Panlobular Emphysema in Young Intravenous Ritalin® Abusers[1-4]

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SUMMARY We studied a distinctive group of young intravenous Ritalin abusers with profound obstructive lung disease. Clinically, they seemed to have severe emphysema, but the pathologic basis of their symptoms had not been investigated previously. Seven patients have died and been autopsied; in four, the lungs were fixed, inflated, dried, and examined in detail radiologically, grossly, microscopically, and by electron probe X-ray microanalysis. All seven patients had severe panlobular (panacinar) emphysema that tended to be more severe in the lower lung zones and that was associated with microscopic talc granulomas. Vascular involvement by talc granulomas was variable, but significant interstitial fibrosis was not present. Five patients were tested for alpha-1-antitrypsin deficiency and found to be normal, as were six similar living patients. These findings indicate that some intravenous drug abusers develop emphysema that clinically, radiologically, and pathologically resembles that caused by alpha-1-antitrypsin deficiency but which must have a different pathogenesis. Talc from the Ritalin tablets may be important, but the mechanism remains to be elucidated.

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Introduction

Some intravenous (IV) drug abusers develop obstructive lung disease that cannot be explained as coexistent asthma or bronchitis (1–4). Its occurrence is uncommon; only 6% of 512 consecutive IV heroin drug abusers were found to have obstructive lung disease by Overland and coworkers (5). However, Pare and colleagues (1) have documented severe airflow obstruction in a cohort of 6 IV methadone abusers followed for many years, suggesting that the disease may be more common in IV drug abusers who inject tablets intended for oral use. Three of the patients of Pare and colleagues had pathologically confirmed emphysema, but there have been no other large studies of the pathologic findings in similar patients. The mechanism by which obstructive lung disease develops in these patients is presently unknown, but talc from tablets intended for oral use may be important (1).

Recently, Sherman and coworkers (2) described six young IV Ritalin® (methylphenidate tablet) abusers with profound obstructive lung disease. The patients' mean age was 36.3 yr, and their mean FEV_1/FVC was 44.5%. They had decreased diffusing capacities, approximately normal total lung capacities, radiographic evidence of hyperinflation, and mildly increased interstitial markings on chest roentgenograms. It was suggested that they suffered from emphysema related in some way to Ritalin abuse. No pathologic information was available for these patients.

We have been interested in elucidating the pathologic basis of obstructive lung disease in Ritalin abusers. Eleven of the 22 patients we have followed with this disease have died, and autopsies were performed on seven. In examining these patients' lungs, we particularly wished to determine whether emphysema was present, how it was distributed, whether any foreign material such as talc was present, and whether other disorders were consistently present. We fixed, inflated, and dried lungs from four patients in order to optimally assess the extent and distribution of disease pathologically and radiographically.

Methods

Patient Selection and Specimen Preparation

Patients 1, 3, and 4 were originally reported by Sherman and coworkers (2); the other patients were IV Ritalin abusers from Seattle who have not been described previously. Patients 1, 2, 5, and 6 were autopsied at Harborview Medical Center (HMC). One lung from each of these four patients was inflated through the bronchus with a mixture of 10% formalin, 25% ethanol, and 33% polyethylene glycol 400 and fixed overnight at a pressure of approximately 25 cm H_2O in a horizontal position while immersed in a pool of similar fixative (6). Each lung was then dried using an intrabronchial air pressure of less than 25 cm H_2O. The dried specimens were scanned on a GE 9800 CT scanner using transverse 1.5 mm collimation, 10 mm image spacing, and high-resolution reconstruction. They were subsequently sectioned in the same plane to permit pathologic-radiologic correlation (6, 7). Representative lung sections were rehydrated in formalin, processed for light microscopy, and stained with either hematoxylin-eosin, Verhoff van Gieson, or Movat pentachrome stains (8, 9). The contralateral lung from each patient was inflated with formalin overnight before sections were taken for light microscopy.

Three additional patients were autopsied elsewhere. The autopsy reports were reviewed, and the remaining wet tissue was examined. Gross photographs were taken of one patient, and routine formalin-fixed histologic sections were prepared and stained as above.

Measurements of Tissue Density, Septal Intercepts, and Crystal Abundance

For tissue density calculations, approximately cubic paired samples of lung tissue (2 to 4 cm^3 each) were removed from upper, middle, and lower lung zones from each dried, inflat-

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ed specimen. The samples were taken from representative uniformly expanded areas free of focal artifacts related to the inflation and drying process and from intercurrent disease. Large airways and blood vessels were avoided. Each sample was precisely measured, soaked in formalin overnight, blotted dry, and weighed.

