types—the aforementioned solitary patterns and a mixed variant. The former is the most common type to arise from the pleura while the latter is the more common peritoneal form. A malignant fibrous form will resemble a fibrosarcoma, while a malignant epithelial form will resemble an undifferentiated or poorly differentiated carcinoma. The most common type of lesion to arise within the pericardium is a mixed lesion. Fibrous lesions are indeed rare and often associated with a pleural lesion, putting the diagnosis of primary pericardial tumor in doubt. Pure epithelial lesions are reported.1

The diagnosis of mesothelioma is often very difficult. Small surgical specimens from the pericardium, without adequate examination of the pleural surfaces, make it impossible to distinguish it from a primary pleural lesion or some other lesion. To standardize criteria for a primary pericardial mesothelioma, Andersen and Hansen set up the following: (1) localization to the pericardium, (2) only metastases to lymph nodes, (3) no other primary tumor, and (4) complete autopsy in case of death.

Electron microscopic studies have added much to the understanding of the very adaptable nature of the mesothelial cell.5-11 In studies on both fibrous and epithelial lesions from the pleura and peritoneum, the similarity and spectrum between different types of mesotheliomas have been worked out. In our case, many of these features were identified and included—microvilli from the surface of the cells, occasional cells containing tonofilaments, desmosomal attachments, extracellular collagen, and acid mucopolysaccharides.

To our knowledge this is the first case reported of a primary pericardial malignant mesothelioma documented by electron microscopy. The clinical, diagnostic, histologic, and electron microscopic aspects were presented to emphasize that with currently available methods, the diagnosis can be made.

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67Gallium Scanning in Talc-Induced Pulmonary Granulomatosis*

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We describe a case of pulmonary granulomatosis in a user who habitually injected methylphenidate (Ritalin) intravenously; symptomatic and objective improvement occurred with corticosteroid therapy. A scan of the lungs using radioactive 67gallium showed an increased concentration of 67gallium throughout both lungs. There was a reduction in abnormal accumulation of 67gallium, improvement in the arterial oxygen pressure and the diffusing capacity for carbon monoxide, and a reduction in the infiltrate on the chest x-ray film two months after the institution of therapy. Before treatment the patient's symptoms and arterial deoxygenation increased despite the cessation of her drug abuse, thus raising the question of a self-perpetuating inflammatory process in a case of pulmonary deposition of talc.

Foreign body embolization of talc-containing material, with resulting pulmonary granulomatosis and pulmonary hypertension, although limited in the number of reported cases, is a well-documented entity.1-7 In this report, we describe a case of talc-induced pulmonary granulomatosis and pulmonary hypertension, in which there was improvement with corticosteroid therapy and in which scanning with radioactive gallium was used for initial and follow-up evaluation.

CASE REPORT

In August 1977, a 25-year-old black woman with a two-year history of drug abuse complained of a nonproductive cough of four months' duration and shortness of breath on exertion (on walking six blocks). Abnormal findings at that time included bilateral expiratory rales and roentgenologic evidence of a diffuse pulmonary interstitial infiltrate and bilateral hilar prominence; there was a reduction of total lung capacity (TLC) (75 percent of predicted), hypoxemia at rest and with exercise (arterial oxygen pressure [PaO2] of 83 mm Hg and 85 mm Hg, respectively), and an alveolar-arterial oxygen tension gradient (P(A-a)O2) which increased with exercise.

The patient refused further evaluation and resumed her intravenous injection of methylphenidate (Ritalin) tablets and heroin, both of which she discontinued two months later after beginning a program of treatment with methadone. At that time, she had injected methylphenidate intravenously four times per day for approximately nine months.

The patient was readmitted seven months after the initial evaluation with the history of increasing dyspnea (with one to two blocks of walking) and syncope. On physical examination, she exhibited diffuse expiratory rales throughout the chest.

