STRUCTURE — FUNCTION CORRELATIONS IN CARDIOVASCULAR AND PULMONARY DISEASES (CPC)

Self-Induced Pulmonary Granulomatosis*
A Consequence of Intravenous Injection of Drugs Intended for Oral Use

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Dr. William C. Roberts: Herein we will discuss pulmonary and cardiac findings in a girl who injected into her systemic veins dissolved drugs originally intended for oral use. Dr. Brownlee will describe the patient.

Dr. William J. Brownlee: An 18-year-old white woman began injecting heroin intravenously at the age of 15 years, about 30 months before her death.

Figure 1. Multiple talc granulomas in pulmonary interstitium (a and a1) and within lumen of pulmonary artery (b and b1). Polarized sections (a1 and b1) are from the same areas shown in a and b, respectively. Refractile material, for most part, represents talc (hematoxylineosin, original magnifications × 60 [a and a1] and × 22 [b and b1]).

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Figure 2. Talc granulomas located within pulmonary artery (a) and close-up of large granuloma adjacent to pulmonary artery (b) (hematoxylin-eosin, original magnifications × 100 [a] and × 220 [b]).

About six months later, she began injecting regularly into her systemic veins various other drugs, including methylphenidate (Ritalin), after dissolving them in liquids. She noted periodic wheezing and exertional dyspnea about 12 months before death, and these symptoms gradually progressed thereafter. The patient died suddenly at home after an episode of severe dyspnea. She had never sought medical care.

At necropsy, the surfaces of both lungs appeared normal; but on sectioning, multiple small (about 1 to 2 mm) relatively firm lesions were present throughout all lobes. Histologically, these little nodules were granulomas containing refractile material typical of talc (Fig 1 and 2). The alveolar septa contained similar refractile material and also numerous inflammatory cells (Fig 3). In addition, the media and intima of many pulmonary arteries

Figure 3. Alveolar septum containing many mononuclear inflammatory cells producing "active-appearing" alveolitis (a). Same section polarized is shown (b). Lumina of septal capillaries contain birefringent particles typical of talc (b) (hematoxylin-eosin, original magnification × 500).
were thickened, and many small pulmonary arteries were totally obstructed by talc-containing granulomas (Fig 2). The heart, which weighed 440 gm, was typical of that observed in cor pulmonale; both the right atrial and right ventricular cavities were dilated, and their walls were quite thickened; the tricuspid valvular anulus was dilated.

Dr. Roberts: This girl obviously died from self-induced pulmonary granulomatosis, causing morphologic evidence of severe pulmonary hypertension. Because it holds the components of the pill together, talc is present in virtually all tablets; and, consequently, if tablets of nearly any variety are dissolved in a fluid and injected into systemic veins, rather than swallowed, pulmonary talc granulomas are the expected consequence. If few talc granulomas form, no functional consequence ensues. If numerous talc granulomas develop, the consequence is either obstruction of the lumina of many pulmonary arteries, producing pulmonary hypertension and cor pulmonale or interstitial pulmonary fibrosis or both. Although nearly all contain talc, the tablets most commonly used for intravenous injection after crushing and dissolving are methylphenidate (Ritalin) (as in our patient), methadone, tripalennamine (Pyribenzamine), propoxyphene hydrochloride (Darvon), phenmetrazine (Preludin), and amphetamines.

Dr. Waller, would you summarize the findings in previously reported necropsies of patients with pulmonary talc granulomatosis?

Dr. Bruce F. Waller: From 1950 to June 1979, at least 16 necropsies of patients with pulmonary talc granulomas from intravenous injection of dissolved tablets were reported (Table 1).1-12 All patients were known to have repeatedly injected intravenously drugs intended for oral use for periods ranging from 2 to 20 years (average, ten years). In each patient, foreign material consistent with talc was present in the pulmonary granulomas. The 16 patients ranged in age from 22 to 52 years (average, 31 years); 13 were men, and three were women. In all 16 patients the granulomas were present in both pulmonary interstitium and in the lumina of the

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*IV, intravenous.
**PA, pulmonary arteries; and I, interstitium.
†Leu, leukocytes; PC, plasma cells; Lym, lymphocytes; and AH, alveolar hemorrhage.
‡MT, medial thickening; IT, intimal thickening; and PL, plexiform lesion.
§RV, right ventricular.

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pulmonary arteries. In 11 patients the interstitium appeared to be the predominant location; in four, the pulmonary arteries were the predominant location; and in one patient, it was not mentioned. The interstitial location led to pulmonary interstitial fibrosis, and the arterial location led to pulmonary arterial narrowing with changes consistent with pulmonary hypertension. The patients who had been taking dissolved tablets intravenously the longest tended to have the talc granulomas located primarily in the pulmonary interstitium, and those with the shortest duration of addiction tended to have the granulomas predominantly in the lumina of the pulmonary arteries. Morphologic evidence (right ventricular hypertrophy or pulmonary arterial changes or both) of pulmonary arterial hypertension was present in 13 of the 16 patients. In addition to the 16 necropsies, at least 13 living patients have been reported to have talc granulomas in pulmonary biopsies. Of them, seven had pulmonary arterial changes indicative of pulmonary hypertension. Thus, of 29 previous reports of cases of pulmonary talc granulomas, 20 had morphologic evidence of pulmonary hypertension, and six had pleomorphic lesions indicating that the pulmonary hypertension was severe. 15

Dr. Roberts: Dr. Waller, what does the roentgenogram of the chest disclose in patients with pulmonary talc granulomatosis?