The number of alveolar septal intercepts per millimeter (reciprocal of mean linear intercept, Lm) was measured by counting the number of alveolar septa that crossed beneath two perpendicular 2.5-mm lines in histologic sections (10). Septal intercepts were measured in approximately 20 uniformly distributed 4-mm-wide fields in each section, and one representative section from each lung field was analyzed. Areas of obvious artifact or intercurrent disease were avoided. Data collection was aided by an image analysis system that included Optimas software (Bioscan, Edmonds, WA) running on an 80386-based personal computer.

Crystal deposition was estimated semiquantitatively using a scale from 1+ for the patient with the fewest visible crystals under polarized light (Patient 5) to 4+ for Patient 3 who had the most visible crystals (table 2). This scale was calibrated by measuring the number of crystals per millimeter of alveolar septum for Patients 3 and 5. The number of birefringent crystals was counted in two representative 4× fields from each patient, and the total length of alveolar septa in the same fields was measured by tracing the septa using the image analysis system. Total septal length was greater than 18 mm in each field. Crystals in and around large vessels were not counted.

Electron Probe X-ray Microanalysis

Five-micron, paraffin-embedded histologic sections from the midlung field from two dried specimens (Patients 1 and 2) were placed on graphite bulk specimen holders and deparaffinized in a 60-degree oven. The specimens were then inserted directly into a JEOL 1200 EX microscope and analyzed using a Link 30 mm^2 Si(Li) detector and a Link AN10,000 analytical system. Collections of intraparenchymal crystals were identified by scanning electron microscopy, and X-ray spectra were collected. X-ray peak integrals were determined using a linear least squares fit with a digital filter to remove high and low frequency components of the spectrum (i.e., noise and underlying continuum). Binary standards were used to determine relative detection efficiencies for the elements measured (11).

Alpha-1-Antitrypsin Assays

Alpha-1-antitrypsin (AAT) phenotyping was performed on serum samples from four patients in Dr. John A. Pierce's laboratory (Washington University, St. Louis, MO) using agarose gel electrophoresis and isoelectric focusing (12). Amounts of immunoreactive AAT were determined either in the clinical laboratory at the University of Washington Medical Center or in Dr. Pierce's laboratory (13).

TABLE 1

PATIENT DEMOGRAPHIC INFORMATION, CLINICAL DATA, AND MOST RECENT LUNG FUNCTION STUDIES

	Patient No.						
	1	2	3	4	5	6	7
Age/race/sex	39/B/F	35/B/F	46/W/F	43/B/F	50/B/M	35/B/M	33/W/M
Cigarettes, pack-years	20	20	100	"Yes"	60	5	20
IVDA-free, yr*	7	1	2	1	8	2	0
AAT†	NL	ND‖	NL	ND	ND	PiM,NL	ND
Supplemental O_2‡	Yes	Yes	Yes		Yes	Yes	Yes
Last pulmonary function tests							
Years before death§	2.3	0.4	3.3	8.8	5.2	2.3	0.7
FVC, L	1.09	1.39	2.1	2.8	1.83	1.47	2.15
% pred¶	(27)	(39)	(53)	(73)	(37)	(25)	(43)
FEV_1, L	0.56	0.41	0.91	1.7	0.77	0.58	0.86
% pred	(16)	(13)	(28)	(54)	(20)	(12)	(21)
TLC, L	5.15	3.37	4.19	5.5	6.72	ND	7.85
% pred	(91)	(66)	(73)	(100)	(96)		(120)
RV, L	2.48	1.79	2.33	2.4	4.78	ND	4.54
% pred	(143)	(117)	(118)	(136)	(230)		(290)
Bronchodilator response in FEV_1, %	+20	+0	+8	+24	+22	−16	+7
D_{LCO}, ml/min/mm Hg	6.9	7.3	11.0	18.1	8.7	ND	14.7
% pred¶	(21)	(25)	(35)	(60)	(24)		(39)

* Interval IV drug abuse was discontinued prior to death.
† Alpha-1-antitrypsin assay results: NL = normal serum level by radial immunodiffusion; Pi M = immunophenotype.
‡ Patient required supplemental home oxygen therapy.
§ Time interval lung function studies were performed prior to death.
‖ Not determined.
¶ Percent predicted values calculated for height, weight, age, and sex (36).

