Sclerosing Alveolitis Induced by Cyclophosphamide

Ultrastructural Observations on Alveolar Injury and Repair

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Adult rats received, intraperitoneally, 20 mg/100 g body weight of cyclophosphamide and were killed 1, 2, 3, 4, 7, 14, 21, and 28 days thereafter. Lung samples were studied by light and electron microscopy. Light microscopy revealed septal and intraalveolar hemorrhages at 2 days and hyaline membranes at 4 days. At 1 to 2 weeks the alveoli were reepithelialized; beyond these intervals there was septal thickening with increased septal cells and interstitial substance. Electron microscopy showed capillary endothelial blebs, membranous pneumocyte injury and sloughing, and severe septal edema at 1 to 2 days. At 4 days some granular pneumocytes appeared altered. At 1 week the alveoli were reepithelialized by prominent granular pneumocytes. Beyond these intervals there was septal thickening with abundant septal cells, debris, collagen, elastin and microfibrils. Some septal elements showed features consistent with "contractile interstitial cells." There was also alveolar collapse indicated by "trapped" granular pneumocytes surrounded by septal cells and fibers. Occasional granular pneumocytes showed large intracytoplasmic cavities. Cyclophosphamide can induce severe injury involving all alveolar components. The partly denuded alveoli are reepithelialized by proliferating granular pneumocytes, thus confirming their importance in alveolar repair. The subsequent development of sclerosing alveolitis suggests that cyclophosphamide may offer a useful experimental model for the study of alveolar injury and repair. The role of the septal "contractile interstitial cells" in the development of septal fibrosis and the possibility that these lesions are reversible remain to be clarified. (Am J Pathol 81:513–530, 1975)

THE CLINICAL IMPORTANCE and relative frequency of iatrogenically induced pulmonary diseases are being increasingly recognized.[1-3] In a recent review, over 30 individual drugs or groups of drugs were linked to various forms of acute and/or chronic lung disorders;[4] if agents such as oxygen, radiation, and some illicitly obtained drugs were added, the list climbs to well over 40. Of the chemotherapeutic agents generally regarded as potentially hazardous to the lungs, nitrofurantoin and busulfan are perhaps the best known;[5-7] more recently, bleomycin has joined the list.[8-10]

Cyclophosphamide (Cytoxan, Endoxan) is a nitrogen mustard–type drug widely used as an antineoplastic and immunosuppressive.[11,12]

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Though cyclophosphamide has proven less toxic than earlier nitrogen mustards, lesions involving various organs and tissues have been reported.[13] Moreover, characteristic urinary bladder, hepatic, and renal lesions have been described clinically and reproduced experimentally.[13-15] Acute respiratory complications following nitrogen mustards, including cyclophosphamide, consist mostly of bronchial hypersecretion, though this seldom constitutes an important part of the clinical picture.[13] However, there are several clinical reports describing chronic pneumonitis with interstitial fibrosis as long-term sequelae partly or totally attributed to cyclophosphamide.[4,16-20]

During the course of a short-term cyclophosphamide-related experiment,[21] we consistently observed small foci of pulmonary hemorrhage. We repeated and extended those experiments in an attempt to establish the sequence of alveolar lesions and repair; preliminary reports on these investigations have been recently published.[22,23]

Materials and Methods

Adult male Fischer rats were given, intraperitoneally, a single dose of 20 mg/100 g body weight of cyclophosphamide in distilled water as previously described,[14] and were sacrificed in groups of three at 1, 2, 3, 4, 7, 14, 21 and 28 days thereafter. Rats given intraperitoneal distilled water and untreated animals served as controls. All animals survived for the duration of the experiments.

Lung samples for light microscopy were fixed in buffered formalin and embedded in paraffin; sections were stained with hematoxylin and eosin and Masson's trichrome.

Small fragments of lung for electron microscopy were fixed in cacodylate-buffered 2% glutaraldehyde for 3 to 6 hours, washed overnight in the same buffer and postfixed in 1% osmium tetroxide for 1 hour. Tissues were then dehydrated in graded ethanols and embedded in Epon.[24] Thick (1-μ) sections were stained with toluidine blue.[25] Thin sections were cut with diamond knives on an LKB automatic ultramicrotome, mounted upon carbon and Formvar-coated copper grids and stained with uranyl acetate and lead hydroxide.[26] Sections were examined with an Hitachi 12A or Phillips 200 electron microscopes. Original magnifications ranged from 1,200 to 11,600; from these photographic enlargements were prepared.

Results

Light Microscopy

The earliest detectable changes were observed at 48 hours after cyclophosphamide administration and consisted of irregularly distributed foci of perivascular edema, septal widening, capillary congestion and minute hemorrhages (Figure 1). Between 4 and 7 days after treatment, many alveoli contained debris and macrophages; focal hyaline membrane formation was seen (Figure 2). The most conspicuous changes, however, were

alveolar cell hyperplasia and a notable increase in septal cellularity and interstitial material (Figure 3). At subsequent intervals, those changes persisted, and the septal fibrosis became focally more severe; between 3 to 4 weeks, occasional alveolar cells displayed considerable atypism (Figure 4).

Electron Microscopy

At 24 hours, increased endothelial pinocytosis was observed; between 24 to 48 hours there was conspicuous endothelial bleb formation and focal sloughing (Figure 5). Also, at 24 hours there was evidence of membranous pneumocyte injury with focal sloughing and basal lamina denudation (Figure 6); concomitantly, prominent septal edema was evident (Figure 7). Alveolar spaces contained abundant macrophages; cell debris, lattice-type, and lamellated inclusion material as well as fibrin were apparent between 48 to 96 hours. Granular pneumocytes displayed frequent extrusion of osmiophilic inclusion material between 24 to 72 hours. At 96 hours, there was evidence of granular pneumocyte injury and necrosis; focal denudation of the epithelial basal lamina and hyaline membranes were evident (Figure 8). Between 1 to 2 weeks after cyclophosphamide injection the alveolar surfaces were covered by granular pneumocytes (Figure 9); these cells remained prominent in number and appearance at subsequent intervals. The septa were consistently widened and contained abundant septal cells, collagen, elastin, microfibrils, and conspicuous cell debris; few inflammatory cells were seen (Figure 10). Some septal cells showed packs of cytoplasmic filaments with cell membrane attachments and appeared partly encompassed within basal laminae (Figure 11). Occasional foci of denuded basal laminae displaying irregular curling were evident (Figure 12). Between 2 to 4 weeks, focal alveolar collapse was recognized by the presence of numerous "trapped" granular pneumocytes which step sections revealed to be completely surrounded by connective tissue elements and fibers (Figure 13). Occasional, large granular pneumocytes displayed conspicuous, irregularly shaped intracytoplasmic lumina (Figure 14). Control lungs displayed no light microscopic or ultrastructural abnormalities.

