bleomycin-induced interstitial disease (n=1); amiodarone-induced interstitial disease (n=2); paraquat poisoning (n=1); radiation-induced pneumonitis (n=2); pneumoconiosis (n=25); lymphangioleiomyomatosis (n=11); chronic eosinophilic pneumonia (n=10); and chronic organizing pneumonitis of unknown cause (n=8). We use the term "chronic organizing pneumonitis of unknown cause" to designate patients who have a pulmonary morphologic picture resembling that of postinfectious organizing pneumonia[14,15] but in whom no infective cause can be identified; this type of disorder has also been described as "bronchiolitis obliterans organizing pneumonia."[8] All diagnoses were based on previously established clinical and morphologic criteria.[1,2,4,5,16–18]

## Results

### Light-Microscopic Observations

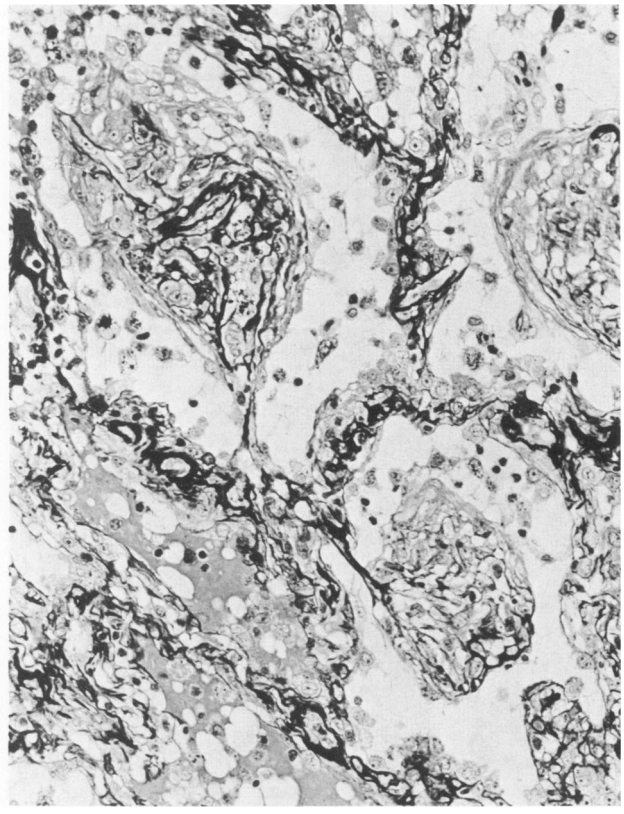
*Patterns of Intraluminal Organization and Fibrosis*

Intraluminal organization and fibrosis were observed in three major patterns. The first two consisted of obvious intraluminal changes and are referred to as "intraluminal buds" and "obliterative changes," respectively. The third pattern was characterized by mural structural changes which resulted from previous intraluminal alterations. Because the sequence of development of this third pattern involves intraluminal components becoming mural components, this pattern is designated as "mural incorporation." When this pattern involves several adjacent alveolar structures, it results in remodeling of the alveolar architecture. This remodeling can be either limited or extensive.

*Intraluminal buds* partially filled the affected air spaces and were composed of variable amounts of cells mixed with, and surrounded by, connective tissue fibers. Buds were located chiefly within alveoli (Figures 1 and 2) and/or alveolar ducts (Figure 3) and were often connected to alveolar walls by narrow stalks (Figure 1). Less frequently, similar intraluminal buds were observed within respiratory or terminal bronchioles and were sometimes connected to the bronchiolar walls either by narrow stalks or by broader bases (not shown). Inflammation and fibrosis were present to a variable extent within intraluminal buds, but fibrosis usually was not prominent.

*Obliterative changes* consisted of clumps of loose connective tissue which filled and obliterated whole lumens of alveoli, alveolar ducts, and/or respiratory or terminal bronchioles. The epithelial lining of areas affected by obliterative changes often had disappeared entirely (Figures 4–6). Inflammation and fibrosis were associated to variable degrees within areas of obliterative changes, but fibrosis was prominent.

*Mural incorporation* was characterized by masses of loose connective tissue, which was morphologically similar to the connective tissue in areas of intraluminal buds or obliterative changes; however, these masses appeared to have fused with, or were incorporated into, alveolar, alveolar ductal, or bronchiolar structures (Figure 7). The surfaces of these structures often were partly or totally reepithelialized. This process of incorporation resulted in thickening of the affected structures, either in limited areas or involving several adjacent alveoli and/or alveolar ducts. Fibrosis of the incorporated tissue masses often was prominent, and inflammation



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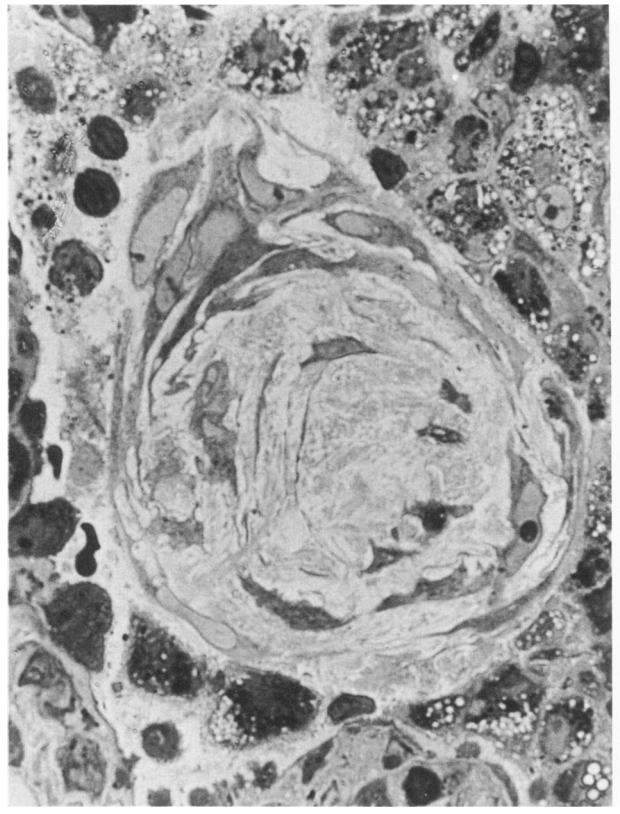

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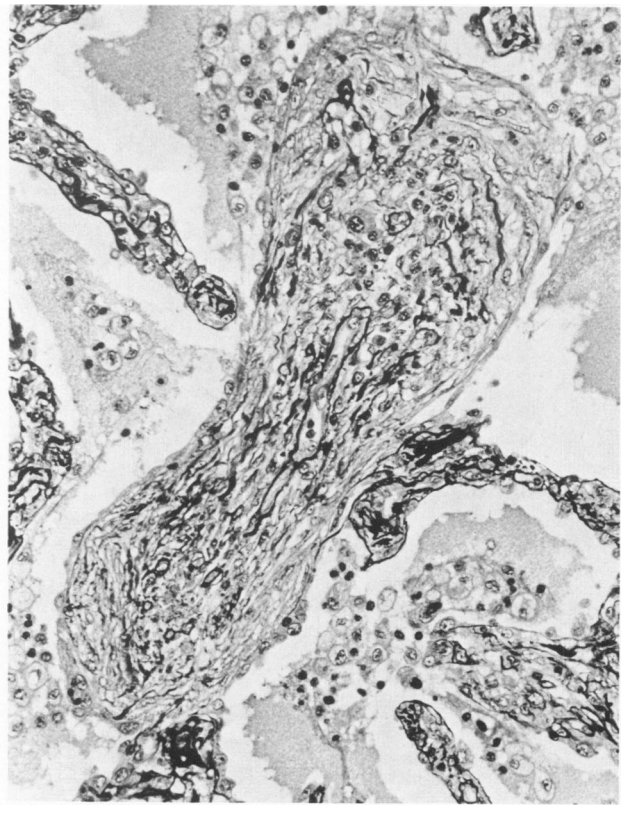

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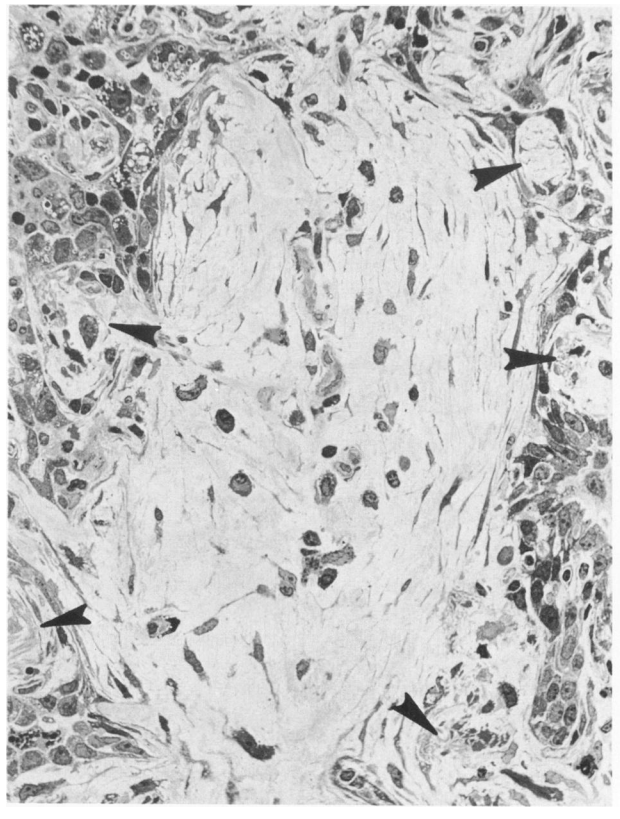