Results

Patient Characteristics

Our patients' clinical characteristics are summarized in table 1. All died of respiratory failure in their fourth or fifth decade. All were hypoxic at rest, and at least six required continuous therapy with supplemental oxygen and bronchodilators. The most recent available pulmonary function tests showed all to have marked reductions in FEV_1 and FVC as well as moderate to marked increases in residual volume. Their response to bronchodilators was variable, with only three of seven showing a significant improvement. Measured single-breath diffusing capacities for CO were markedly reduced. Clinically, all were thought to have severe obstructive lung disease, probably emphysema. The recorded smoking histories ranged between 5 and 100 pack-years. Five died after prolonged mechanical

TABLE 2

SUMMARY OF PATHOLOGIC FINDINGS

	Patient						
	1	2	3	4	5	6	7
Inflated/dried lung	Yes	Yes	No	No	Yes	Yes	No
Panlobular emphysema	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Centrilobular emphysema	No	No			Very mild	Mild	
Gross fibrosis	No	No	No	No	No	No	No
Talc deposits*	2+	3+	4+	3+	1+	2+	3+
Inflammation†	0–1+	1–2+	1+	3+	1+	1+	3+
Vascular lesions‡	0–1+	1–2+	3+	2+	0–1+	1+	2+
Microscopic fibrosis§	0	Trace	1+	0	0	Trace	1+
Bullae/cysts	< 1 cm	None	None	None	< 2.5 cm	< 2 cm	None

* Graded subjectively where 1+ is the least amount visible microscopically in any patient and 4+ is the most dense deposition in any patient.
† Graded subjectively 0 (absent) to 3+ (marked).
‡ Frequency of stenotic or occlusive vascular lesions graded subjectively from 0 (absent) to 3+ (frequent).
§ Graded from 0 (absent) to 4+ (honeycomb lung).