Discussion

Adult rats given a single dose of cyclophosphamide sustained notable alveolar injury involving all components of the wall. Early changes included endothelial cell and membranous pneumocyte disruption and sloughing, focal hyaline membrane formation, severe septal edema, and

moderate granular pneumocyte injury. Subsequent changes consisted of granular pneumocyte hyperplasia, septal cell proliferation, and septal fibrogenesis with focal alveolar collapse.

This sequence of events in alveolar injury and repair is basically similar to that observed in a variety of human diseases and experimental models.[27-32] Earlier work with high oxygen concentrations and other models suggested that capillary endothelial cells were the initial target in alveolar injury;[33] however, subsequent investigations indicated that both endothelial capillary and epithelial injury may develop more or less synchronously.[29,30] While those phenomena were thought to lead to septal edema,[34-36]more recent work on isolated perfused lungs ventilated with various gaseous mixtures[37-39] and bleomycin toxicity experiments[40] indicated that injury to larger pulmonary vessels may also contribute to septal edema development. If sufficient alveolar injury and leakage occur, hyaline membrane formation may follow regardless of the causal agent of injury.[28,30] Alveolar reepithelialization on the basis of granular pneumocytic proliferation appears likewise nonspecific; indeed, the consistent observation of this phenomenon led to the concept that granular pneumocytes may be the reserve cell for alveolar repair regardless of the initial injury.[28,30,31,41-43] And inferentially, it has been suggested that conditions such as desquamative interstitial pneumonia may result from different causes rather than being a distinct disease entity.[44,45] The occurrence of atypical granular pneumocytes in various forms of alveolar injury is well known; this finding is most conspicuous when alkylating or radiomimetic agents are the culprits.[6,46] However, morphologically similar cells may also be observed in oxygen-induced lesions,[30] and their long-term significance remains undetermined. Our observations of septal cell proliferation, focal collapse, and septal fibrogenesis follow very closely those made in radiation- and oxygen-induced injuries;[28,30,43,47] light microsctpic and ultrastructural findings in bleomycin-induced lesions seemingly conform to the same pattern.[8,9,40] The presence of irregular and curled basal lamina in areas of severe injury appears to confirm their role in orderly alveolar reconstruction.[48] The recently described septal "contractile interstitial cells,"[49] presumed to play a role in ventilation/perfusion ratio, were also observed in our material. Structurally and functionally similar cells sharing some features of fibroblasts, and smooth muscle elements (myofibroblasts) have evoked considerable interest and have been described in a variety of reparative and proliferative tissues.[50-52] Though their actual significance in our experimental model remains unclear, it is tempting to speculate on their possible role in alveolar septal repair.

The pathogenesis of drug-induced pulmonary diseases remains con-

troversial; a possible immune mechanism has been repeatedly suggested.[4] In the case of cyclophosphamide, however, the possibility of direct alveolar injury by its alkylating chains merits consideration. The original rationale that led to the linking of the cyclic phosphoric group to the actively alkylating chains to form cyclophosphamide was the high concentrations of phosphatases and phosphamidases known to be present in some malignant neoplasms; it was assumed that those enzymes would split and consequently activate the drug within the tumors, thereby avoiding the systemic effects of earlier nitrogen mustards.[13] However, it became apparent that the liver was capable of activating the drug,[53] and that to a lesser extent kidneys and lungs could play a similar role.[54] The metabolic potential of the lung was also indicated in a report on carbon tetrachloride–induced alveolar injury.[29] A recent review emphasizes the complexity of the lungs' metabolic activities other than their respiratory role and the relationships between some hepatic and pulmonary functions, including the deactivation of biologically active substances.[55,56] Earlier clinical reports on coexistence of hepatic and pulmonary diseases also point in that direction.[57] These data as well as our observations suggests that at least the initial phases of cyclophosphamide-induced alveolar injury may be due to the direct toxic effect of the alkylating portions of the drug which may be activated elsewhere and/or *in situ*. This notion parallels previous clinical speculation.[16]

Noteworthy in our experimental model was that a single dose of cyclophosphamide proved capable of producing substantial alveolar injury. But however extensive these lesions may appear, the notion of possible reversibility cannot be discounted. Experimental evidence suggests that similarly severe alveolar lesions caused by high oxygen concentrations may in fact be to a large extent reversible if the animals are successfully weaned from the oxygen.[43,47] And although some alveolar abnormalities could be demonstrated morphologically and morphometrically, functional recovery appeared almost complete.[43,47] Clinical observations also indicated that some patients with extensive drug-induced alveolar fibrosis may partially recover following withdrawal of the offending drug aided at times by corticoid therapy.[7,18] In this context, it is of interest that in the late stages of our experiments we observed granular pneumocytes with conspicuous intracytoplasmic cavities the development of which has been recently suggested as a possible initial step in alveolar reconstruction.[58]

We conclude that our experiments on cyclophosphamide-induced alveolar injury or some modification thereof—including a different schedule of drug administration or, possibly, a combination with other substances—may provide useful experimental models. These, in turn, would facilitate

the study of variable patterns of alveolar injury and repair as well as the possibility of arrested development and reversibility of the lesions.

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[*Illustrations follow*]

Legends for Figures

Figure 1—Rat lung 48 hours after cyclophosphamide administration. Note congestion and focal septal and intraalveolar hemorrhages. (H&E, × 140)

Figure 2—Rat lung 96 hours after administration of cyclophosphamide. Notice persistent focal hemorrhages and the presence of hyaline membranes (*arrows*). (H&E, × 160)

Figure 3—Rat lung 1 week after cyclophosphamide injection. Note septal hypercellularity and increased interstitial material. Some hyaline membranes are evident (*arrows*). (H&E, × 180)

Figure 4—Rat lung 4 weeks after cyclophosphamide administration. Notice abundant cells and fibrillar material in the widened septa. Alveolar cells are conspicuous and focally atypical (*arrow*). Alveolar lumina contain desquamated cells and debris. (Masson's trichrome, × 460)

Figure 5—Alveolar capillary 24 hours after cyclophosphamide injection. Notice extensive endothelial cytoplasmic disruption and large blebs (*b*) with rupture of the cell membrane. Less severe injury is evident on the epithelial aspect (*arrows*). (× 12,100)

Figure 6—Alveolus 24 hours after cyclophosphamide administration. Note severe membranous pneumocyte injury with focal basal lamina denudation (*arrows*). A granular pneumocyte (*gp*) appears unaltered. (× 13,800)

Figure 7—Alveolar septum 48 hours after cyclophosphamide administration. Notice the widening of the septal space (*S*), the indistinctly outlined fibers, and the abundant debris. (× 14,700)

Figure 8—Alveolus 96 hours after cyclophosphamide injection. Note severe alterations in the cytoplasm of the granular pneumocyte (*gp*); rupture of the cell membrane and nuclear changes are also evident. (× 13,600) **Inset**—Focally denuded basal lamina (*arrow*) is partly covered by cytoplasmic debris (*d*) and fibrin (*f*). (× 23,500)

Figure 9—Alveolar space (*A*) is lined by numerous prominent granular pneumocytes (*gp*). Capillaries (*C*) and abundant fibrillar stroma are also seen. One week after injection of cyclophosphamide. (× 12,600)