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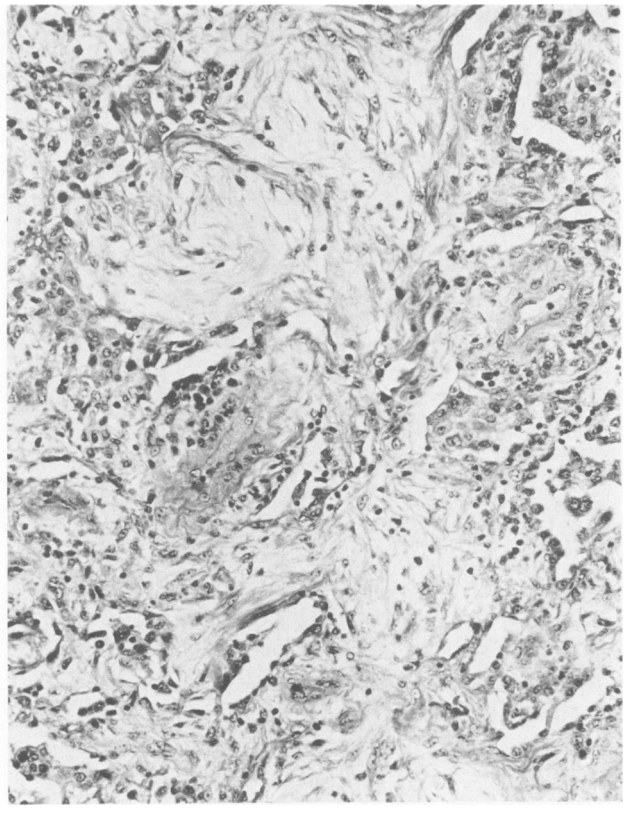
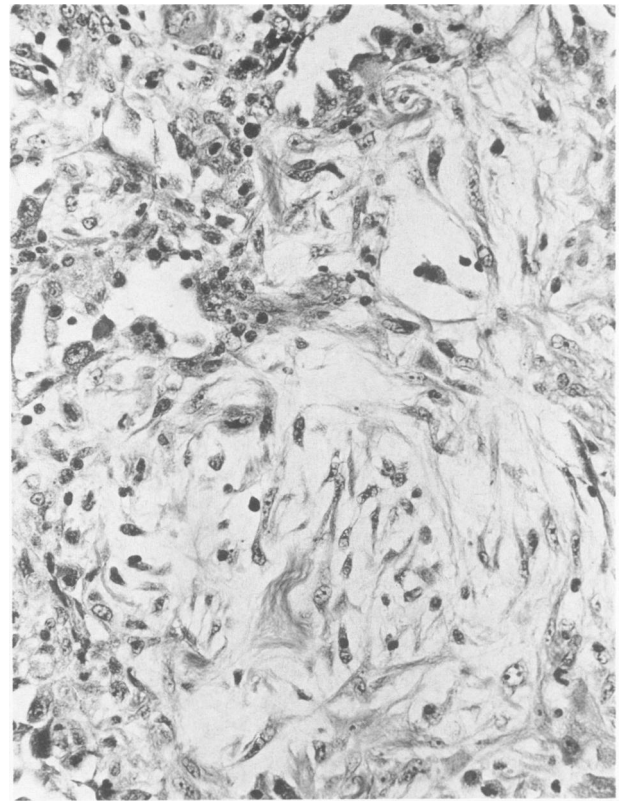
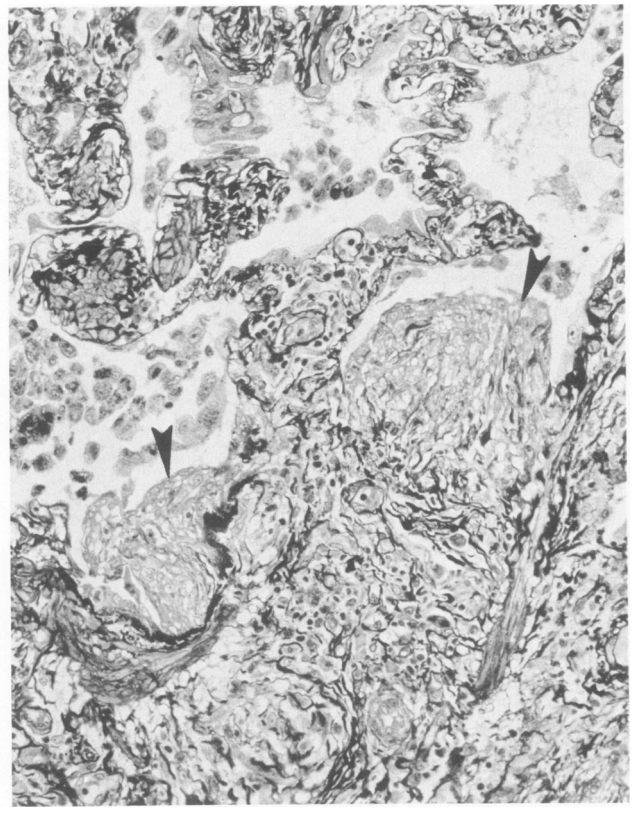
**Figure 1**—Two intraalveolar buds are attached to the alveolar walls by thin stalks (see electron micrograph of similar area in Figure 10). These buds have a relatively poor cell content and are composed mainly of loose connective tissue fibers. Chronic organizing pneumonia of unknown cause (PAM stain, ×300) **Figure 2**—Avascular intraalveolar bud is surrounded by alveolar macrophages and lymphocytes. Note the concentric arrangement of elongated fibroblasts and collagen bundles and the absence of an epithelial lining. Hypersensitivity pneumonitis. (Plastic-embedded tissue, toluidine blue stain, ×700) **Figure 3**—Polypoid intraluminal mass composed of fibrous tissue and inflammatory cells contains centrally located vessel and occupies the lumen of an alveolar duct. Same biopsy as in Figure 1. (PAM stain, ×300) **Figure 4**—Alveolar duct has been completely obliterated by mass of loose connective tissue containing a few inflammatory cells and connective tissue cells; a small blood vessel is also present. Regularly spaced posts (*arrowheads*), found along the periphery of this mass, represent sites of previous openings of alveoli into this duct. Hypersensitivity pneumonitis. (Plastic-embedded tissue, toluidine blue stain, ×300)







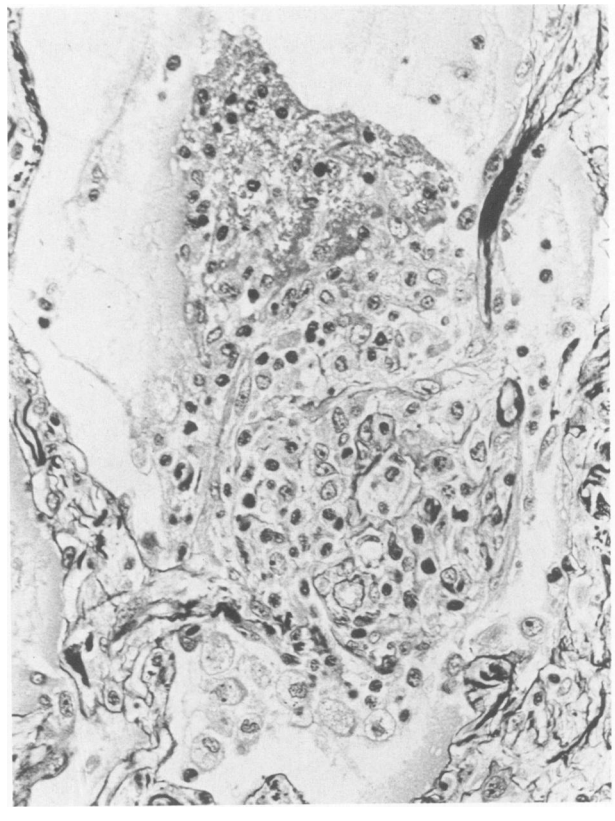


**Figure 5**—Intraluminal fibrosis involves several adjacent alveolar spaces and is associated with focal but marked remodeling. Bleomycin toxicity. (Masson stain, ×150) **Figure 6**—Higher magnification of area similar to that in Figure 5. Inflammatory cells and elongated connective tissue cells are present in area of intraluminal fibrosis and remodeling. Note epithelial cell changes in adjacent areas. Bleomycin toxicity. (Masson stain, ×300) **Figure 7**—Two areas of mural incorporation (*arrowheads*) into walls of respiratory bronchioles are clearly outlined by the PAM stain. Idiopathic pulmonary fibrosis. (×300) **Figure 8**—Lesion that is connected to the alveolar walls and is considered to be an intermediate stage in the formation of an intraalveolar bud consists of an accumulation of fibrin and inflammatory cells. Organizing pneumonia of unknown cause. (PAM stain, ×400)

and focal necrosis were sometimes present. Obliterative changes and mural incorporation appeared to participate in focal remodeling of the lung parenchyma.

### *Morphologic Findings Common to All Forms of Intraluminal Organization*

Some morphologic characteristics were common to all patterns of intraluminal organization. The intraluminal masses generally consisted of loose connective tissue and usually had a relatively poor cellular content. The cells and connective tissue fibers had a parallel or concentric arrangement, with most of the cells having elongated shapes. Clusters of alveolar macrophages often surrounded areas of intraluminal organization, especially intraluminal buds. The epithelial lining over areas of intraluminal organization was either absent (and then replaced by elongated cells or macrophages), discontinuous, or morphologically abnormal. The vascularization was poor (only a few capillaries) or absent, and the areas of intraluminal organization usually did not contain elastic fibers detectable by light microscopy with the Verhoeff stain.

The (PAM) stain (Figures 1, 3, 7, and 8) highlighted the differences between the areas of intraluminal organization and the alveolar structures. Basement membranes and related materials (stained black by this method) were scarce in areas of intraluminal organization, in which they were related mainly to connective tissue cells. In contrast, basement membranes and related materials were abundant in alveolar structures, because of the presence of the epithelial lining cells, capillary endothelial cells, and interstitial connective tissue cells. The Giemsa stain often showed purple-stained areas in freshly organized intraluminal buds, obliterated airways, and patches of recent mural incorporation, presumably due to their high content of proteoglycan material.

Superimposed on the three patterns of intraluminal fibrosis described above, some samples showed exudative or fibrotic changes which were considered to be preliminary stages and sequelae of these patterns of intraalveolar organization, respectively.

### *Exudative Changes*

Exudative changes were observed mostly in association with intraluminal buds and more rarely with obliterative changes and mural incorporation. Exudative changes included intraluminal masses of fibrin aggregated with macrophages and other inflammatory cells (Figure 8). Unlike hyaline membranes (which are composed of fibrin and cell debris and are apposed to the alveolar walls), these masses usually were detached from the alveolar walls. More rarely, true hyaline membranes were also observed. Intermediate stages between fibrinous exudation and intraalveolar fibrosis consisted of partly organized masses that were connected to alveolar walls or alveolar tips by stalks arising from the organized parts of the buds (Figure 8). Inflammatory cells, especially plasma cells and macrophages, were more abundant than in more mature stages, especially in intraluminal buds located in alveolar ducts (Figure 3) and respiratory or terminal bronchioles.

### *Intraluminal Fibrosis and Pulmonary Remodeling*

Collagen deposition was present in areas of intraluminal buds, obliterative changes, and mural incorporation, thus inducing, at least to some extent, intraluminal fibrosis. Remodeling processes were associated with confluence of septal and intraalveolar fibrous tissue and collapse or disappearance of the preexisting air spaces. Because of this, the late stages of intraluminal fibrosis appeared as fibrotic changes involving both the lumens and the walls of alveolar structures (Figures 5 and 6). These changes mostly followed obliterative changes and mural incorporation and resulted either in limited patches or in large, widespread areas of remodeling. Limited patches were localized mainly at alveolar tips or on openings of alveolar ducts. In both the widespread and the limited forms, the fibrotic masses sometimes sealed off adjacent alveoli. The epithelial lining was absent or covered parts of the intraluminal fibrotic masses in a process of reepithelialization. In areas where interstitial fibrosis was also present, some epithelial cells appeared either as large, isolated cells or as glandlike structures without visible connections to alveolar lumens. Furthermore, when there was severe, widespread intraluminal organization (eg, in patients with paraquat poisoning or drug-induced diseases), proliferating, atypical bronchiolar epithelium was observed in the vicinity of organized areas.