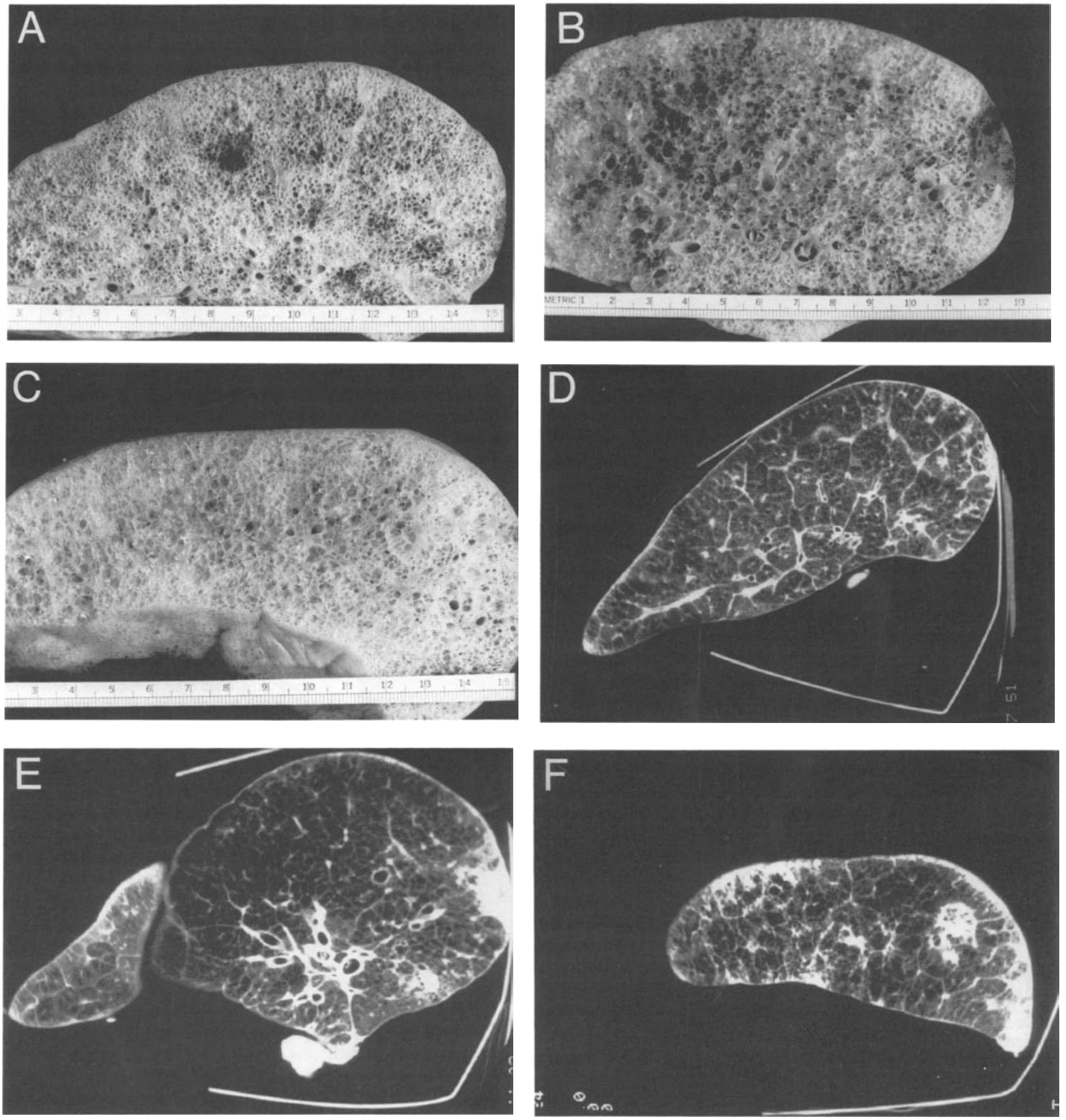

Fig. 1. Gross pathologic findings and HRCT studies from Patient 1. Transverse sections from the upper (A, D), middle (B, E), and lower (C, F) zone of the inflated, dried left lung are shown next to the HRCT scan at approximately the same level. Internal scale is in centimeters.

ventilation, one died after refusing mechanical ventilation, and one was found dead of a drug overdose.

Pathologic Findings

The gross pathologic findings were remarkably constant (table 2). At autopsy each patient's lungs were markedly expanded, and in several cases the lungs met in the midline anteriorly to partially hide the heart. They displayed severe air trapping and did not collapse after removal from the thorax. Enlarged air spaces could be seen through the smooth, thin plurae. When sectioned, panlobular emphysema was obvious in each case. There was subtle prominence of the interstitium in some cases, but there was no definite fibrosis in any patient.

The distribution and severity of emphysema were best visualized in inflated, air-dried lung specimens from four patients. Each had pronounced panlobular emphysema that affected the lung