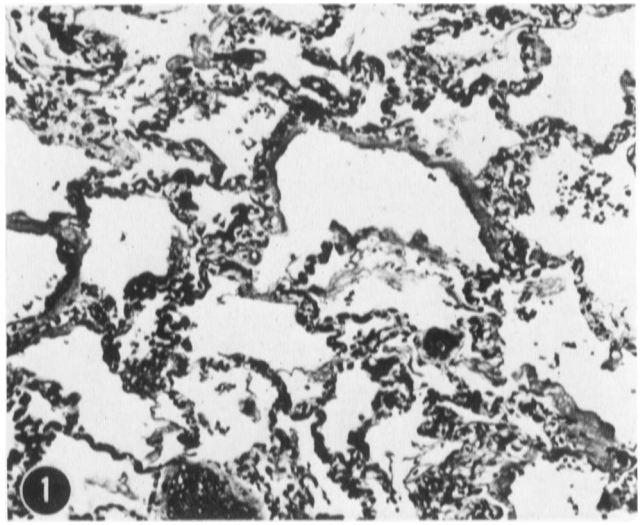
Figure 10—Adjacent alveoli (*A*) and capillaries (*C*). 2 weeks after cyclophosphamide administration. Notice exceedingly abundant interstitial material, particular collagen, as well as numerous cytoplasmic processes of septal cells (*sc*). (× 7100)

Figure 11—Septal cell with conspicuous bundles of cytoplasmic filaments (*cf*). An indistinct basal lamina (*arrow*) is seen. Notice abundant surrounding collagen (*c*) and elastin (*e*). Two weeks after administration of cyclophosphamide. (× 12,000) Inset—Higher power view of cytoplasmic filaments (*cf*) and dense bodies (*arrows*) (× 26,500)

Figure 12—Alveolus 2 weeks after cyclophosphamide injection. The irregular epithelial basal lamina displays conspicuous curling; note the sloughed granular pneumocytes (*gp*). The edematous septum (*S*) shows debris and abundant microfibrils (*mf*). (× 17,100)

Figure 13—Markedly thickened alveolar septum displaying two recognizable granular pneumocytes (*gp*) encompassed by stromal components. Notice prominent collagen (*c*), elastin (*e*), and abundant debris (*d*). Three weeks after cyclophosphamide. (× 15,300)