## Electron-Microscopic Observations

### *General Features*

The *connective tissue* in intraluminal buds, as well as in obliterative changes and mural incorporation (Figures 9–12), was mainly composed of poorly defined collagen bundles or of thin, separated collagen fibrils which were loosely arranged in an abundant electron-lucent matrix. This matrix contained irregular masses of finely fibrillar material resembling fibrin or basement membrane components (Figures 9–11). The matrix usually also contained a network of small stellate electron-dense spicules that probably represented proteoglycans.[19] Elastic fibers were usually absent in intraluminal buds; however, on rare occasions they were found in lesions of mural incorporation, in which the lumi-

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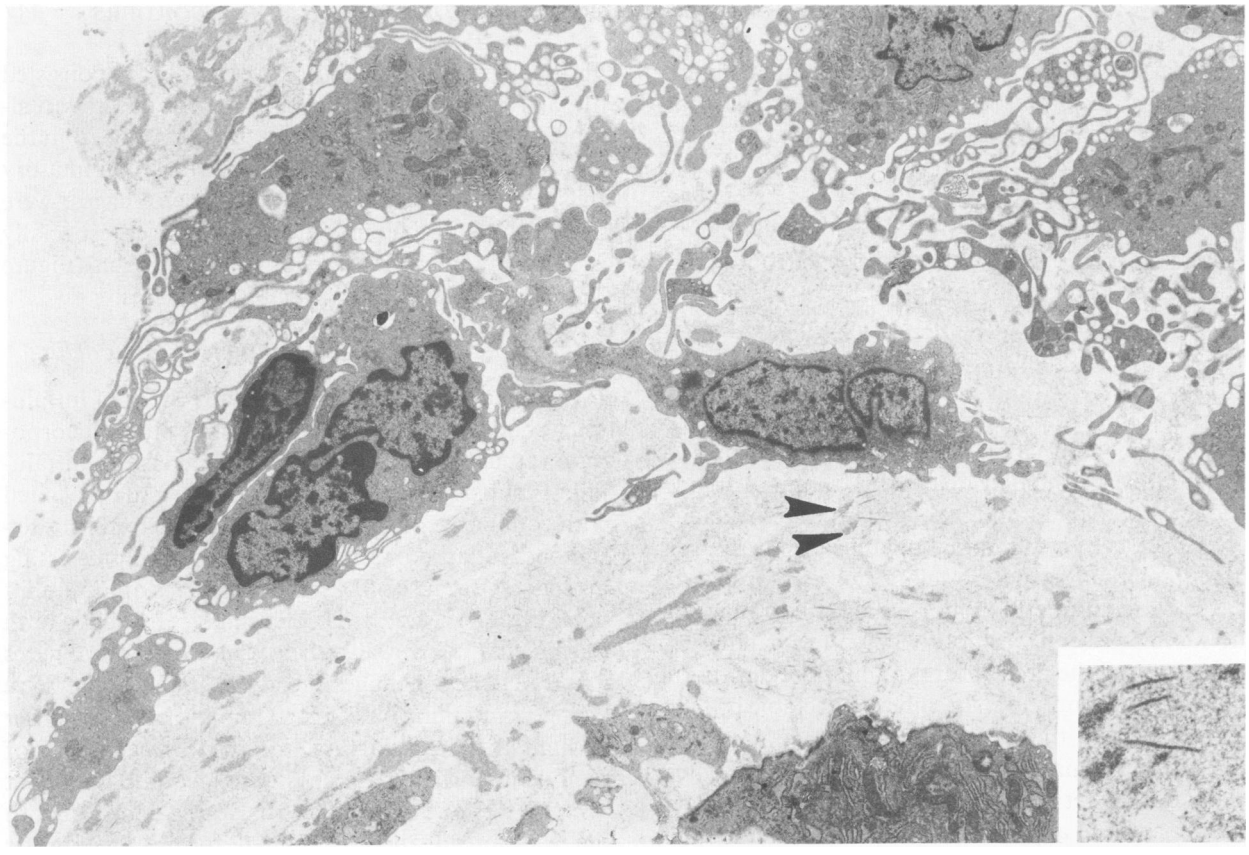

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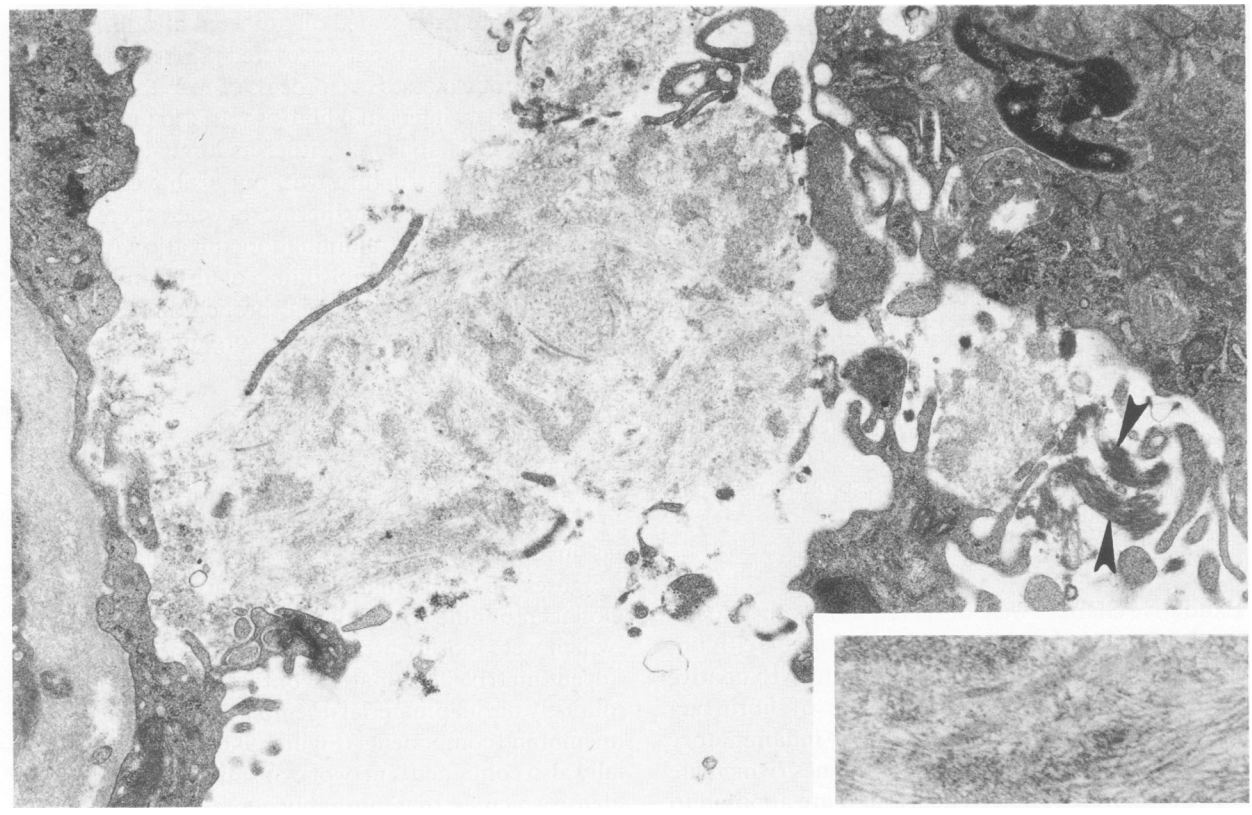


**Figure 9**—Electron micrograph of part of the surface and subjacent area of an intraalveolar bud. The surface layer is composed of macrophages. The underlying zone contains a fibroblast, collagen fibrils (see **Inset**) and amorphous electron-dense material (*arrowheads*). Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×7000 and ×18,000) **Figure 10**—Electron micrograph of stalk connecting an intraalveolar bud (*right*) with the alveolar wall (*left*). The surface of the bud is composed of macrophages (*upper right*) and fibrin (*arrowheads*). **Inset** shows electron-dense material and connective tissue microfibrils in stalk. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×15,000 and ×54,000)

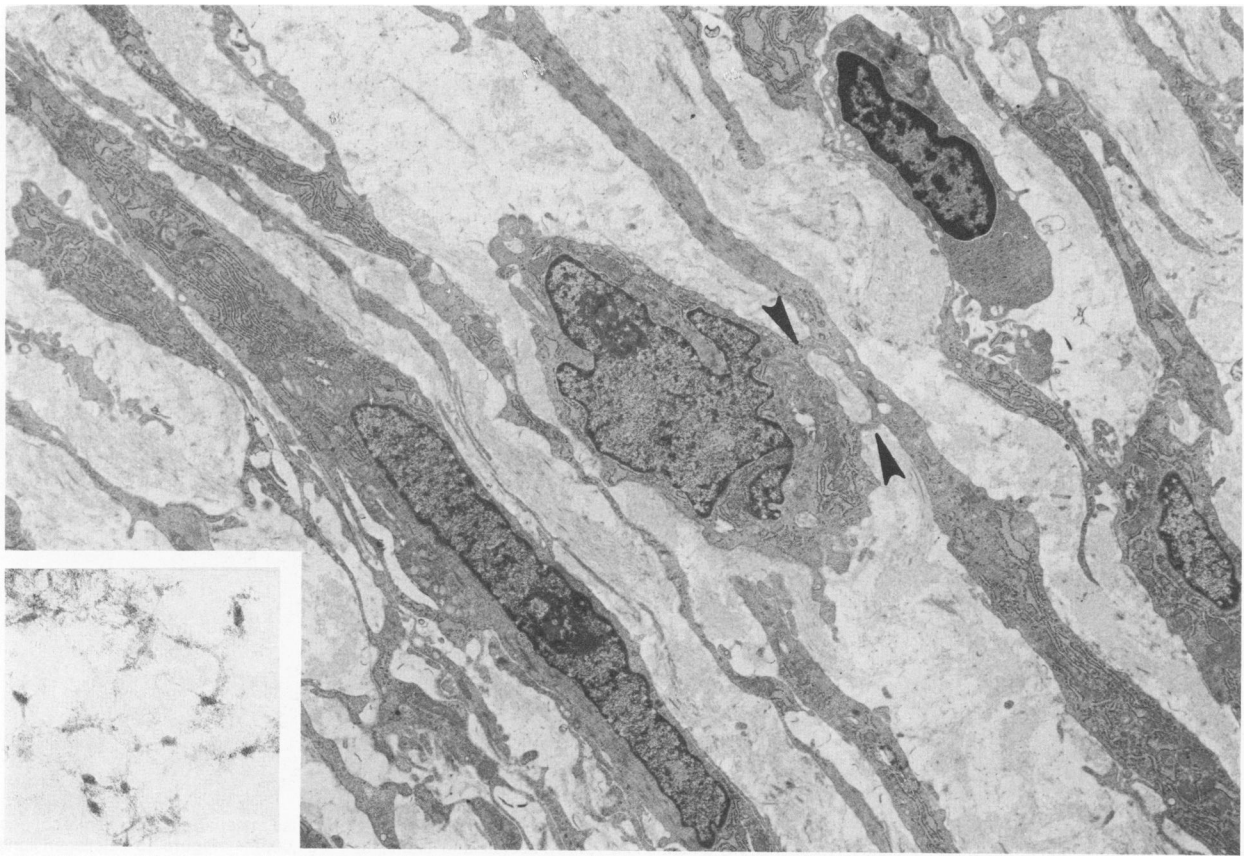
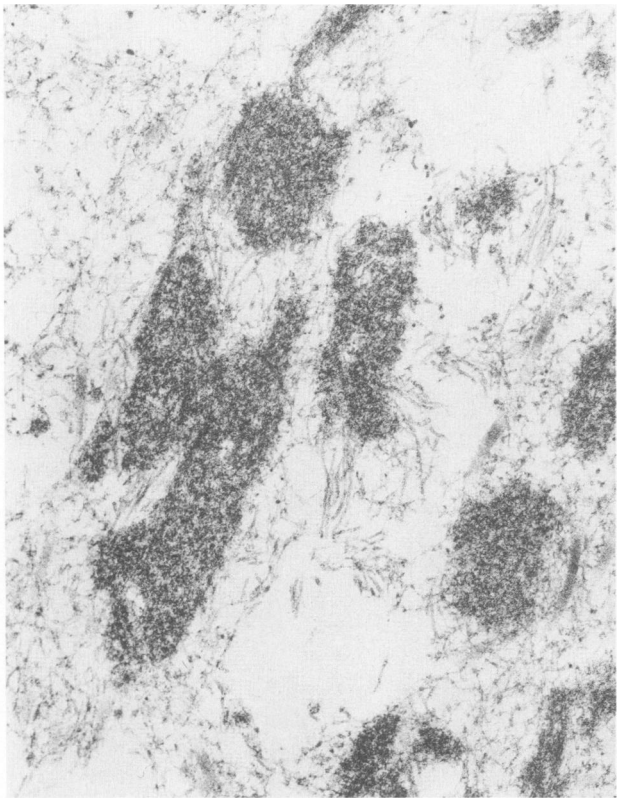