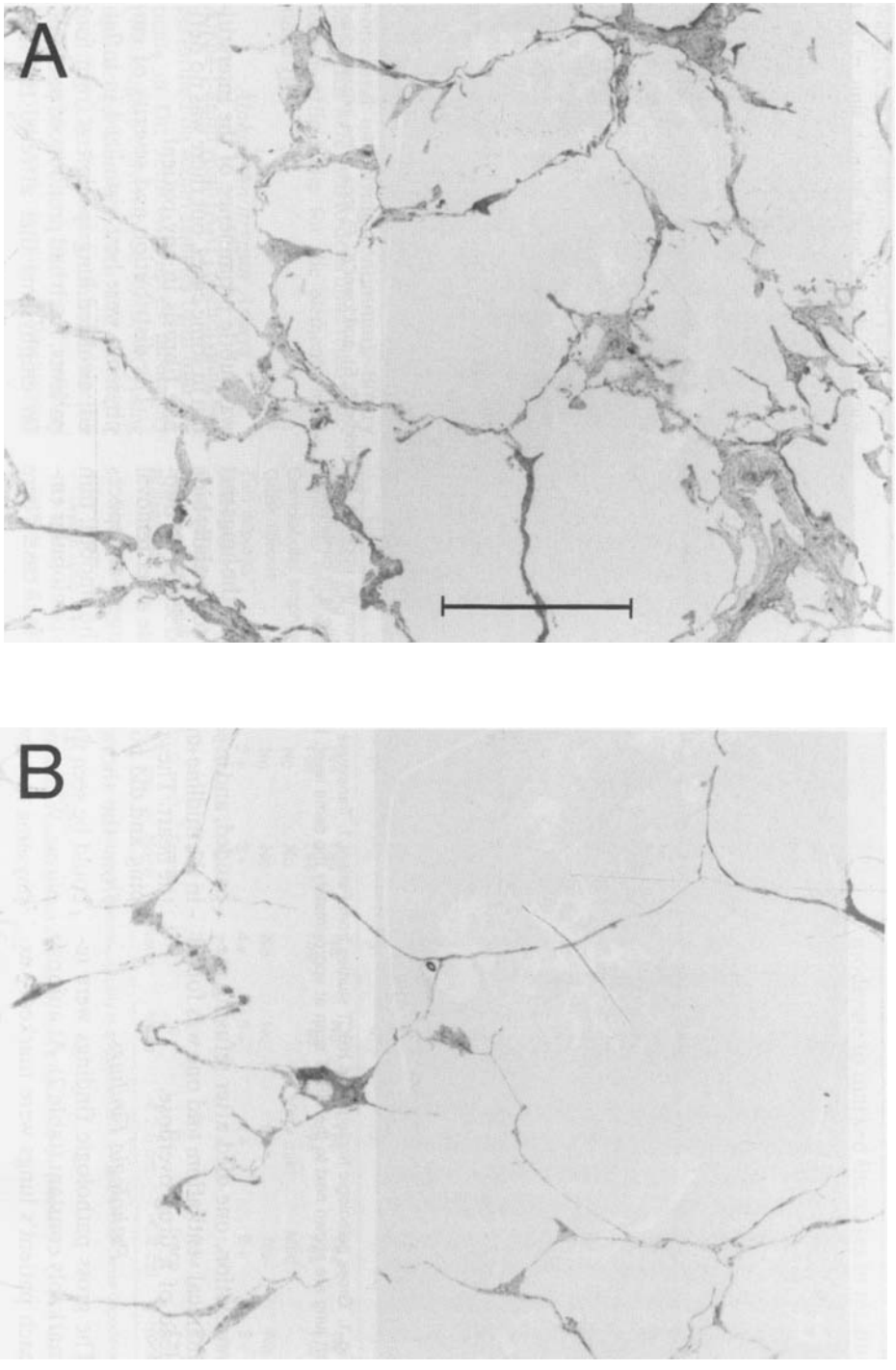

Fig. 2. Histologic appearance of lung from Patient 1. Microscopic sections were taken from the upper (A), middle (B), and lower (C) lung zones from the inflated, dried left lung. Sections were stained with hematoxylin-eosin and photographed at same magnification. Bar in A represents 1 mm.

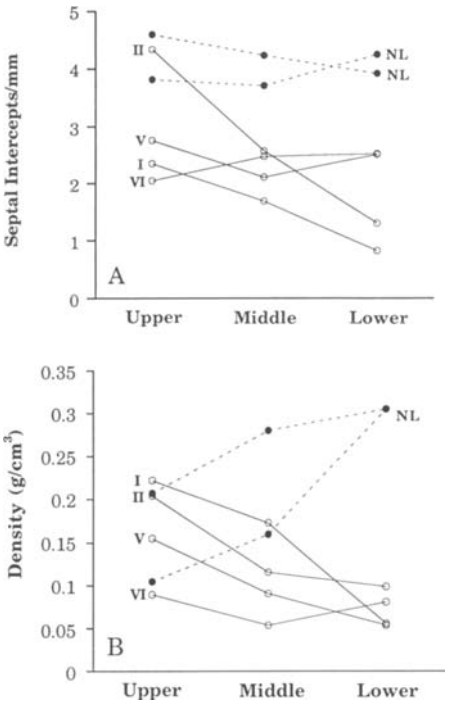

Fig. 3. Quantification of emphysema. A. Septal intercepts per millimeter (reciprocal of mean linear intercept) was measured as described in METHODS. Data points represent the mean intercepts from 40 2.5-mm line segments per histologic section. The SEM for each datum point averaged 0.18 intercepts/mm. B. Tissue density was measured in paired samples from the upper, middle, and lower lung zones from each of the inflated, dried specimens. Lines connect mean densities for each patient. The standard deviations for each pair averaged 0.011, 0.017, and 0.026 g/cm³ at the upper, middle, and lower levels, respectively. Roman numerals refer to patients as listed in the Tables; NL refers to data from two normal lung specimens.