Figure 14—Markedly thickened septum showing a small slit-like alveolar lumen (*A*); a granular pneumocyte displays an intracytoplasmic cavity (*ic*). Notice abundant stroma, septal cells (*sc*) and remnants of two granular pneumocytes (*gp*) in upper center. Four weeks after cyclophosphamide injection. (× 7100)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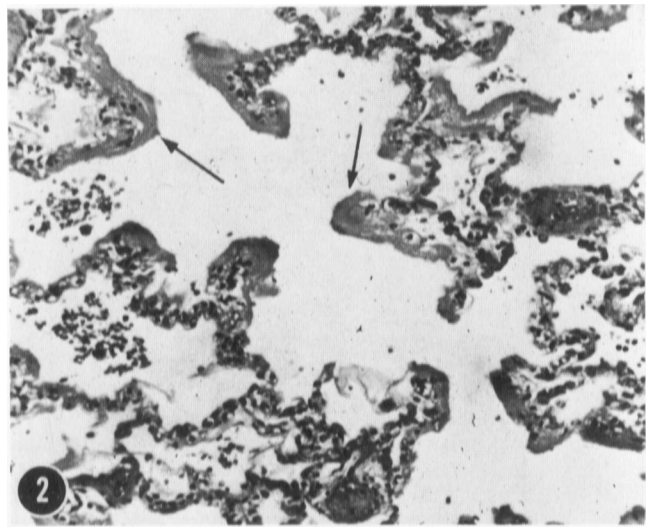