**Figure 11**—Interior of an intraalveolar bud contains a parallel arrangement of fibroblasts with elongated cytoplasmic processes forming intercellular contacts (*arrowheads*); a lymphocyte with a dark nucleus is also present. The stroma is composed of loose connective tissue that is rich in proteoglycan granules (see **inset**) but lacks elastic fibers. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×7500 and ×54,000)

nal surfaces had been reepithelialized. Collagen fibrils sometimes exhibited increased granularity and fragmentation. These changes, which were particularly well demonstrated by the Kajikawa stain (Figure 13), resembled those which have been reported to occur as the result of collagen degeneration in implanted bioprosthetic cardiac valves.[20]

The *cell populations* within the connective tissue framework of intraluminal buds and areas of obliterative changes and mural incorporation were relatively poor. Most of the cells were elongated, stellate or spindle-shaped fibroblasts and/or myofibroblasts (Figure 11). These cells were arranged concentrically or in parallel and were interconnected through long and slender cytoplasmic processes which made contact with one another, forming an irregular network interspersed between the connective tissue bundles. A few inflammatory cells were sometimes present, such as lymphocytes and mast cells. The latter usually exhibited partial degranulation and thin, straight filopodia. Alveolar macrophages often surrounded partially the connective tissue masses (Figure 9) and sometimes had an elongated shape along the edges of these masses (Figure 14). Capillaries were usually absent. However, in sections in which a connecting stalk was present between a bud and an alveolar wall, a capillary was sometimes observed within or close to this stalk. These capillaries had narrow lumens, thick endothelial cells, and thick basement membranes.

The *surfaces of intraluminal buds* usually were covered by flattened cells. Some of these cells had characteristic features of alveolar macrophages, such as filopodia and numerous cytoplasmic inclusions (Figure 14). They did not have a basement membrane and usually were loosely apposed to one another, with no junctional structures. Other flattened cells on the surface of the buds had characteristics of fibroblasts or myofibroblasts (Figures 15 and 16), including cytoplasmic bundles of microfilaments, abundant rough endoplasmic reticulum with dilated cisterns, and occasional cytoplasmic lipid droplets. These cells were either isolated or connected to each other by junctional structures such as nexus-like contacts between long cytoplasmic processes (Figure 16). A few of the surface cells exhibited some fea-



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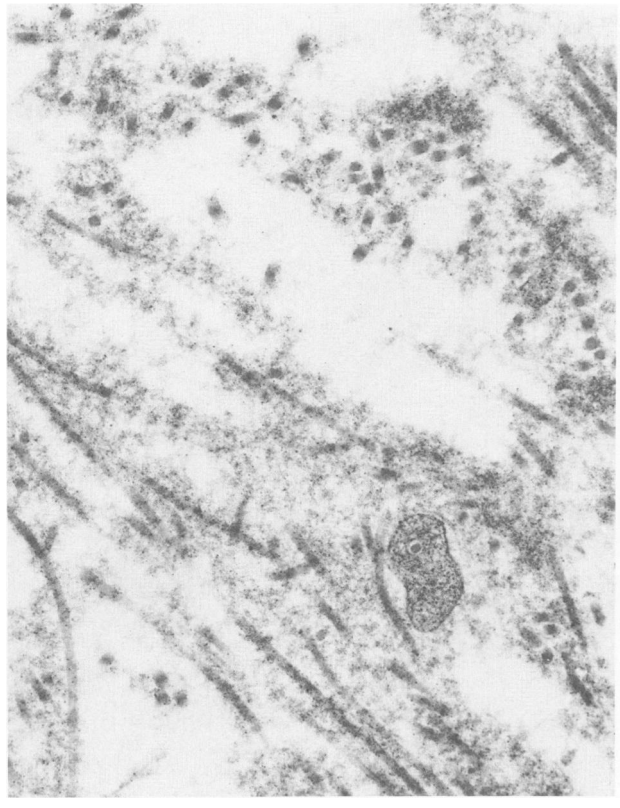

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**Figure 12**—High magnification of connective tissue stroma in an intraalveolar bud, showing amorphous electron-dense material, collagen fibrils, connective tissue microfibils, and proteoglycan granules. Hypesensitivity pneumonitis. (Uranyl acetate and lead citrate, ×54,000) **Figure 13**—Collagen fibrils in this area of an intraalveolar bud appear disrupted and are associated with granular material. Hypersensitivity pneumonitis. (Kajikawa stain, ×23,500)

tures of epithelial lining cells: they appeared somewhat polarized, with an apical surface which often had short microvilli and a smooth basal surface surrounded by a discontinuous basement membrane.

*Early Stages*

In early stages of intraluminal organization with exudative changes, the most important features included 1) large strands of fibrin, located either on the surface of, or within, organizing buds, and 2) large numbers of inflammatory cells, especially plasma cells, which were particularly numerous in buds located in alveolar ducts or respiratory bronchioles. A most important feature, encountered especially in patients with hypersensitivity pneumonitis, consisted of evidence of a "leak" in epithelial mural structures adjacent to sites of luminal exudation. In these instances a limited defect in the alveolar epithelial lining and in its basement membrane was observed; and various types of cells, including fibroblasts and inflammatory cells, appeared to be migrating through this defect from the alveolar wall to the air space (Figure 17).

*Late Stages*

In late stages, characteristically represented by areas of obliterative changes, mural incorporation, and remodeling, the connective tissue had a more mature appearance than in intraluminal buds, with less edema, fewer proteoglycan spicules, and occasional elastic fibers (Figures 17 and 18); capillaries were less scanty and had thick endothelial cells and basement membranes. Inflammatory cells were usually absent. The surfaces of some of the intraalveolar fibrotic masses were still lined by flattened macrophages and/or fibroblasts. However, epithelial cells which were cuboidal or irregular in shape and contained few or no characteristic lamellar bodies of Type II pneumocytes had grown in some places over the connective tissue or over the surrounding flattened cells (Figures 14 and 18). These epithelial cells had no hemidesmosomes or other specialized structures along their basal surfaces, but had a continuous basement membrane and often contained, mainly in their basal portions, prominent bundles of intermediate filaments. In some areas the resulting epithelial layer was discontinuous. The process of re-

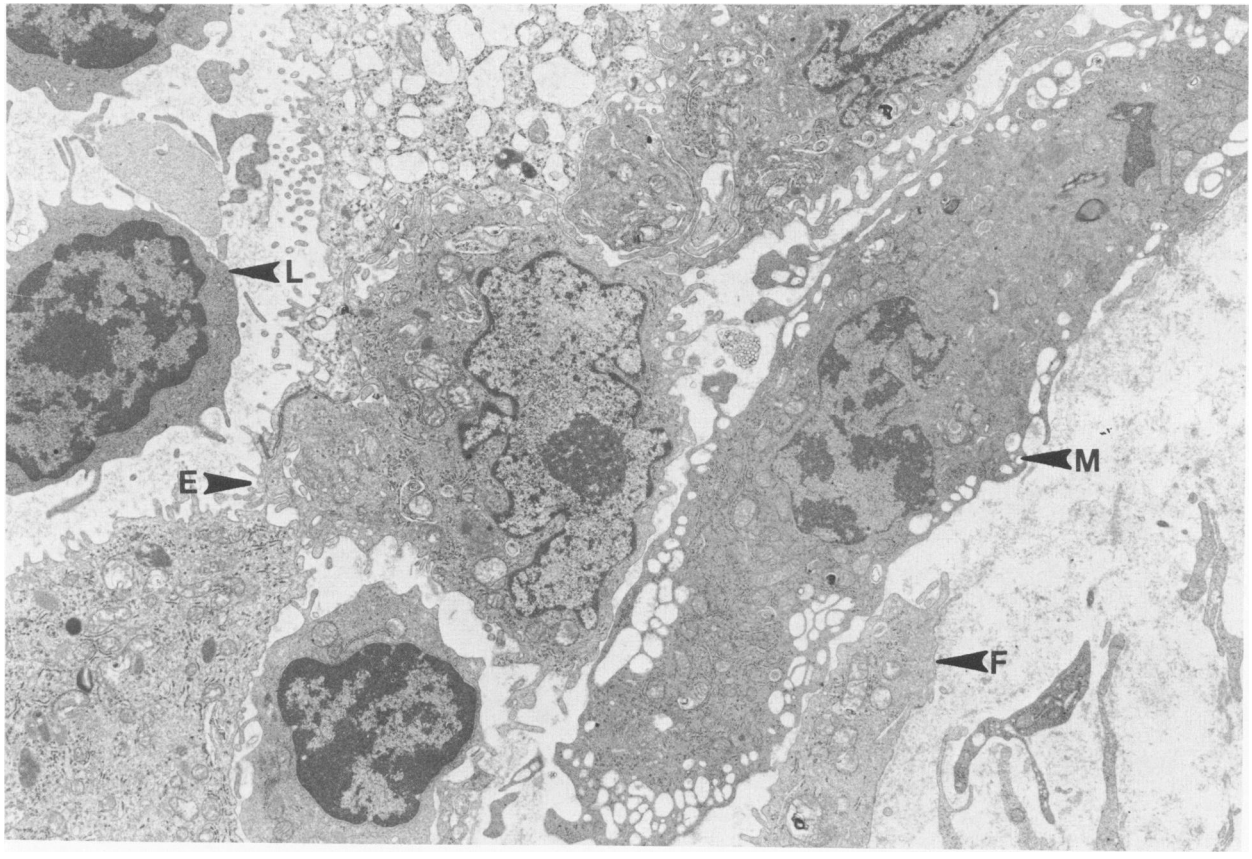



**Figure 14**—Connective tissue at the surface of an intraalveolar bud is shown at the *lower right*. The surface lining of this bud is complex: note part of a fibroblast (*F*) and an elongated macrophage (*M*), which are covered by a layer of several epithelial cells (*E*) with differentiated intercellular junctions and surface microvilli. Three lymphocytes (*L*) are also present. This arrangement of cells is interpreted as evidence of reepithelialization of the intraalveolar bud. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×7500)

epithelialization appeared to arise from contacts between the intraluminal connective tissue masses and the mural structures. Some epithelial cells were large, isolated, and entirely surrounded by connective tissue (Figure 19). Others formed small, often asymmetrical, glandlike structures or lined remodeled areas, sometimes contributing to sealing off collapsed and coalescent alveolar structures (Figure 18).