Dr. Waller: The roentgenographic changes appear, to some extent at least to be dependent on the stage of the process at which the patient is examined. When the pulmonary granulomas are few in number, the pulmonary parenchyma is normal by radiographic examination. When the pulmonary granulomas are widespread and fatal, the pulmonary parenchyma by roentgenographic examination may still be normal. 4,12,16 Thus, a normal roentgenogram of the chest does not rule out the presence of extensive pulmonary talc granulomatosis. In a study of 17 living patients who administered intravenously at least 2,500 to 50,000 dissolved tablets of methadone during periods ranging from one to nine years, ten patients had normal and seven had abnormal chest roentgenograms. 15 The abnormalities consisted of widespread nodules measuring 1 mm or less in diameter (seven patients) and diminished pulmonary volumes (two patients). Surprisingly, pulmonary infarcts appear to be infrequent, despite the frequent total obliteration of the lumina of many pulmonary arteries. Of course, the patients with pulmonary hypertension may have dilated pulmonary trunks and right ventricular and right atrial cavities. The electrocardiogram in the latter patients also may provide evidence of right ventricular hypertrophy and right atrial abnormality.

Dr. Roberts: Dr. Waller, what alterations in pulmonary function occur in patients with pulmonary talc granulomatosis?

Dr. Waller: Relatively few reported necropsies of cases of fatal pulmonary granulomatosis were from patients who had pulmonary function tests during life, and most patients with pulmonary function tests have not had the pulmonary granulomatosis confirmed anatomically (biopsy or necropsy). Nevertheless, several patients who took dissolved tablets intravenously for long periods have undergone tests of pulmonary function. 12,14 The major functional abnormality is a slowed diffusion of air from the alveolar spaces to the alveolar capillaries (decreased diffusing capacity). A second abnormality described is an increased period of time to expel a certain amount of pulmonary air (diminished forced expiratory volume in one second and diminished midexpiratory flow rate). These latter disturbances may result in an increased pulmonary volume (ie, hyperinflation). Whether or not this diminished expiratory flow rate and increased residual pulmonary volume are the result of the pulmonary granulomatosis or whether they are the result of associated cigarette smoking, which is extremely common in the drug addicts, is unclear. Surprisingly, despite the extensive distribution of the pulmonary talc granulomas, systemic arterial hypoxia is usually absent; or at least, cyanosis, except terminally, is uncommon. Dyspnea is the usual symptom resulting from the pulmonary talc granulomatosis. Again, clinical evidences of pulmonary infarcts are not reported.

Dr. Roberts: I have a few comments regarding pulmonary morphologic findings in patients with talc granulomatosis. As shown in Figure 1, numerous birefringent particles may be present throughout the pulmonary parenchyma. These birefringent particles are more numerous in alveolar septa not containing granulomas than in the granulomas per se. The alveolar septa usually contain many mononuclear inflammatory cells, producing a very “active”-appearing diffuse alveolitis as a consequence of the talc granulomatosis (Fig 3). The inflammatory cells generally consist of lymphocytes, plasma cells, and eosinophils; or at least, this was the finding in our patient. In our patient, large numbers of plasma cells and eosinophils were present in many alveolar septa. The alveolitis is consistent with the pulmonary functional abnormality of slowed perfusion of air from alveolar space to alveolar capillary. There has been
very little comment regarding alveolitis in previous reports on pulmonary talc granulomatosis. Another infrequently mentioned abnormality in the lungs of these patients is the presence of hemosiderin-laden macrophages within the alveolar spaces. We interpret this abnormality, which was quite extensive in our patient, as resulting from a rupture of the membranes of alveolar capillaries, allowing extravasation of erythrocytes and other blood products into the alveolar spaces (Fig 4). Thus, it might be possible to find hemosiderin or iron deposits in the pulmonary expectorates; however, talc spicules or granulomas are infrequent in the alveolar spaces.

I have one final comment regarding diagnosis. Some patients with pulmonary talc granulomatosis initially have evidence of severe pulmonary hypertension. A male patient with pulmonary talcosis, who was previously studied by us, was initially diagnosed as having primary or idiopathic pulmonary hypertension. The finding of evidence of severe pulmonary hypertension in a man should arouse suspicion of the possibility of pulmonary talc granulomatosis as the cause of the pulmonary hypertension, because most patients with primary pulmonary hypertension are women, and most patients with pulmonary talc granulomatosis are men.

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