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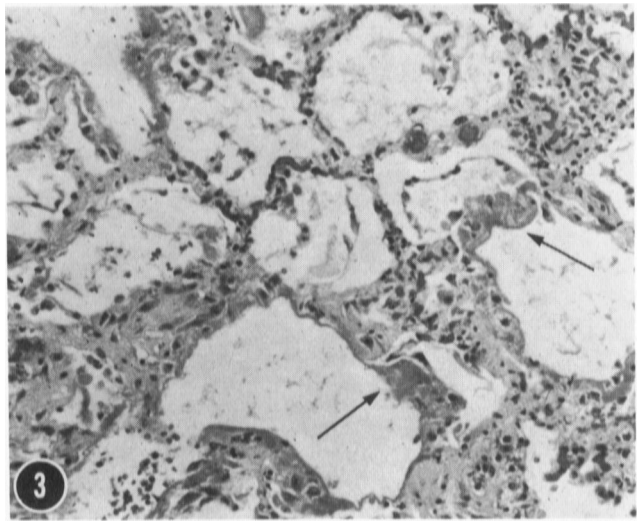
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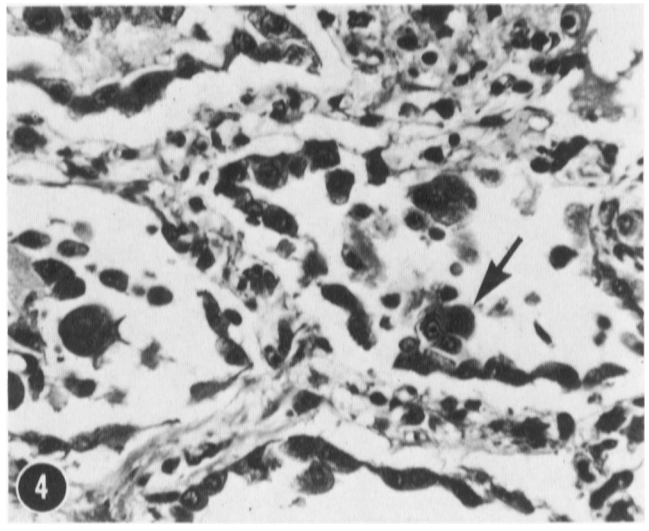
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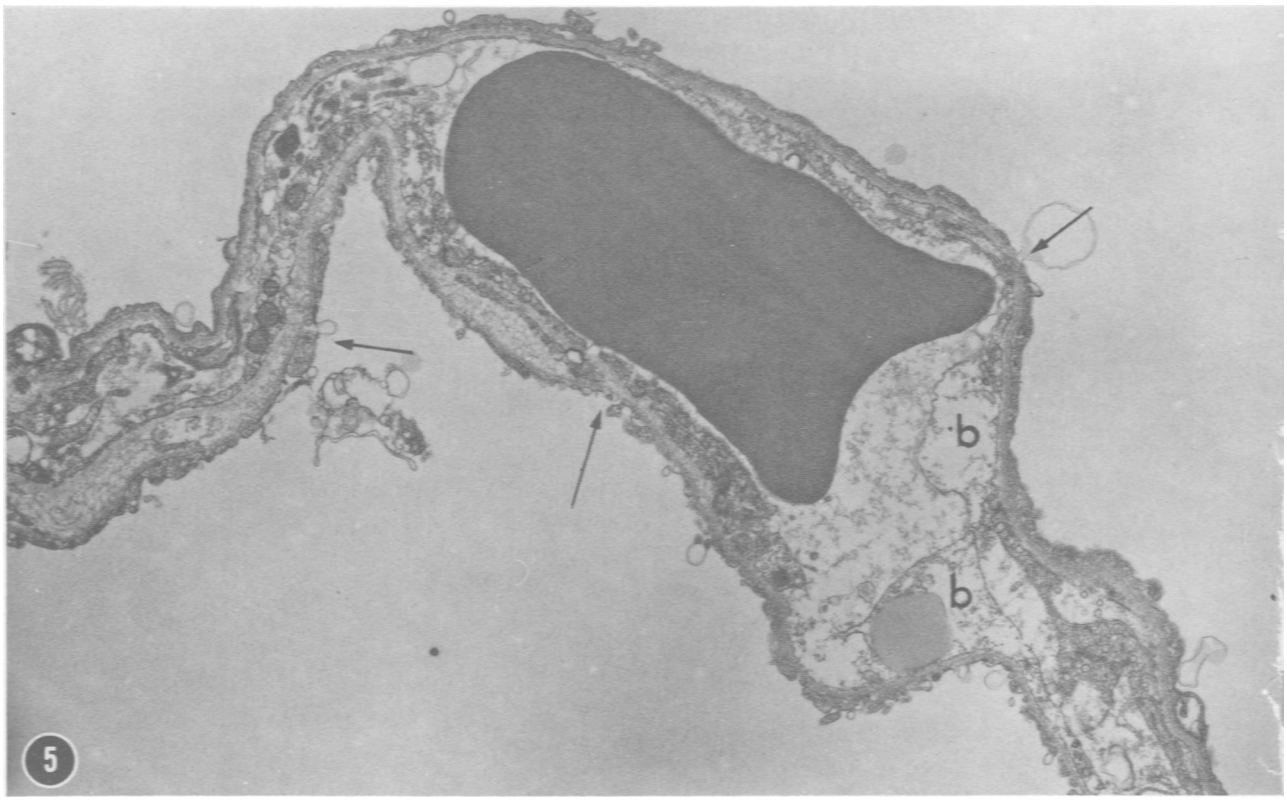