In areas of mural incorporation, obliteration, and remodeling, intraluminal fibrosis was often characterized by more or less complete fusion between intraluminal connective tissue masses and mural structures, with no epithelial or surface lining remaining on either side of the zone of fusion. In the continuum of connective tissue thus formed, a clear distinction between previously luminal and previously mural components was sometimes difficult, especially when interstitial fibrotic changes were associated with intraluminal organization. However, areas with normal capillaries and elastic fibers were likely to represent remnants of alveolar structures. Loops of loosely arranged, denuded basement membranes with no corresponding epithelial or vascular structures were often seen, forming complicated whorls or foldings; these structures seemed to belong to collapsed and subsequently coalescent alveolar structures (Figures 18 and 19). Processes of fibroblasts or myofibroblasts were interspersed between some of these denuded basement membranes. These processes were apposed to the luminal side of the basement membranes and represented parts of connective tissue cells migrating into the air spaces (Figures 18 and 19).

## Incidence of Various Patterns of Intraluminal Fibrosis in the Different Interstitial Lung Disorders (Table 1)

### *Intraluminal Buds*

Both the frequency and the degree of this change varied considerably according to the disease. It was observed in each of our 8 cases of chronic organizing pneumonitis of unknown cause: it was mild in 4 cases, moderate in 2, and severe in 2. Intraluminal buds were also very frequently observed in hypersensitivity pneu-

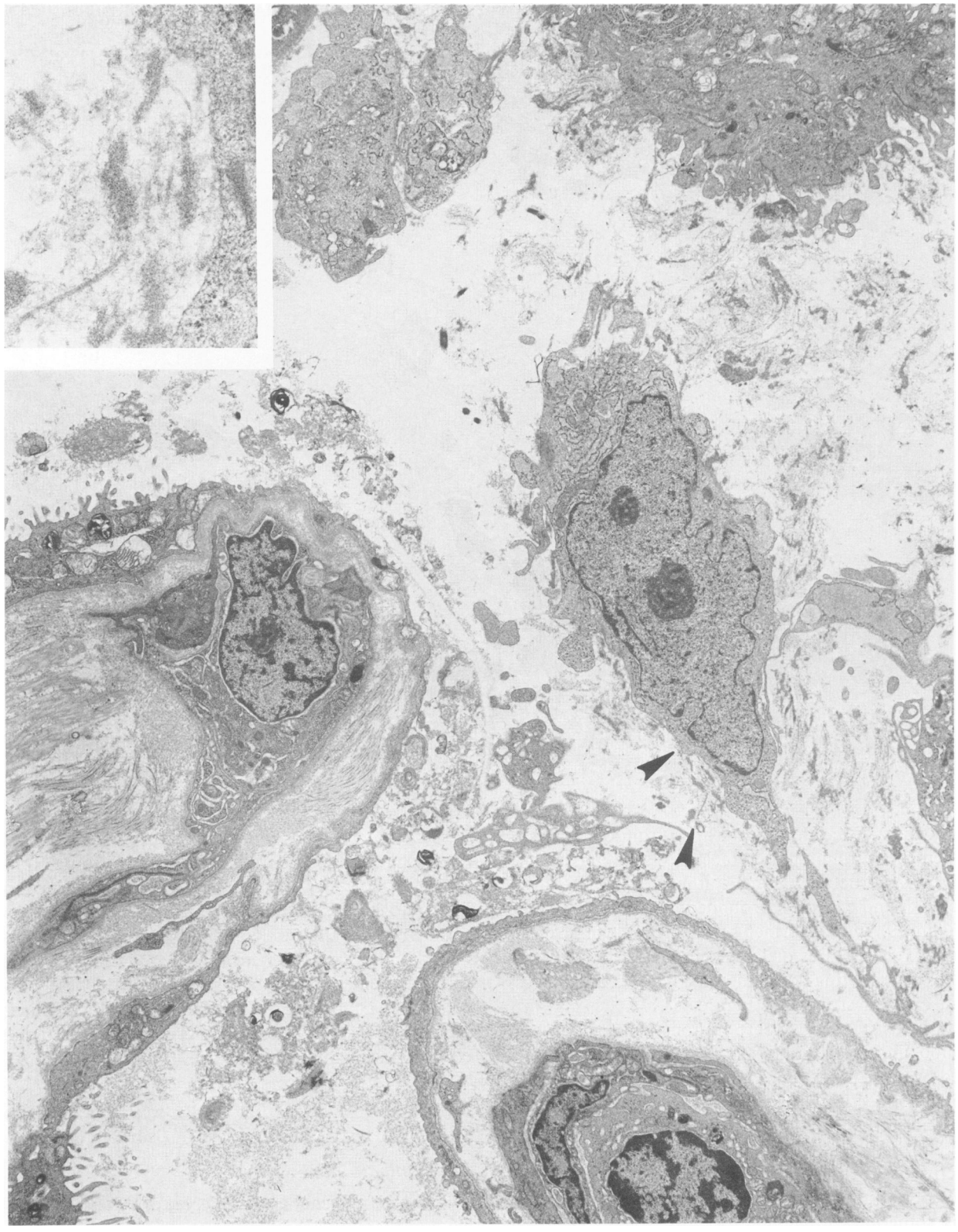
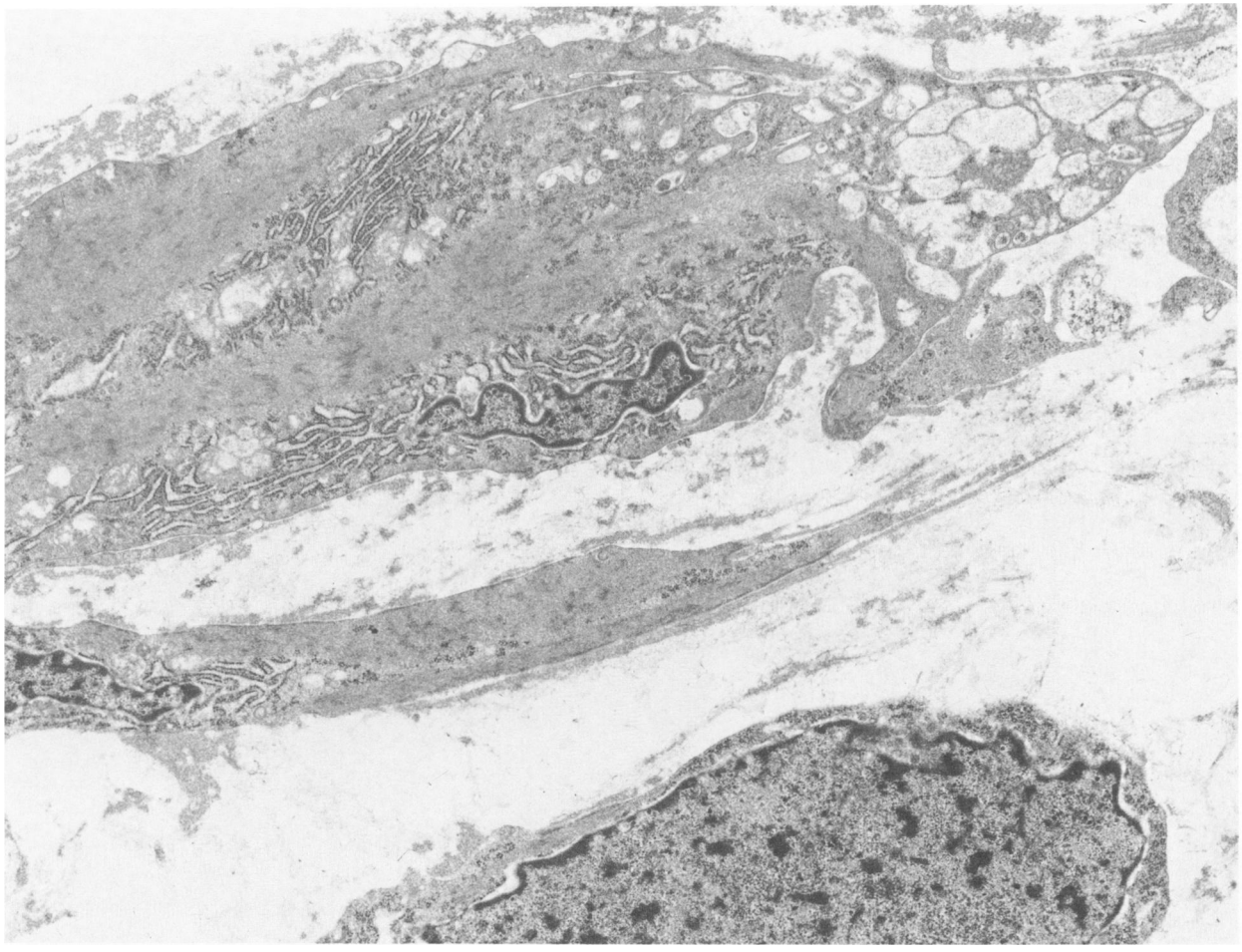


**Figure 15**—Elongated fibroblast forms part of the surface of area of mural incorporation without reepithelialization. The surface of the fibroblast (*arrowheads*) is associated with collagen fibrils (**Inset**). The tips of two alveolar septa (*left* and *lower right*) are lined by Type I and Type II pneumocytes and contain capillaries, collagen, and elastic fibers. Dermatomyositis. (Uranyl acetate and lead citrate, ×8500 and ×30,000)

**Figure 16**—Surface of area of mural incorporation is lined by elongated myofibroblasts that contain numerous ribosomes and cytoplasmic filaments. Amiodarone toxicity. (Uranyl acetate and lead citrate, ×16,000) **Figure 17**—Portion of alveolar septum showing area of loss of continuity of epithelial lining and basement membrane (*arrowheads*). Macrophagelike and fibroblastlike cells appear to be passing through this gap in the wall. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×8000)