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pulmonary fields, a loud pulmonic second sound, and a grade-5/6 systolic ejection murmur at the second left intercostal space. The chest x-ray film taken on admission showed a diffuse reticulonodular infiltrate with pulmonary vascular prominence (Fig 1). Results of the laboratory evaluation, which included normal levels of serum immunoglobulins, were unremarkable. Pulmonary function tests demonstrated normal expiratory flow rates, a slight reduction in forced vital capacity, a TLC of 3.92 L (68 percent of predicted), and carbon monoxide diffusing capacity (D) of 11.9 ml/min/mm Hg; blood gas levels included a PaO₂ of 72 mm Hg at rest, with a P(A-a)O₂ of 28 mm Hg. Cardiac catheterization disclosed a marked elevation of pulmonary arterial pressures (80/23 mm Hg; mean, 48 mm Hg). Transbronchial biopsy of the lung was performed and showed deposition of birefringent particles, consistent with tale, eliciting a granulomatous reaction with giant cells and fibrosis of the septa.

A diagnosis of pulmonary hypertension secondary to tale-induced granulomatosis was made. A scan with radioactive ⁶⁷gallium demonstrated abnormal uptake of gallium throughout both pulmonary fields (Fig 2). The patient, who was discharged on a regimen of prednisone (80 mg daily) and tolazoline (Priscoline; 50 mg every four hours) noted an increase in her exercise tolerance as an outpatient. A repeat evaluation two months after hospitalization showed a PaO₂ of 88 mm Hg, with a P(A-a)O₂ of 11 mm Hg, D of 16.1 ml/min/mm Hg, and TLC of 3.71 L. On a repeat chest x-ray film the interstitial infiltrate was less prominent. A repeat scan with gallium demonstrated a reduction in the abnormal uptake, especially in the perihilar areas (Fig 3). Three months after the second admission, the patient was found comatose at home, and she died several days later, never having recovered consciousness.

At autopsy, abnormal findings were practically limited to the cardiopulmonary system. The right lung weighed 360 gm, and the left lung weighed 260 gm. The main vessels showed focal yellowish discoloration consistent with early atherosclerotic changes. Atelectasis was seen in the left lower lobe and

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Figure 1. Left, Posteroanterior chest roentgenogram shows diffuse bilateral infiltrate and hilar vascular prominence. Right, Close-up view of right lower pulmonary field.

Figure 2. Scan with ⁶⁷gallium shows diffusely increased concentration of ⁶⁷gallium throughout both lungs (posterior projection, 96 hours after intravenous injection of 7 mCi of ⁶⁷gallium citrate).
in the posterior part of the right lower lobe, right upper lobe, and left upper lobe. The surface of the lung was very smooth, pinkish, and glistening. The heart weighed 425 gm, with hypertrophy of both right and left ventricles. The coronary arteries showed focal arteriosclerosis, particularly of the anterior descending artery, without narrowing of the lumen. The right ventricle and atrium were dilated. The liver weighed 1,690 gm and was passively congested.

On microscopic examination, there was generalized deposition of talc in the lungs, particularly in the bronchiolar walls and just peripheral to small and medium-sized bronchi (Fig 4). A secondary granulomatous reaction and fibrosis were again seen in the septa. The pulmonary parenchyma showed the complete spectrum of pulmonary hypertension, including arterial medial hypertrophy and hyperplasia, intimal fibrosis, aneurysmal dilation, rupture of vessels, and formation of plexiform and angiomatoid lesions (Fig 5). It is interesting to note that liver and spleen showed deposition of very small particles of talc with no striking reaction around them.

**DISCUSSION**

Intravenous injection of orally intended medication which contains talc as a filler may lead to pulmonary granulomatosis and pulmonary hypertension. Wendt and associates in 1984 noted a case of angiothrombotic hypertension in an addict using a combination of paregoric and tripelennamine ("blue velvet"), and Puro et al later experimentally produced these lesions in rabbits with injected talc alone or tripelennamine that contained talc. Foreign body embolization and pulmonary hypertension from intravenous use of methylphenidate (Ritalin), as well as other talc-containing tablets, have subsequently been described.

Pulmonary hypertension has been a frequent finding in the reported cases of foreign body embolization. In a review of the literature in 1976, Arnett et al noted that 13 of 21 biopsy-proven cases had morphologic evidence of pulmonary hypertension, with four cases having the changes of severe pulmonary hypertension. Robertson et al presented data from catheterization in four patients with talc embolization showing mild to severe elevation in pulmonary arterial pressures.