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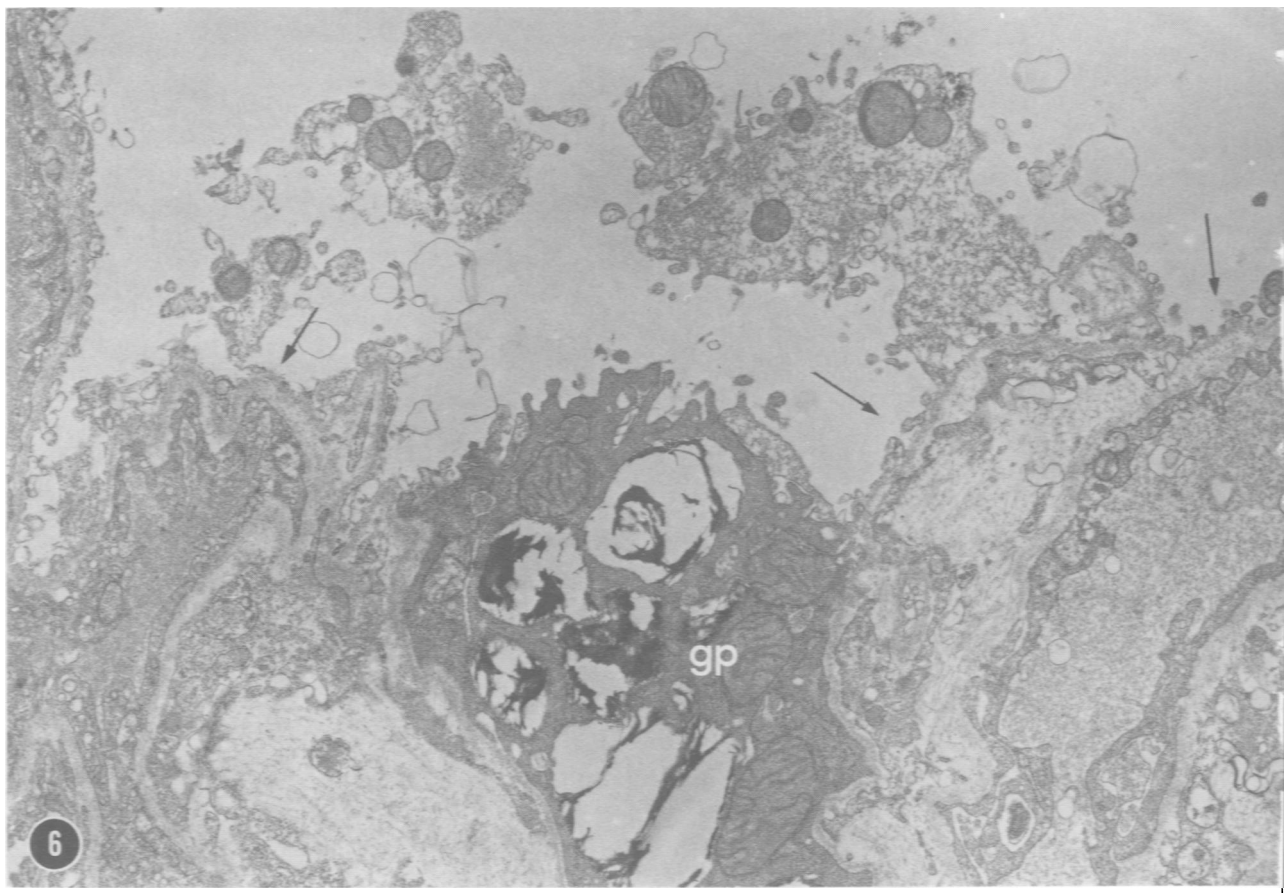
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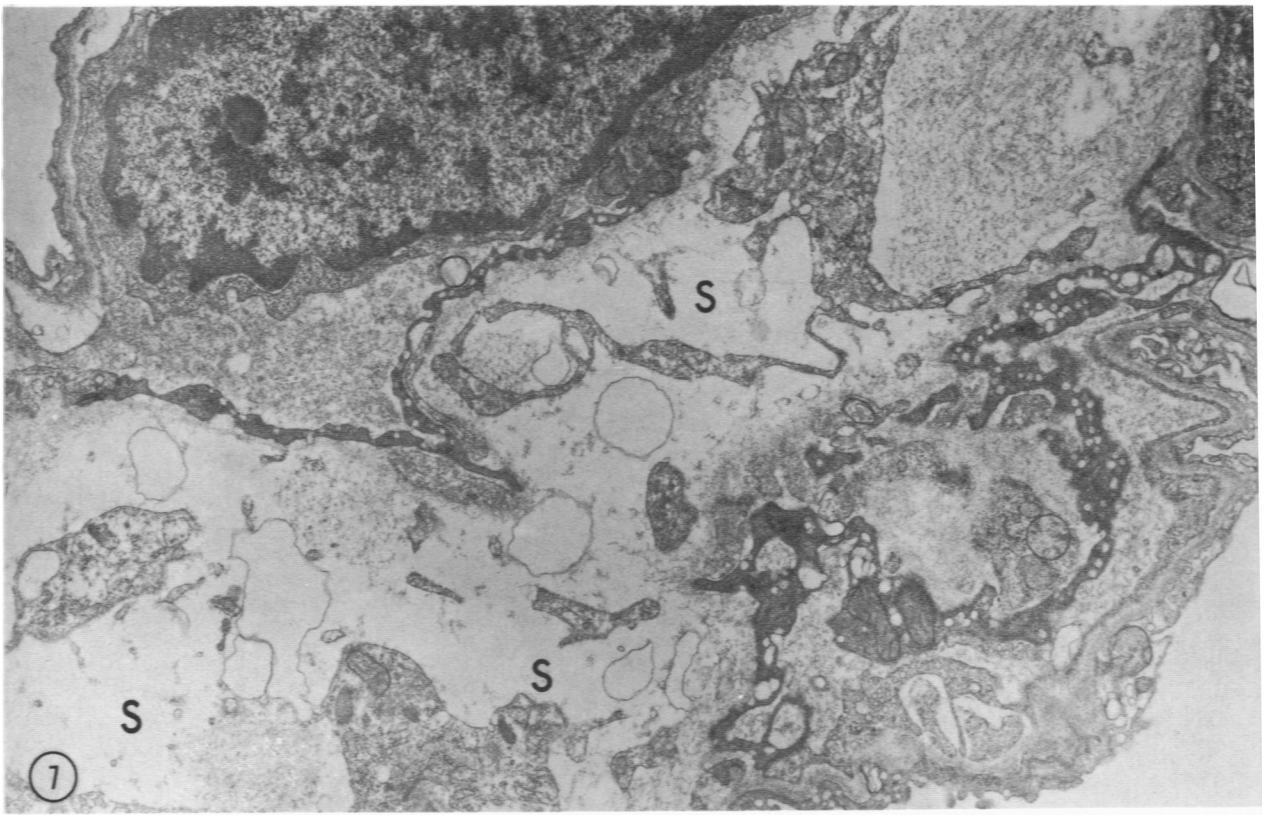
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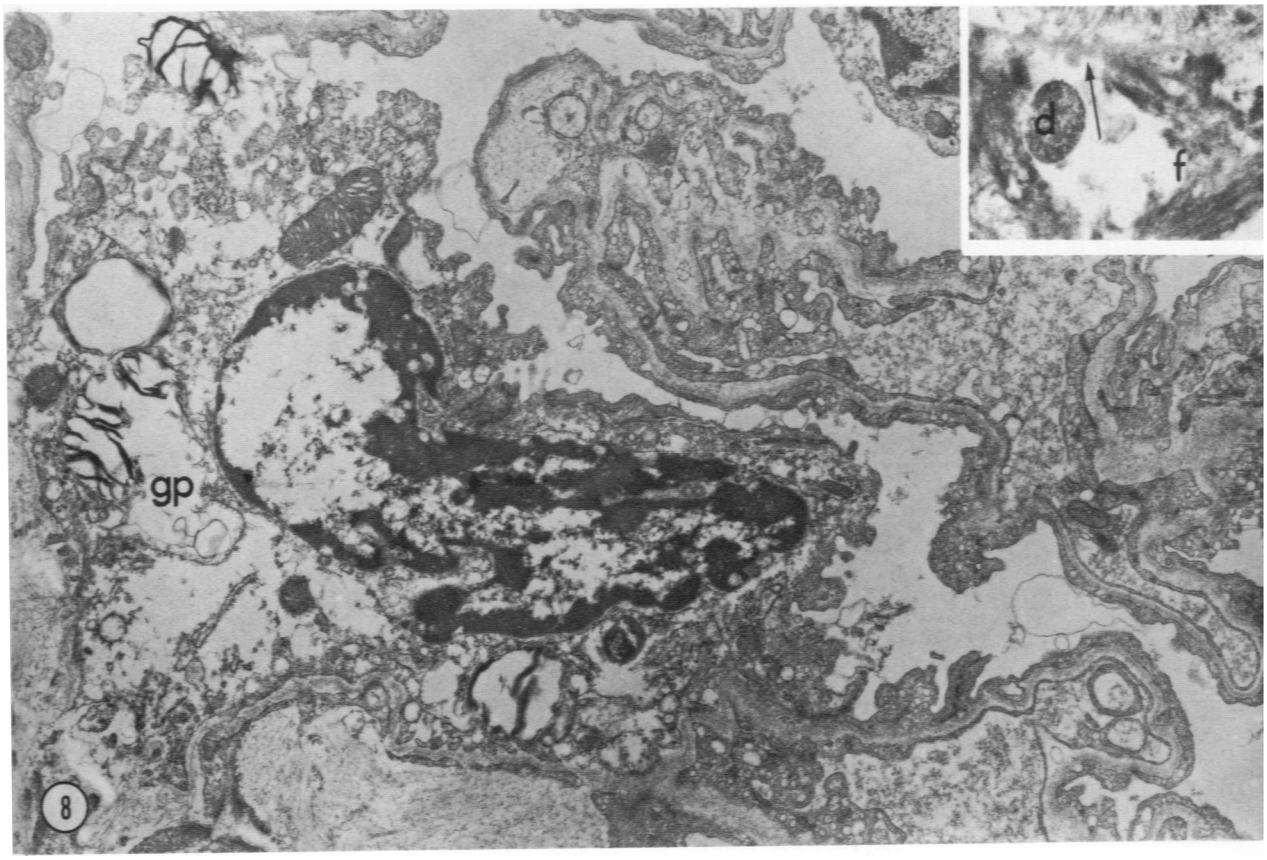
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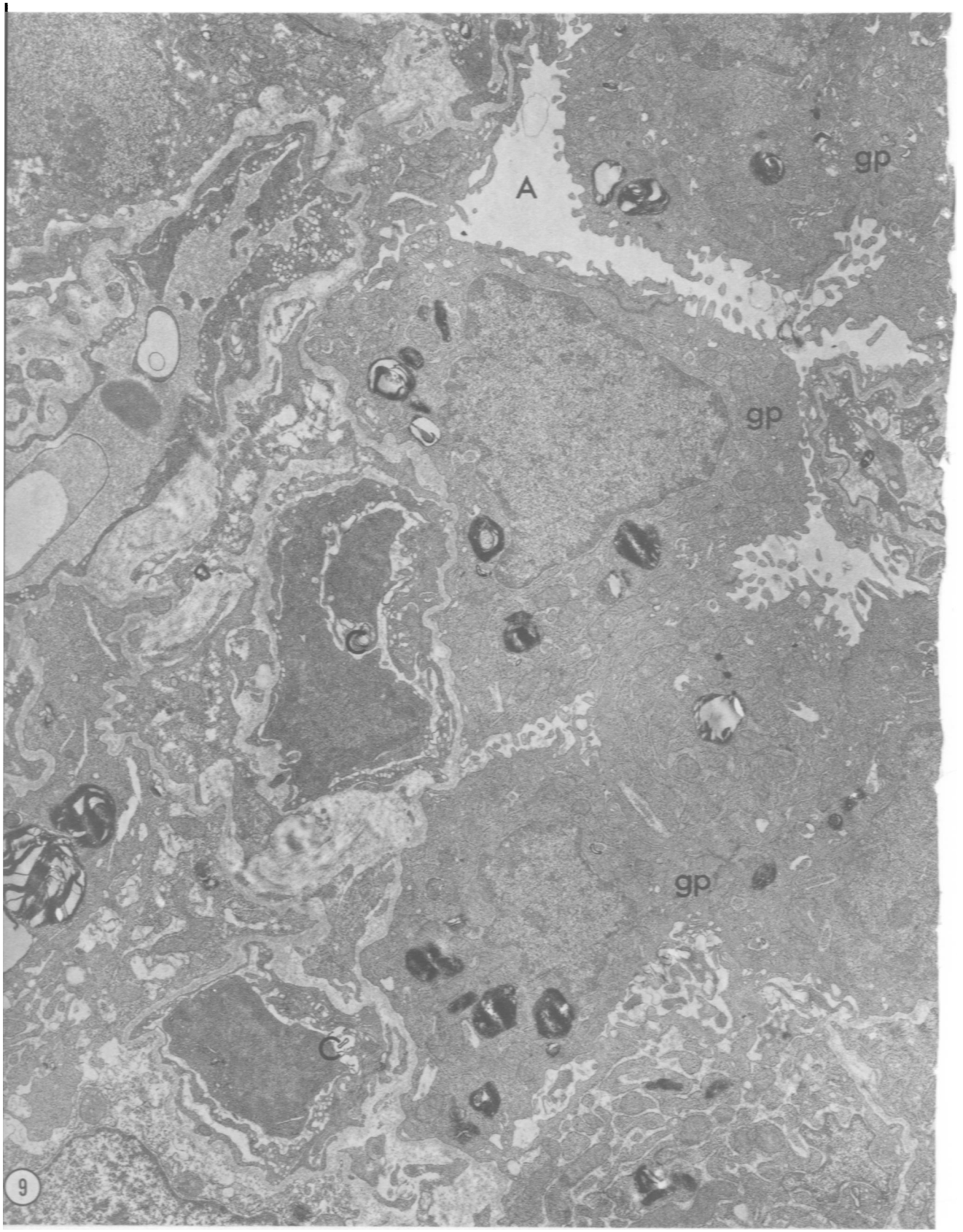