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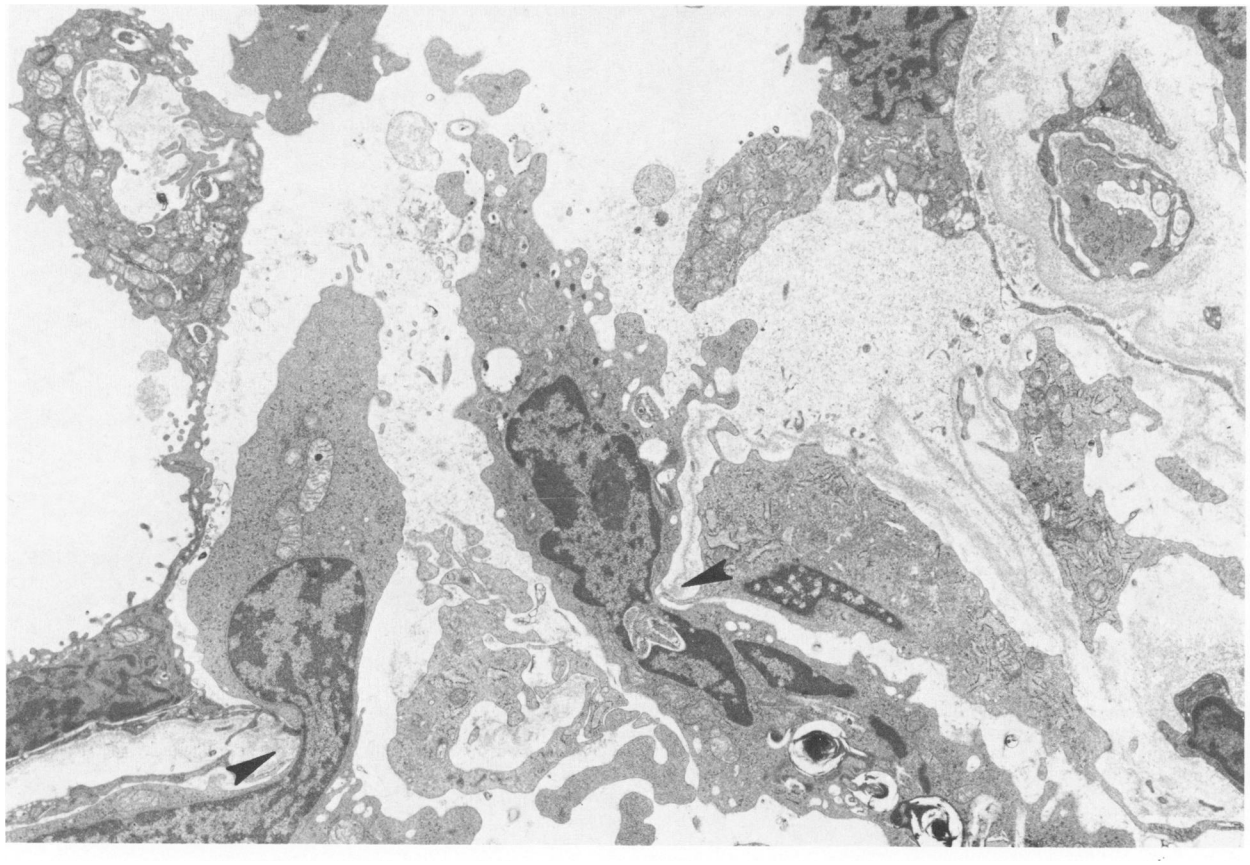

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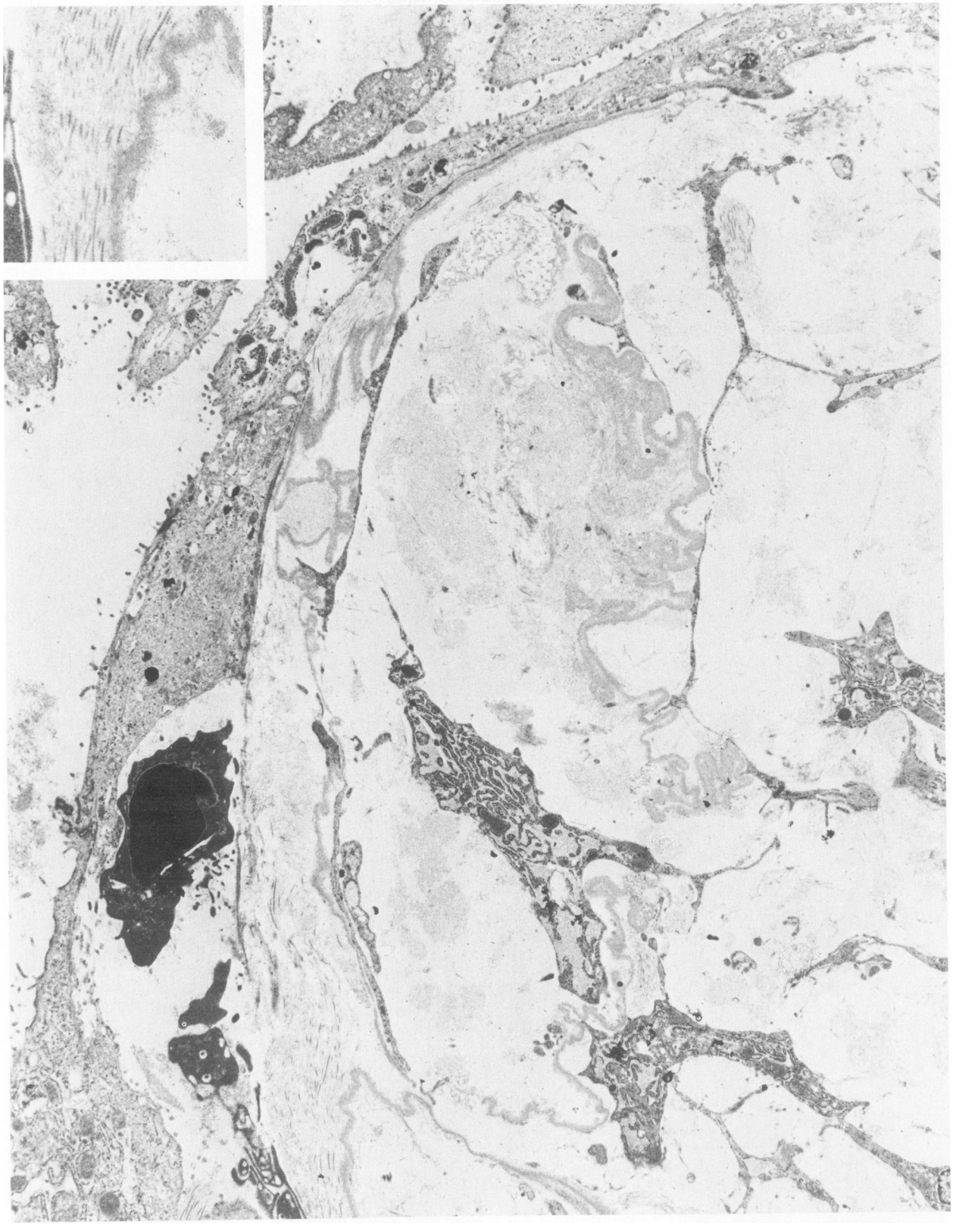
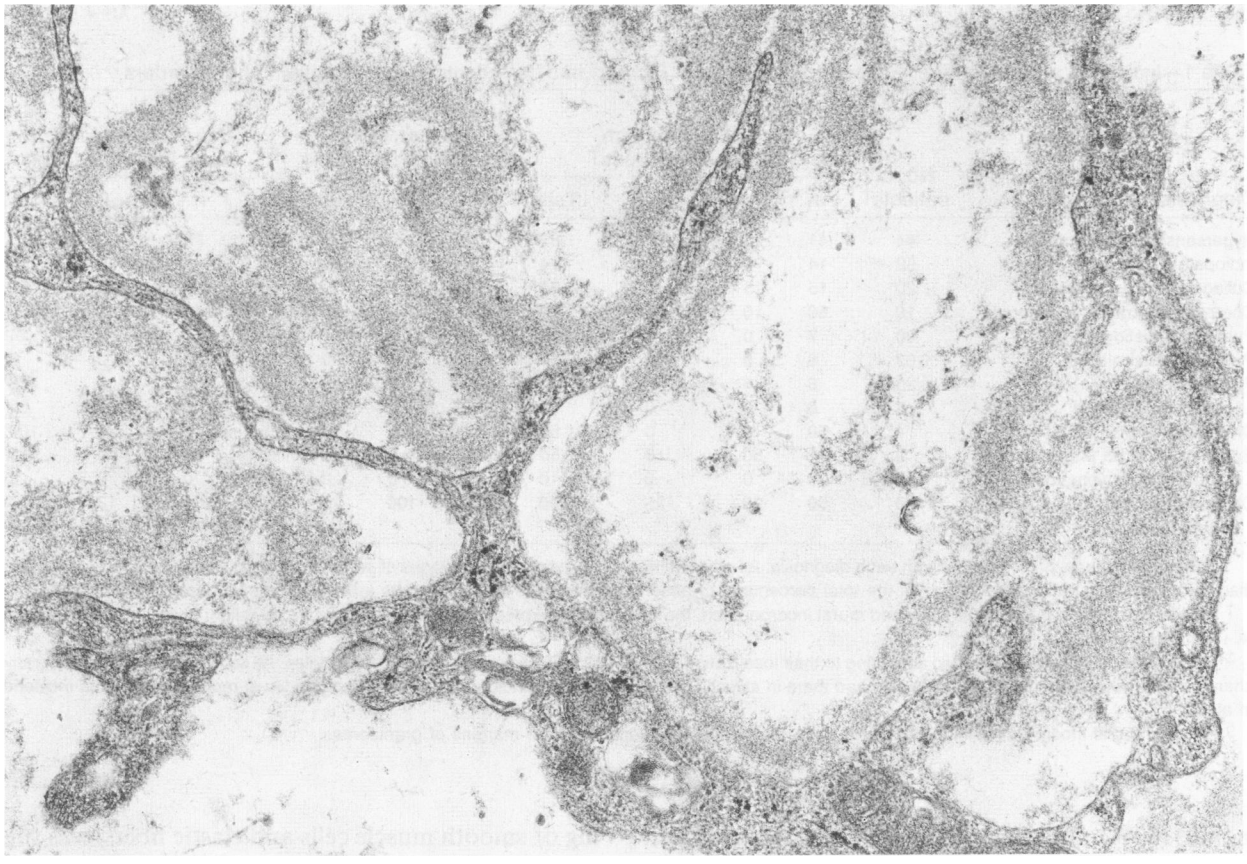


**Figure 18**—Area of mural incorporation and remodeling showing several loops of basement membranes, which appear to have been derived from preexisting alveolar structures. Fibroblasts with elongated cytoplasmic processes are interspersed between the basement membranes. Collagen fibrils (see **inset**) are present on both sides of the basement membranes. Elongated cells with surface microvilli form a continuous surface layer. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate stain, ×8500 and ×16,000).