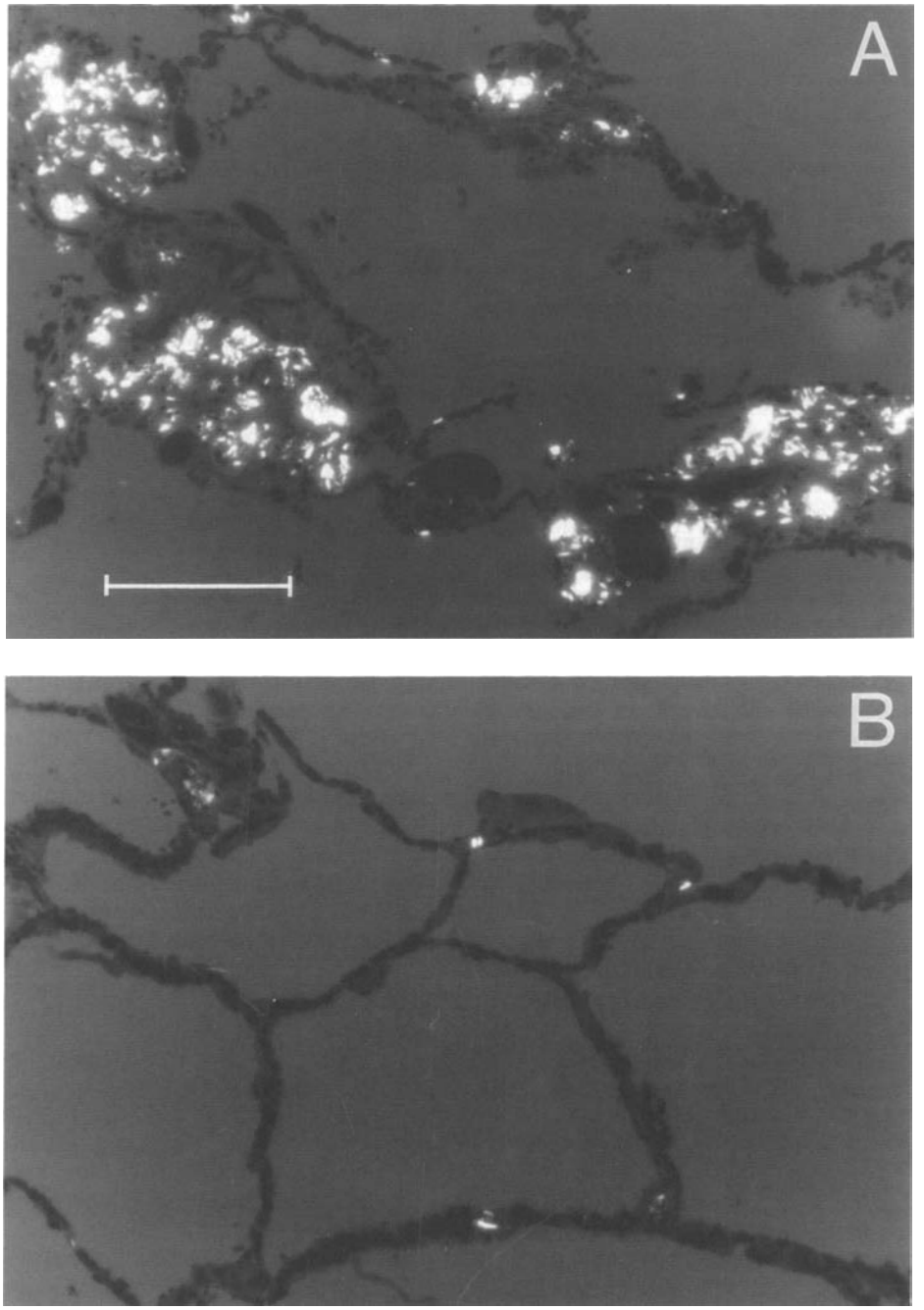

Fig. 4. Talc deposition in lung tissue. A. Patient 3 (most visible talc of any patient and graded 4+). B. Patient 5 (least visible talc of any patient and graded 1+). Sections were stained with hematoxylin-eosin and photographed at same magnification under polarized light. Bar in A represents 200 μm.

bases more severely than the apices (figure 1). The visible air spaces were typically less than 1 mm in diameter in the apices but more than 2 mm (usually 3 to 4 mm) in diameter in the bases. The loss of alveolar septa was easily apparent histologically (figure 2), and there were concomitant decreases in tissue density and the number of alveolar intercepts per millimeter (figure 3).

Very mild centrilobular emphysema was seen in the apices of two of the dried lungs (Patients 5 and 6). The same two patients also had apical subpleural and intraparenchymal bullae ranging in size up to 2.5 and 2 cm, respectively. Neither centrilobular emphysema nor bullae were seen in the lung bases of any patient.

The high resolution CT images correlated extremely well with the gross pathologic appearance of the dried, inflated specimens (figure 1). Regions of severe panlobular emphysema appeared as areas of low attenuation. Normal-sized alveolar air spaces were, as expected, too small to be visible by CT, but as the size of the emphysematous air spaces increased above approximately 1 to 2 mm in diameter, individual air spaces could be visualized. Centrilobular emphysema appeared as mottled, low attenuation areas on the CT images, with the most severe abnormalities located in the vicinity of terminal bronchioles and displaced slightly from secondary lobular septa. Bullae were clearly visualized. The CT images showed well-defined localized opacities in the two patients with pulmonary infections caused by *Candida*, *Aspergillus*, and herpes simplex.