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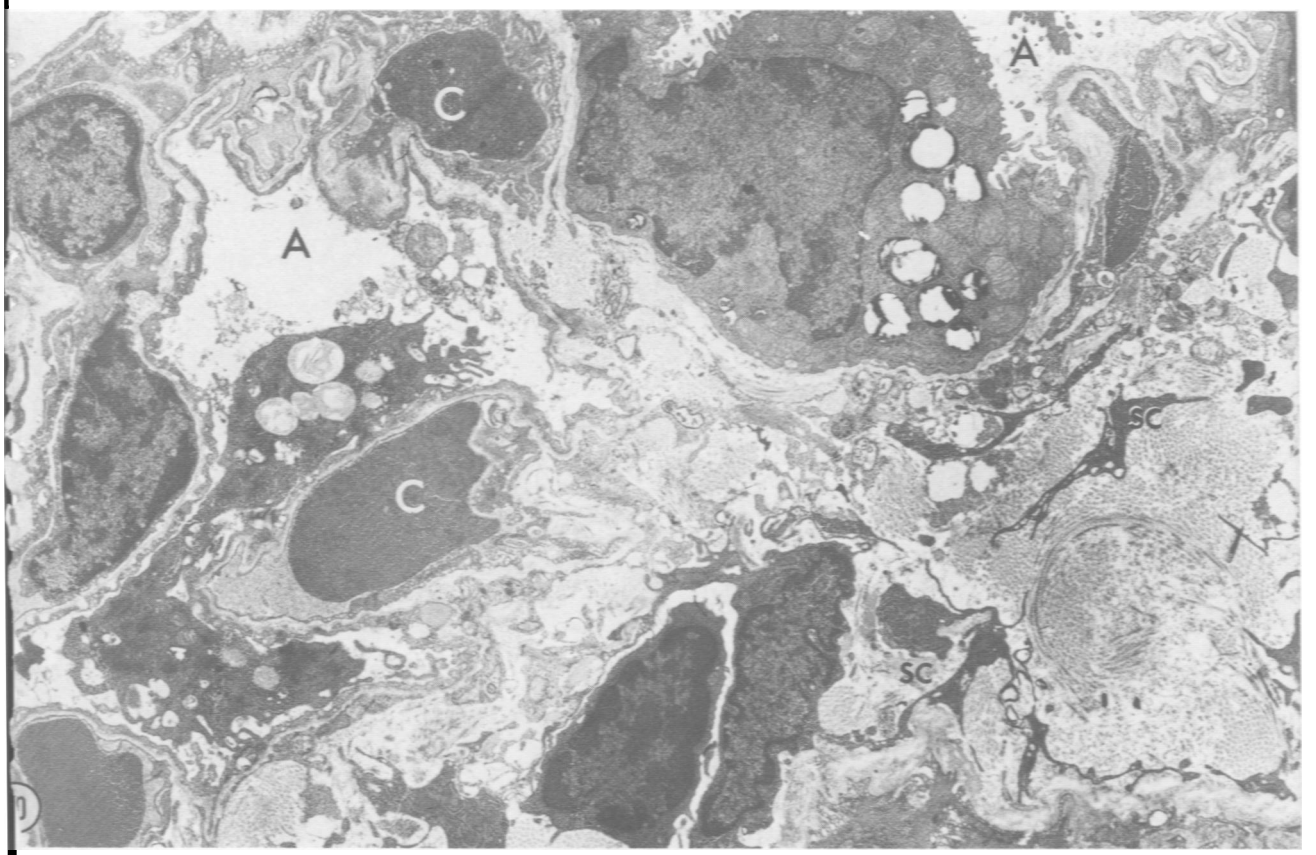
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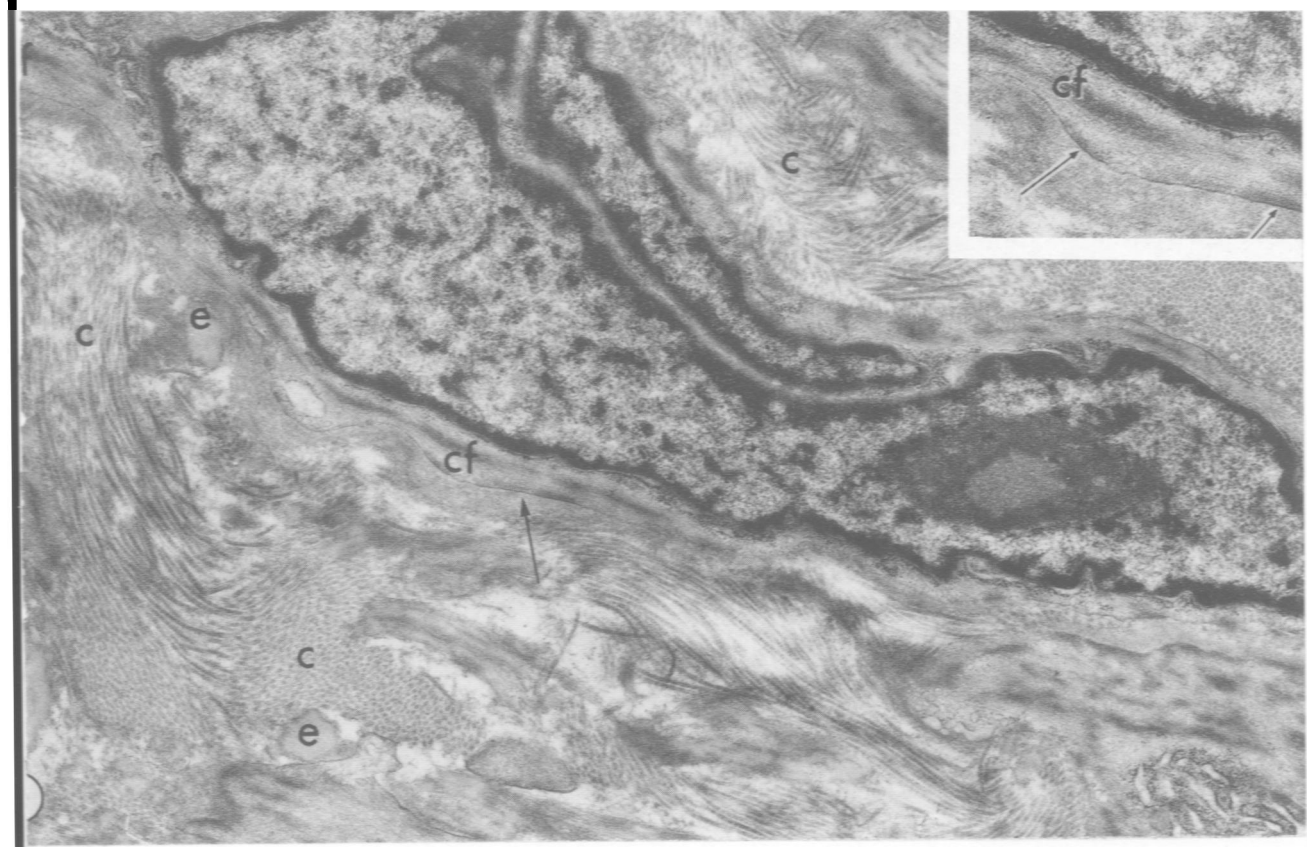
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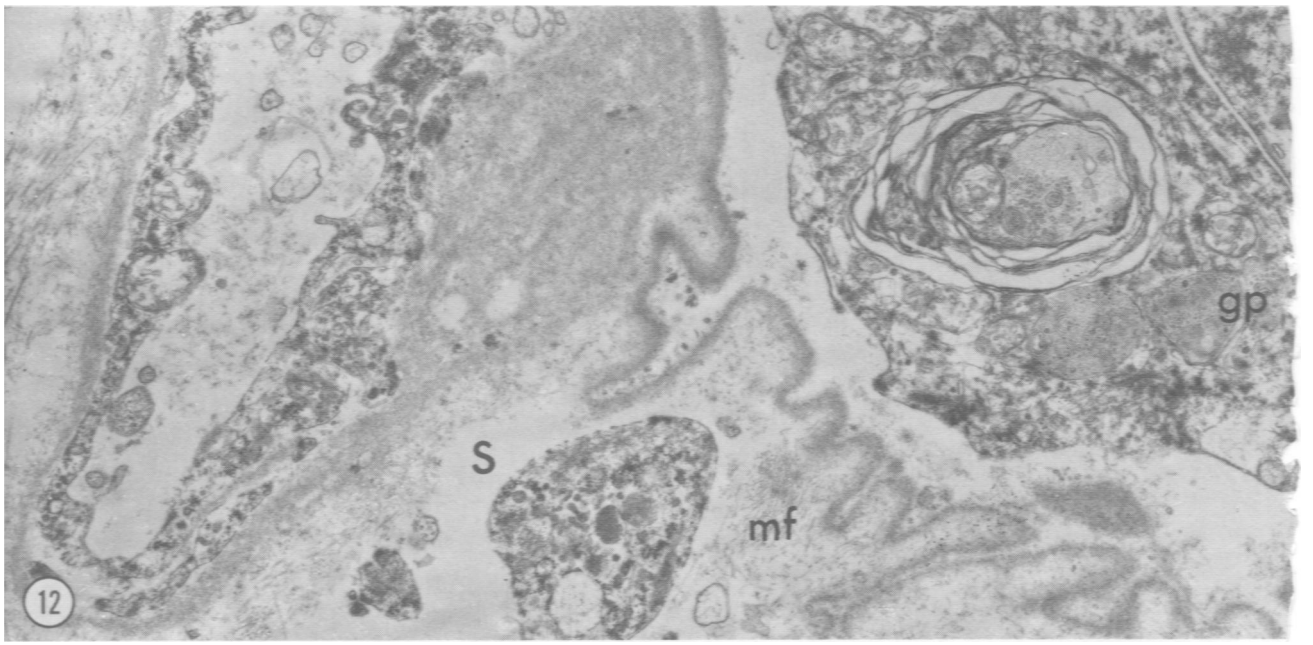