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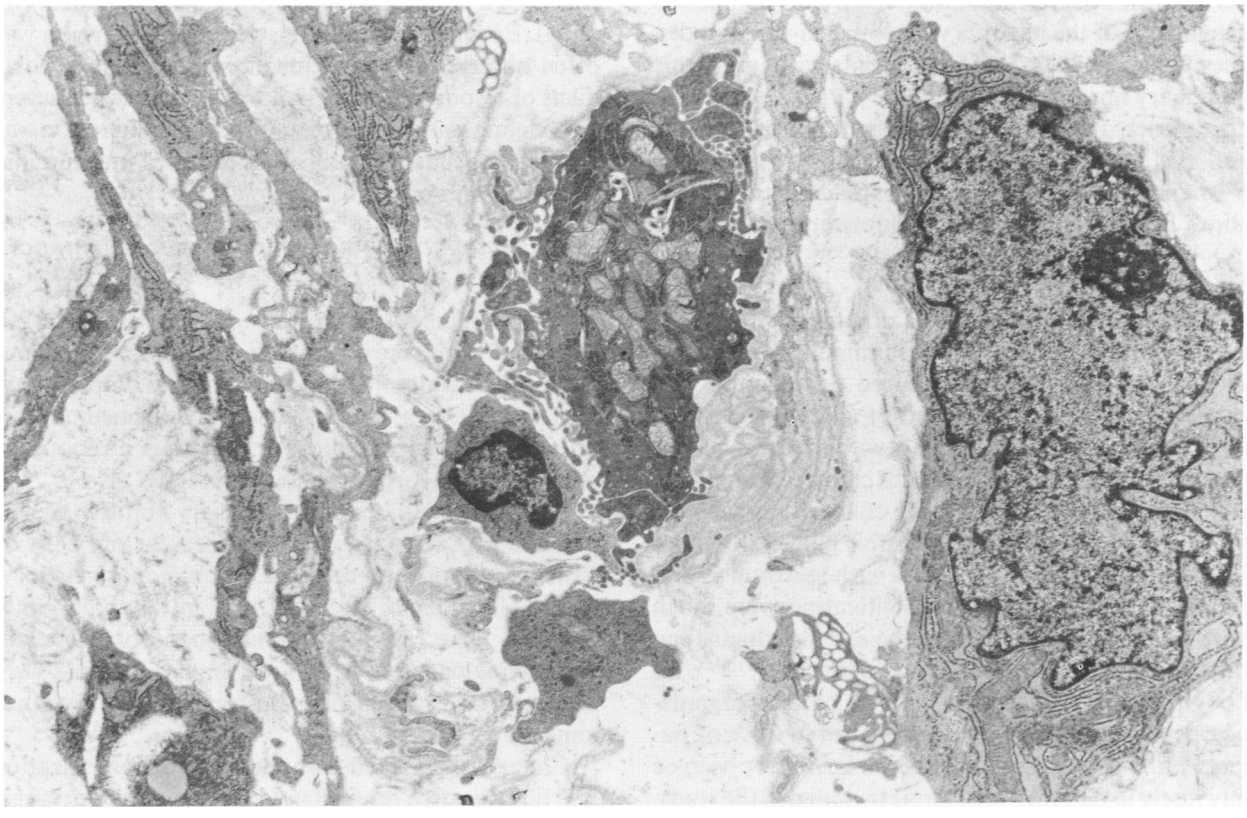

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**Figure 19**—Elongated cytoplasmic processes of a fibroblast are surrounded by loops of basement membrane (which are the only remnant of previous alveolar structures) and spicules of proteoglycan material. Hypersensitivity pneumonitis. (Uranyl acetate and lead citrate, ×35,000) **Figure 20**—Area of severe remodeling, showing an isolated epithelial cell which is surrounded by convoluted basement membranes, numerous fibroblasts, and a few inflammatory cells embedded in a loose stroma containing proteoglycan spicules. Amiodarone toxicity. (Uranyl acetate and lead citrate, ×9200)

Table 1—Incidence and Severity of Patterns of Intraluminal Fibrosis in 373 Patients With Interstitial Lung Disorders

| Diagnosis | No. of patients* | % Patients with intraluminal buds† | | | | % Patients with obliterative changes‡ | | | % Patients with mural incorporation† | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | + | + + | + + + | Total | Alv | AD | Br | + | + + | + + + | Total |
| Hypersensitivity pneumonitis | 44 | 41 | 23 | 2 | 66 | 48 | 26 | 23 | 32 | 23 | 20 | 75 |
| Indiopathic pulmonary fibrosis | 92 | 14 | 0 | 0 | 14 | 19 | 13 | 4 | 22 | 36 | 16 | 74 |
| Collagen-vascular diseases | 20 | 15 | 15 | 0 | 30 | 25 | 5 | 0 | 50 | 20 | 10 | 80 |
| Chronic eosinophilic pneumonia | 10 | 60 | 10 | 0 | 70 | 40 | 10 | 75 | 60 | 40 | 0 | 100 |
| Pulmonary histiocytosis X | 90 | 7 | 0 | 0 | 7 | 2 | 0 | 1 | 24§ | 0 | 0 | 24§ |
| Pulmonary sarcoidosis | 62 | 6 | 0 | 0 | 6 | 2 | 0 | 0 | 3 | 0 | 0 | 3 |
| Pneumoconioses | 25 | 8 | 4 | 0 | 12 | 8 | 0 | 0 | 28 | 0 | 0 | 28 |
| Legionnaire's disease | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60 | 0 | 0 | 60 |
| Drug-induced pneumonitis | 4 | 50 | 0 | 0 | 50 | 75 | 25 | 0 | 25 | 50 | 25 | 100 |
| Radiation-induced pneumonitis | 2 | 0 | 50 | 0 | 50 | 50 | 0 | 0 | 50 | 50 | 0 | 100 |
| Lymphangioleiomyomatosis | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 9 |
| Chronic organizing pneumonia of unknown cause | 8 | 50 | 25 | 25 | 100 | 100 | 100 | 75 | 37 | 50 | 13 | 100 |

* Number of patients is the number with each diagnosis. All other numbers express the percentages of patients showing each type of change in each diagnostic group; in each group, "total" is the total percentage of patients showing the type of change indicated, independent of severity.

† For the presence of intraluminal buds and mural incorporation, the changes are expressed as follows: 0, absent; +, slight or focal; + +, moderate; + + +, severe.

‡ Obliterative changes are classified according to their localization: Alv, alveoli; AD, alveolar ducts; Br, bronchioles. All samples which had obliterative changes in alveolar ducts or bronchioles also had them in alveoli. Therefore, the total incident of obliterative changes is represented by the incidence in alveoli.

§ Areas of mural incorporation in histiocytosis X were almost always located at the margins of granulomas.

monitis (66%), chronic eosinophilic pneumonia (70%), and drug-induced pneumonitis (50%). This change was seen in 30% of the patients with collagen-vascular diseases, but only in 14% of the patients with idiopathic pulmonary fibrosis and 12% of the patients with pneumoconioses. It was extremely uncommon in patients with histiocytosis X (7%) and pulmonary sarcoidosis (6%) and was not observed in patients with Legionnaire's disease or lymphangioleiomyomatosis.

### *Luminal Obliteration*

This pattern of intraluminal organization was observed less frequently than intraluminal buds and was found in all cases of drug-induced pneumonitis and chronic organizing pneumonitis of unknown cause. It was observed in 48% of patients with hypersensitivity pneumonitis, 40% of patients with chronic eosinophilic pneumonia, 25% of patients with collagen-vascular diseases, 19% of patients with idiopathic pulmonary fibrosis, and only 2% of the patients with sarcoidosis and histiocytosis X. The sites of obliteration were much more frequently the alveoli or the alveolar ducts than the bronchioles. "Bronchiolitis obliterans,"[1,9,11] although seen in 75% of patients with chronic organizing pneumonia of unknown cause and in 23% of patients with hypersensitivity pneumonitis, was observed only rarely in all other conditions included in the study. Obliteration of alveolar ducts was so marked in some samples that only the presence around an area of loose connective tissue of regularly arranged "posts," consisting of smooth muscle cells and elastic fibers, was suggestive of a preexisting opening of an alveolar duct (Figure 4). Extensive smooth muscle cell proliferation was often observed in the vicinity of obliterated alveolar ducts or respiratory bronchioles, especially when severe remodeling was also present. Luminal obliteration was usually associated with all other forms of intraluminal organization and fibrosis.

### *Incorporation of Intraalveolar Organized Fibrotic Masses Into Alveolar Walls*

This change was observed to some degree in all diseases in the study group. It was the predominant pattern of intraluminal fibrosis found in biopsy specimens of patients with hypersensitivity pneumonitis, drug-induced pneumonitis, and chronic eosinophilic pneumonia. Incorporation was observed also in 73% of patients with idiopathic pulmonary fibrosis, 75% of patients with collagen vascular diseases, and 28% of patients with pneumoconioses. In pulmonary histiocytosis X, in which other patterns of intraluminal organization were usually absent, incorporation and remodeling occurred in 24% of the patients and were observed mostly in marginal areas of healing granulomas.

Changes associated with intraluminal organization and fibrosis often resulted in focal or extensive derangement of alveolar architecture, with concomitant formation of scar tissue and microcysts. In our study group, the extensive type of remodeling was mostly observed