The response of talc-induced pulmonary disease to corticosteroid administration has been variable. Moskowitz in 1970 reported a case of pneumoconiosis from chronic inhalation of talc, which responded to administration of high doses of steroids. Corticosteroids were

![Figure 3](https://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21134/)

**Figure 3.** Scan with $^{67}$gallium two months after institution of corticosteroid therapy. Concentration of $^{67}$gallium, particularly in perihilar areas, has decreased (posterior projection, 96 hours after intravenous injection of 7 mCi of $^{67}$gallium citrate).

![Figure 4](https://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21134/)

**Figure 4.** Polarized light exposes talc particles with varying amounts of fibrosis around them (hematoxylin-eosin, original magnification × 40).

![Figure 5](https://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21134/)

**Figure 5.** Deposition of talc with secondary fibrosis and vasculature showing effects of advanced pulmonary hypertension (hematoxylin-eosin, original magnification × 40).
subsequently used for treatment in cases of foreign body embolization, but without evidence of response until the recent case report of Smith and co-workers.

The case noted herein is the second report of improvement in this disease with steroid therapy. In this young woman, arterial oxygenation, D, abnormal findings on chest roentgenograms, and symptoms of exertional breathlessness were improved after treatment. Thus, although severe granulomatosis and fibrosis were present, as noted on necropsy, there is evidence of reduction in the severity of the acute inflammatory process with treatment. Even though gas transfer improved, pulmonary volumes were minimally reduced from levels before treatment, a finding that is unexplained.

Scanning with $^{67}$gallium, which has not previously been reported with foreign body embolization and granulomatosis, revealed in this patient abnormal uptake throughout both pulmonary fields. The abnormal uptake was reduced after several months of treatment with high doses of corticosteroids. Concurrent with the decreased activity on scans with $^{67}$gallium, there was a reduction of the interstitial infiltrate on chest roentgenograms.

Scans of the lungs using radioactive $^{67}$gallium citrate, which is bound within the lysosomal fraction of reticuloendothelial cells, macrophages, lymphocytes, and polymorphonuclear leukocytes, have been used in the evaluation of a variety of neoplastic, infectious, and inflammatory processes. Increased uptake of gallium, which was initially described in pulmonary disease with neoplasm, occurs with bacterial pneumonia, pyogenic abscess, active tuberculosis, active sarcoidosis, fungal infection, pneumoconiosis, systemic lupus erythematosus, eosinophilic granuloma, and chronic interstitial pneumonitis.

Several studies have observed that the concentration of $^{67}$gallium is proportional to the activity of the inflammatory process. Niden et al. noted that in diffuse interstitial disease of various causes, the uptake on scans with $^{67}$gallium correlates with the activity of the inflammatory process present on pulmonary biopsy, a finding that Crystal and co-workers reported in idiopathic pulmonary fibrosis. It is reasonable to assume a similar situation in talc-induced pulmonary granulomatosis. While the reduction in the abnormal concentration of $^{67}$gallium that occurs after steroid therapy may indicate improvement in the disease in this case, such a conclusion must remain speculative, since corticosteroids may directly depress the uptake of $^{67}$gallium itself without affecting the disease. It can be said that the abnormal uptake on scans with $^{67}$gallium was reduced at a time when there was also improvement in the patient's symptoms, arterial oxygenation, and roentgenographic appearance on chest x-ray films. For the evaluation of the patient with talc embolization and granulomatosis, scanning with $^{67}$gallium provides an additional tool for use with clinical, pulmonary function, and routine radiologic parameters.

While the pathophysiology of the granulomatous reaction in talc-containing foreign body embolization has not been fully established, there are several observations worth noting. In the case reported herein, there appeared to be progression of the disease after the patient discontinued the intravenous injection of medication. There was no evidence by history (from the patient and other observers) or by physical examination that the patient intravenously injected medication after switching to a program of treatment with methadone in October 1977. Nevertheless, the severity of her breathlessness markedly increased from October (when she was breathless after walking six blocks) to March of the following year (when she was breathless at walking less than a block or climbing one flight of stairs). Her arterial oxygenation deteriorated as well, with her $P(A-a)O_2$ changing from August ($PaO_2$ of 83 mm Hg and $P(A-a)O_2$ of 17 mm Hg) to March ($PaO_2$ of 72 mm Hg and $P(A-a)O_2$ of 28 mm Hg).