Microscopic examination revealed crystalline foreign material within the residual alveolar septa in all patients. This material resembled talc in that it consisted of platelike crystals that were strongly birefringent under polarized light (figure 4). Additional evidence that much of the crystalline material was talc was provided by electron probe X-ray microanalysis. In the two cases examined, the crystals contained only magnesium

and silicon; in one case the Mg:Si ratio was 37:63, whereas it was 36:64 in the other (not shown). The theoretical Mg:Si ratio is 39.1:60.9 for talc (14).

The amount of talclike material and its arrangement within tissue varied between patients (table 2 and figure 4). The patient with the least material (Patient 5) had 5.5 ± 0.3 crystals/mm of alveolar septum (mean ± SD). In his lungs, the crystals were usually distributed individually within septa although a few collections were present at the confluence of septa (figure 4B). Other patients had more crystals, and collections of crystals were both larger and more numerous. Collections were often located near vessels the size of precapillary arterioles, but larger vessels were only occasionally associated with talc collections. The patient with the greatest crystal burden (Patient 3) had 15.3 ± 3.9 crystals/mm, excluding collections near larger vessels (figure 4A).

The amount of inflammation associated with the talclike material also varied (table 2). In some patients the crystals seemed to lie free within the interstitium, and only a few crystals were surrounded by macrophages. Other patients displayed a marked macrophage response to the crystals, and there were numerous loosely formed talc granulomas. The inflammatory reaction seemed to be independent of the amount of talclike material but was most severe in patients who had used drugs recently and least pronounced in those who had discontinued their IV drug abuse long before death (tables 1 and 2). In none of the patients was the inflammatory infiltrate composed of neutrophils, lymphocytes, or plasma cells.

Interstitial fibrosis was entirely absent in three patients and was minimal in the remaining patients. When present, stainable collagen was found as thin shells surrounding collections of crystalline material. Occasionally, the interstitium appeared widened on sections stained with hematoxylin-eosin, but the Movat pentachrome stain showed that the widening was not fibrosis as defined by accumulation of saffron-positive collagen but was due to increased alcian-blue-positive extracellular matrix material. No pneumoconiosislike lesions were present in any patient, and there was no pleural fibrosis.

Stainable elastic tissue also seemed to be reduced. Elastin was virtually absent from all talc granulomas and from the vicinity of individual crystals. Occasional elastin fibers could be found in intervening alveolar septa that were free of crystals.

Occlusive vascular lesions (15) could be found in the small arteries in all patients, but the number varied substantially (table 2). There appeared to be a rough correlation between the number of occlusive vascular lesions and the amount of talc in the lungs.

Four of the patients had goblet cell metaplasia in the bronchioles, one had mucous gland hypertrophy, and three had large amounts of mucus in the airways. In two patients there was thickening of bronchiolar basement membrane zones, but none had significant eosinophil infiltrates in the airway walls. No patient had bronchiectasis. All patients had systemic deposits of talc; they were grossly visible in the liver and spleen of two patients.

Discussion

A primary goal of this study was to determine the pathologic basis of the severe chronic airflow obstruction that develops in some young intravenous Ritalin abusers. All seven patients examined at autopsy had severe panlobular emphysema, and some had variable numbers of talc granulomas, inflammatory infiltrates, and occlusive vascular lesions. Pathologic features seen in chronic bronchitis and asthma were inconstantly present and tended to be mild. Thus, the dominant disease, and the only disease consistently present in these patients, was panlobular emphysema.

Panlobular emphysema is not commonly recognized in IV drug abusers, although it has been reported in methadone abusers. Groth and coworkers (3) and Vevaina and colleagues (4) have both reported patients who developed severe panlobular emphysema associated with pulmonary talc granulomas without pulmonary fibrosis. Neither patient had a family history of lung disease, and no industrial exposure to talc or other toxins was identified. Pare and colleagues (1) have also reported pathologically confirmed panlobular emphysema in three IV methadone abusers and radiographic evidence of emphysema in three clinically similar patients. All six of their patients had superimposed pathologic disorders including bullae in all six and progressive massive fibrosislike lesions in four. Our seven patients differ both in terms of their preference for Ritalin over methadone and their lack of interstitial fibrosis.

A second goal was to obtain evidence to suggest the most likely pathogenetic mechanism in these patients. Cigarette smoking is the most common cause of emphysema in the United States, and although all of our patients smoked, it seems unlikely that their disease was due primarily to cigarette smoking. Cigarette smoking is most closely linked to centrilobular emphysema, not to panlobular emphysema (16). Only two of our patients had detectable centrilobular emphysema, and in them the disease was mild and confined to the upper lungs. In contrast, all patients had severe and diffuse panlobular emphysema that preferentially involved the lung bases. Moreover, our patients were younger than most with cigarette-related emphysema, and most had relatively brief smoking histories.