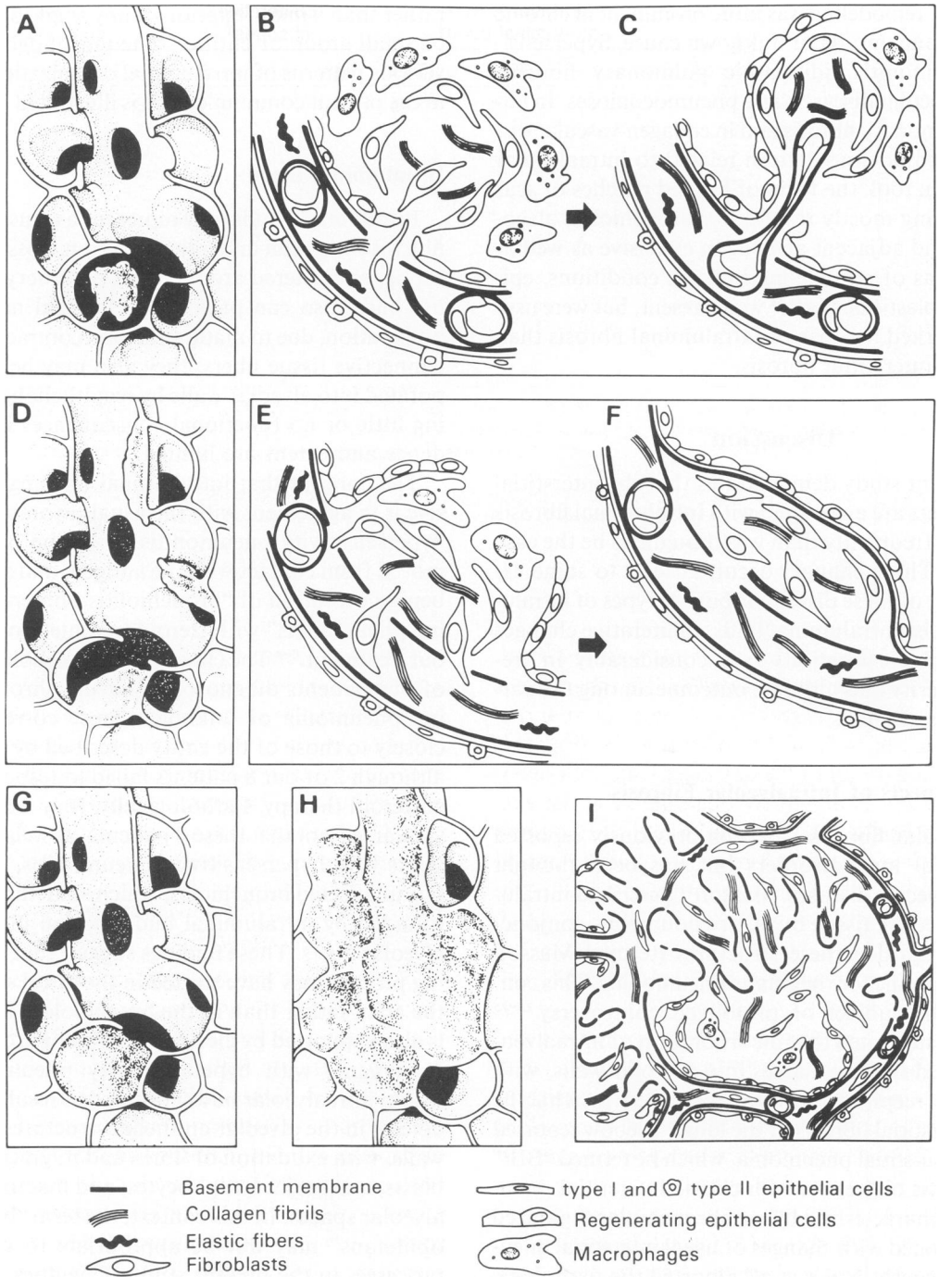


**Figure 21**—Pathogenesis of intraluminal fibrosis. **A**—Diagram of an intraalveolar bud which projects into the lumen of an alveolus and is attached to the alveolar wall by a thin stalk. **B**—Early stage of an intraalveolar bud is characterized by fibroblasts migrating through a defect in the alveolar epithelial basement membrane. The bud contains a small amount of collagen, and its surface is lined by macrophages. **C**—In later stages, the bud becomes lined by regenerating epithelial cells and may contain capillaries. **D**—Diagram of areas of mural incorporation. **E** and **F**—Fibroblasts in an area of mural incorporation have migrated into the luminal region (**E**) through defects in the alveolar epithelial basement membrane. This area is incorporated into the alveolar wall (**F**) as it becomes reepithelialized. **G**—Diagram of an area of obliteration of an alveolus. **H**—Diagram of an area of pulmonary remodeling related to the obliteration of an alveolar duct and several adjacent alveoli. **I**—Convoluted segments of remnants of epithelial basement membranes remain in fibrotic areas which represent former lumens of obliterated alveoli.

in patients with drug-induced pneumonitis, chronic eosinophilic pneumonia, and Legionnaire's disease. The focal type of remodeling was more prominent in chronic organizing pneumonia of unknown cause, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, collagen-vascular diseases, and pneumoconioses. In idiopathic pulmonary fibrosis and in collagen-vascular diseases, the remodeling pattern related to intraalveolar fibrosis often took the form of limited patches of scar tissue affecting mostly respiratory bronchioles, alveolar ducts, and adjacent alveoli. In extensive as well as in focal areas of remodeling in these conditions, epithelial metaplastic changes[21] were present, but were usually less marked in areas of intraluminal fibrosis than in areas of interstitial fibrosis.

## Discussion

The present study demonstrates that the interstitial lung disorders are associated with intraluminal fibrosis much more frequently than was thought to be the case previously. These changes occur, at least to some extent, in most of these disorders, but the types of intraluminal fibrosis (intraluminal buds, obliterative changes and mural incorporation) vary considerably in frequency, severity and ultimate outcome among the various entities studied.

### General Aspects of Intraalveolar Fibrosis

Intraalveolar fibrosis has been previously reported in interstitial lung disorders but has been thought limited to specific diseases. Masson[22] described intraluminal connective tissue buds, or "bourgeons conjonctifs," and regarded these structures (termed Masson bodies) as specific for rheumatic pneumonitis. This concept was the subject of prolonged controversy.[23-25] Spencer[2,10] suggested that incorporation of intraalveolar organized fibrotic masses into alveolar walls, with subsequent reepithelialization, occurred in what he called "interstitial fibrosis of the lung." Liebow reported a type of interstitial pneumonia, which he termed "BIP" (bronchiolitis obliterans with classic interstitial pneumonia), as characterized by intrabronchiolar organized plugs associated with changes of usual interstitial pneumonia.[1] Recently, Epler et al[8] reported the pathologic and clinical features of "bronchiolitis obliterans organizing pneumonia," in which plugs of edematous granulation tissue involve terminal and respiratory bronchioles and extend into alveolar ducts. Intraluminal fibrosis has also been described in paraquat toxicity,[26-37] Legionnaire's disease,[38] drug-induced pneumonitis,[11,39] collagen-vascular diseases,[40-45] and hypersensitivity pneumonitis.[19] Thus, intraluminal fibrosis is a widespread phenomenon in the interstitial lung disorders and probably represents a type of response to injury rather than a manifestation of any single disease entity or small group of entities. The morphogenesis of the various patterns of intraluminal organization described in the present communication is illustrated in Figure 21.

### Intraluminal Buds

Intraluminal buds may represent a transient form of fibrosis which can undergo resorption, possibly by macrophages clustered around their periphery. Intraluminal buds also can progress to luminal narrowing or obliteration, due to maturation and contraction of their connective tissue fibers; they also may become incorporated into alveolar walls by reepithelialization, leaving little or no functional consequences if their incidence and extent are limited.

The concept that intraluminal buds can be regressive is in agreement with the usual favorable course of hypersensitivity pneumonitis when the patient is removed from contact with the antigen, and also with the benign evolution of "bronchiolitis obliterans organizing pneumonias" with steroid treatment or even without treatment.[6-8] The clinical and morphologic features of our patients diagnosed as having chronic organizing pneumonia of unknown cause correspond very closely to those of the entity described by Epler et al,[8] although 2 of our 8 patients failed to respond to corticosteroid therapy. Pathologically, they were also very similar, except that these 8 patients, as well as some patients with hypersensitivity pneumonitis, had numerous unaffected bronchioles, which sometimes were surrounded by intraluminal buds located in alveoli and alveolar ducts. These findings suggest that the organizing process may have started in the distal structures of the acini rather than in the bronchioles. This concept is also supported by electron-microscopic observations in patients with hypersensitivity pneumonitis,[19] in whom intraalveolar buds appeared to result from small defects in the alveolar epithelial structures of alveolar walls, with exudation of fibrin and migration of fibroblasts, mast cells, lymphocytes, and macrophages into alveolar spaces. In this context, the term "bronchiolitis obliterans" may not be appropriate to describe the processes in the present study. This does not exclude the possibility that lesions similar to those described in the present study sometimes occur primarily within bronchioles as a result of other processes, including inhalation of toxic fumes,[48] bronchiolar infections,[49] or other causes.[50-53] In this regard, "bronchiolitis obliterans" and "intraalveolar buds" may represent similar patterns of response to injury in bronchioles versus alveolar ducts and alveoli, respectively.

### Obliterative Changes

Obliterative changes may result from expansion of intraalveolar buds. However, broad areas of damage or disappearance of the epithelial lining usually occur in areas of obliterative changes, suggesting that these lesions are related to more severe injury than is the case with intraluminal buds. When luminal obliteration occurs, alveolar structures that had been separated from each other by an air space become joined by connective tissue which fills the obliterated air space. Concomitant reduction of functional alveolar-capillary units and vascular redistribution may result from this change. Therefore, obliterative changes likely induce permanent remodeling.

### Mural Incorporation

Mural incorporation can be considered as a minor form of alveolar tissue remodeling that results in permanent thickening of alveolar walls. In drug-induced pneumonitis, in paraquat poisoning, and also to some extent in Legionnaire's disease, the architectural changes that we observed in association with intraluminal fibrosis were prominent and were similar to those observed in healing stages of diffuse alveolar damage described in the adult respiratory distress syndrome.[9,46-48,54] In diffuse alveolar damage, however, the changes are more extensive, more acute, and usually more homogeneous than those described in the present study. In diffuse alveolar damage, two types of alterations (which are considered to be sequential) have been described: 1) exudative lesions, with hyaline membrane formation and/or intraalveolar fibrin, and 2) an organizing process leading to fibrosis.[54] In descriptions of the latter process, emphasis usually has been placed on the resulting interstitial fibrosis, but associated intraalveolar fibrosis also has been found, especially in paraquat lung.[26-37]

Comparisons often have been made between the changes in diffuse alveolar damage and the early features that are supposed to occur in idiopathic pulmonary fibrosis.[4,54] Spencer[10] described intraluminal organization as occurring rarely in idiopathic pulmonary fibrosis, and then mainly in the form of incorporation of fibrous masses into alveolar walls; however, the results of our study suggest that intraluminal fibrosis occurs more commonly in idiopathic pulmonary fibrosis than has been thought to be the case previously. In fact, while intraluminal buds were rarely observed in this disease, incorporation and remodeling patterns clearly occurred in association with interstitial changes, at least to some extent, in more than 70% of our cases of idiopathic pulmonary fibrosis. These changes appear to reflect the tendency of this disease to follow a course of progressive, severe fibrosis, as opposed to other disorders in which such changes either occur to a very limited extent (sarcoidosis and histiocytosis X) or tend to be regressive (hypersensitivity pneumonitis and "bronchiolitis obliterans organizing pneumonia").

### Morphogenesis of Intraalveolar Fibrosis

The crucial feature in the morphogenesis of the various patterns of intraluminal fibrosis that develops in human diffuse alveolar damage, in the animal model of paraquat toxicity, and in other disorders is the migration of fibroblasts or myofibroblasts to the luminal side of partially disrupted and denuded epithelial basement membranes through a defect induced in the alveolar epithelial lining and in its basement membrane by injury or inflammation.[46,47] The various chemotactic and growth-inducing factors, including fibronectin,[55] that are released by activated macrophages and other inflammatory cells[5,55] probably play a role in inducing septal fibroblasts or myofibroblasts to migrate through the epithelial defect, to replicate and to produce connective tissue components, which are deposited beyond the luminal side of the epithelial basement membrane.[37] The epithelial defect produced by certain types of initial injury or stimulus may be limited, and may result only in intraalveolar bud formation, as is often the case in hypersensitivity pneumonitis.[19] When the alterations are more severe, as in conditions resulting in diffuse alveolar damage, severe intraalveolar fibrosis, with collapse and obliteration of alveolar lumens, is more likely to occur. The connective tissue components produced by fibroblasts and/or myofibroblasts in intraalveolar locations can seal off the gap in the damaged alveolar epithelial layer. This process, in frequent association with some degree of atelectasis, gradually results in a fibrous tissue mass which comprises intraluminal and collapsed mural components. A further step in the organizing and remodeling process is reepithelialization of the surface of this composite mass by cells which may be derived either from remnants of the alveolar lining or from bronchiolar cells.[21] When this step has been completed (which does not always occur), the fibrous tissue mass is no longer intraluminal, but has become incorporated into the thickened interstitium. In this situation, which is characteristically observed in idiopathic pulmonary fibrosis, the intraluminal and interstitial components of the final changes often are difficult to distinguish. The PAM stain is useful in making this distinction, because it outlines areas of incorporation (Figure 7).

In conclusion, different patterns of intraluminal organization and fibrosis were observed by light- and electron-microscopic study in a large group of patients

with various interstitial pulmonary disorders. The overall frequency of these phenomena varied according to the different disease entities. Some of the patterns of intraalveolar fibrosis were observed preferentially in certain conditions. The mechanism common to all patterns of intraluminal fibrosis was the migration of fibroblasts and myofibroblasts from the interstitial compartment into air spaces, through defects caused by injury or inflammation in the epithelial lining and its basement membrane. This mechanism plays an important role in processes of remodeling, because it mediates the fusion of adjacent alveolar structures by intraalveolar connective tissue components. The severity and extent of intraluminal organization and/or fibrosis, which in some circumstances are reversible lesions, depend in part on the nature and severity of the initial epithelial injury and on the associated interstitial changes.

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