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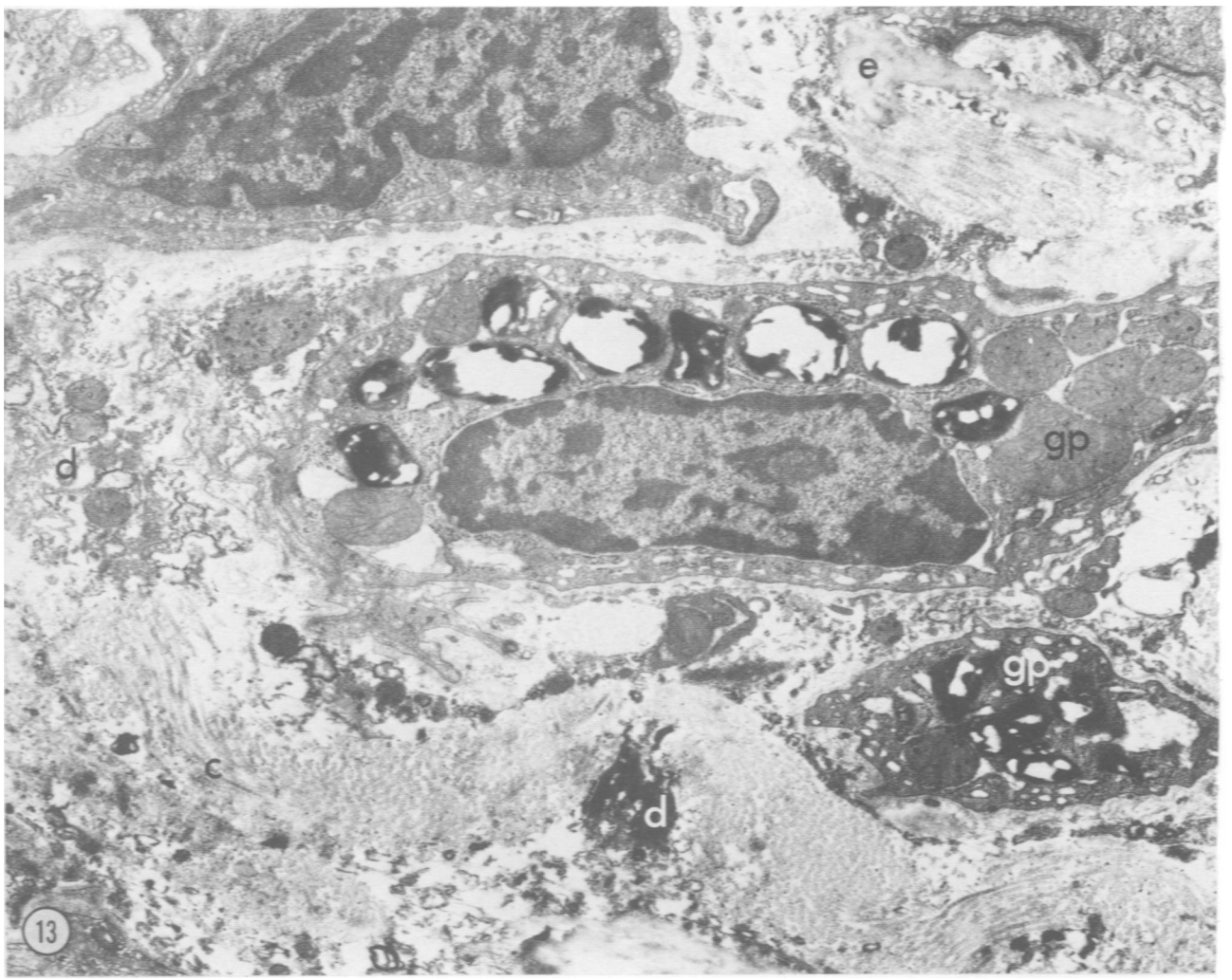
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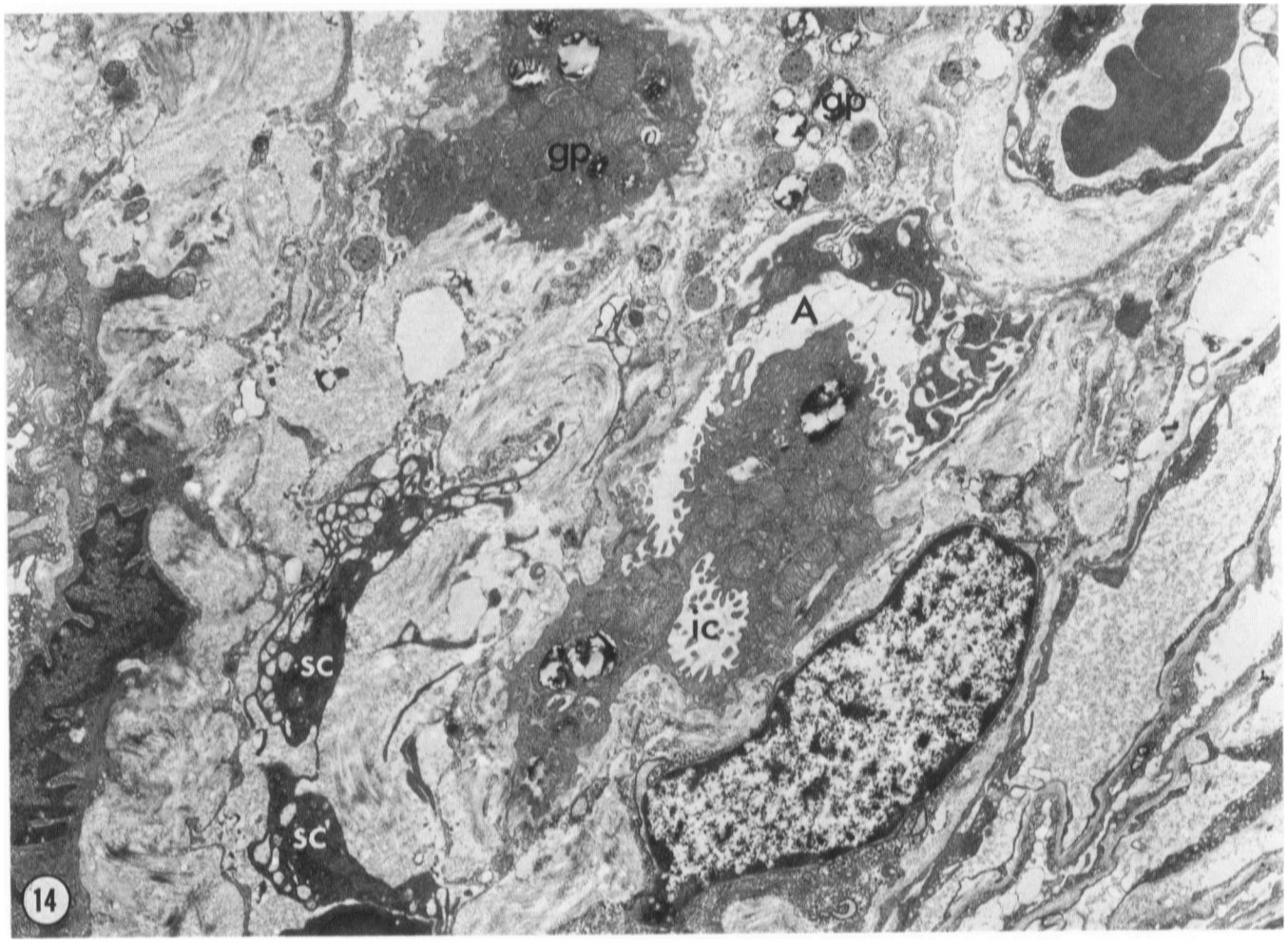
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