Necropsy of this patient showed deposits of talc throughout the vascular bed and interstitium in both lungs. A variable pattern of deposition, with some cases having primarily either vascular or interstitial involvement, has been previously noted; and it has been suggested that the cause of such variability is unknown.

It is reasonable to believe that the type, as well as the amount, of material injected, and the type of host response are involved with the lungs' processing of intravascular foreign material. Not all substances that are embolized into the pulmonary vasculature will elicit such a dramatic response of the tissue; for example, starch injected intravenously will occlude small vessels but without a reaction of the tissue to the starch spheres; however, talc, when injected experimentally, will cause endothelial proliferation, with giant cells within the endothelial masses and narrowing of vessels and, later, extravascular crystals associated with granulomas.

The exact mechanism of the damage from talc to tissue has not been delineated, but talc-induced injury to the lungs in modern mining, industrial, or cosmetic exposure is rare, although individual cases with excessive exposure have been reported. The viability of macrophages and their ability to phagocytize colloid particles are not reduced by cosmetic-grade talc dust. In embryonic pulmonary explants grown in vitro, crystalline talc alone, unlike silica or asbestos, does not stimulate an outgrowth of fibroblastic cells, suggesting that the cellular response to talc may be dependent on its association with free silica or asbestos dust.

It is of interest whether the response to talc may be immunologically mediated, perhaps through delayed cellular hypersensitivity. Unanue and Benacerraf found a marked difference in the response of tissue to embolization of insoluble beads linked to proteins into the lungs of immunized and nonimmunized guinea pigs. Unlike the nonimmunized animals, in which very mild foreign body granuloma were produced, severe and progressive granulomas developed in the immune guinea pigs.

Roberts and Moore have suggested that actual damage to pulmonary tissue may be of importance in the development of a delayed hypersensitivity response. In an animal model of hypersensitivity pneumonitis...
oped by Moore et al., insufflation of pigeon antigen caused a humoral response, with no evidence of cellular hypersensitivity or alteration of tissue; however, if these animals were first given BCG vaccine intravenously and then were challenged with the inhalation of the antigen, they developed the histologic changes of cellular hypersensitivity. Certain antigens, as Bice et al. reported with Micropolyspora faeni testing in rabbits, may serve as their own immunologic adjuvant, and formation of granulomas in certain cases may be associated with the activity of the adjuvant.

Whether talc presented by embolization, perhaps with tissue damage or adjuvant effect, causes its effect through an immunologically mediated process is unproven but it is a possibility that should be considered, in light of the variability of the extent of the parenchymal involvement, the progression of the disease beyond the time of the initial insult, and the response of the process to corticosteroid therapy. Immunologic testing, such as with macrophagic migration inhibition and lymphocytic stimulation testing, which were not done in this patient, would provide a fertile area of future investigation.

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Reversible Central Apnea in an Infant with Cyanotic Heart Disease*

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The purpose of this report is to present the findings in a neonate with tetralogy of Fallot and a history of prolonged sleep-related apnea requiring resuscitation. At a baseline arterial oxygen pressure of 46 mm Hg, his preoperative responses to carbon dioxide during non-REM sleep (26.1 and 26.6 ml/kg/min/mm Hg of alveolar carbon dioxide tension [Paco2]) were identical to those reported in near-miss sudden infant death syndrome. Following a systemic-pulmonary arterial shunt, the arterial saturation reached 95 percent, and no further apnea occurred. The prompt normalization of the response to carbon dioxide following surgery (75.2 and 75.4 ml/kg/min/mm Hg of Paco2) indicates that, unlike infants with the sudden infant death syndrome, a low sensitivity to carbon dioxide in infants with cyanotic heart disease may be dependent on hypoxemia and, thus, reversible.

Infants are now being identified in whom prolonged sleep-related apnea is associated with an abnormality in central carbon dioxide responsiveness. Patients with central hypoventilation syndrome, for example, have essentially no ventilatory sensitivity to carbon di-

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