Our patients are similar to patients with AAT deficiency in terms of age, type of emphysema, and distribution of disease (17, 18), yet their disease cannot be explained by inherent AAT deficiency. Dr. John A. Pierce (Washington University, St. Louis, MO) performed AAT phenotyping studies on one of the seven patients in this study and on three clinically similar living patients and found that all had normal AAT phenotypes and normal serum levels of AAT (not shown). In addition, at least five other patients have been tested and found to have normal serum levels of immunoreactive AAT. None of the autopsied patients had cirrhosis. We have not found any patient with this syndrome to have either an abnormal AAT phenotype or decreased amount of serum AAT.

All seven of our patients injected Ritalin tablets but there is little to suggest that methylphenidate itself is pathogenic. To our knowledge there have been no reports of emphysema related to oral methylphenidate therapy using recommended doses. Higher local concentrations of the drug might be obtained transiently within the lung after injection of partially dissolved tablets, but it remains to be shown that these concentrations cause emphysema. The occurrence of panlobular emphysema in IV methadone abusers also argues against a primary role for methylphenidate (1, 3, 4).

Tablet-compounding materials and other particulate matter in Ritalin tablets could be important. Talc, microcrystalline cellulose, and other insoluble materials are included in tablets intended for oral use. When injected intravenously, they persist in the lungs (and other organs) and have been recognized to cause vascular disease and pulmonary fibrosis (14, 15, 19). Particular attention has focused on talc as an inciting agent in the development of emphysema (1, 3, 4).

Talc is included in Ritalin tablets (19, 20), and birefringement platelike crystals with the elemental composition of talc were recovered from our patients' lungs. Talc has also been identified in the lungs of emphysematous IV methadone abusers (1, 3, 4).

Emphysema could be caused by particulate material through at least three mechanisms. Repeated microemboli lodging within pulmonary capillaries might cause emphysema, perhaps through ischemic necrosis of alveolar septa (3, 4). Indeed, Strawbridge induced panlobular emphysema in rabbits by repeatedly injecting inert particles of caledon blue R.C. (21). On the other hand, there is no direct evidence that this mechanism is operative in humans, and it is interesting to note that embolic occlusion of larger vessels by thromboemboli does not cause emphysema with appreciable frequency. Others have suggested that widespread septic microemboli such as from contaminated drugs can cause emphysema (1, 22).

A third hypothesis is that pulmonary macrophages engulf particulate embolic material and subsequently elaborate elastases and proteases that in turn cause emphysema. It has been shown that macrophages are capable of releasing elastases and other proteases in response to such stimuli as mineral dusts (23–25). Moreover, emphysema can be induced in experimental animals simply by insufflating elastase into their lungs (26). In our patients, much of the talc was associated with macrophages or lay within macrophage-derived foreign body giant cells. Stainable elastin was virtually absent in the immediate vicinity of these talc granulomas even though it was detectable elsewhere. In addition, our patients' emphysema tended to be worse in the lung bases where blood flow is greater and greater trapping of embolic material presumably occurs (27, 28). These observations are consistent with the idea that embolized talc or other material causes localized imbalances between proteases and antiproteases that ultimately result in emphysema. Whether the hypothetical unopposed proteases are simply not inhibitable by AAT, like some macrophage elastases (29), whether they have escaped from a normally sequestered phagocytic microenvironment, or whether they are misdirected cell-bound proteases (30, 31) is not yet known. Our observations suggest that experimental systems designed to study the response of macrophages to talc particles may help unravel the mechanism of disease in these patients. They also suggest that it may be possible to establish an animal model of emphysema based on chronic intravenous talc injection.

Emphysema is not a frequently recognized complication of IV drug abuse. The apparent rarity of this syndrome might be because the affected patients do not seek medical care or die of other causes before their lung disease becomes manifest. Alternatively, there may be variable individual susceptibility to the causative agent, or the inciting agent(s) may not be present in all injected drugs. Compounding agents can vary, as can the presence of mineral contaminants, and even the precise composition of talc can vary (32, 33). Finally, emphysema may simply be underrecognized in these patients. High resolution CT scans clearly demonstrate emphysema in dried lung specimens (7, 34) and can be used to identify and grade emphysema in living patients (34, 35). CT may be helpful in evaluating other IV drug abusers for the presence, type, and distribution of emphysema.

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