Pulmonary Alveolar Proteinosis
Report of a Case from Australia

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In 1958, Rosen, Castleman and Liebow described 27 cases of a new disease which they called pulmonary alveolar proteinosis and since then, about the same number of cases have been reported elsewhere in the literature.

It is a condition with characteristic pathology in which the pulmonary alveoli are filled with a thick mucoprotein and to a lesser extent proteaceous coagulum and a clinical course which appears to follow a reasonably regular pattern, although occasional variations do occur. Symptoms mostly appear insidiously and are characterized by malaise, cough, dyspnea and weight loss over a period of some months. There may be low-grade fever, chest pain and occasional hemoptyses. Later, cyanosis, finger clubbing and pulmonary insufficiency become prominent, and bacterial and mycotic infections may complicate the picture. Chest x-ray films show diffuse, generalized and at first nodular infiltration, with sometimes a peculiar butterfly-like effect radiating from each hilum. Mortality is about 25 per cent despite heroic treatment in some cases.

Most patients have been reported from North America, but other isolated cases have been described from Western Europe, Great Britain, Japan, New Zealand, and now Australia. A review of the literature concerning the disease recently has been recorded by Sanders, Kahn and Sbar and by Kroecker and Korfmar.ch.

The following case history of a 46-year-old man with this disease, undiagnosed during life, is presented as one of the first to be recognized in Australia:

CASE REPORT

The patient had lived in Australia for five years after immigrating from England. A com-pulsory chest x-ray examination carried out in 1958 was normal. He was in good health until June, 1960 (11 months prior to admission to hospital) when he first complained of some tiredness and cough which persisted for several months. He then developed vague lower abdominal cramp-like pains with vomiting and diarrhea and occasional blood-stained feces. Shortly after this, he noticed the cough and shortness of breath after exertion becoming worse and also night sweats and increasing general malaise. He was treated with antimicrobials (chloramphenicol, penicillin and sulphonamides) by his private physician without much relief of symptoms. During the ten weeks preceding admission, his cough was accompanied by white and frothy but occasionally "ginger" colored sputum, recurrent pyrexias and a loss of some 21 pounds in weight. There was no family history of severe illness or allergic disease; he himself had no previous sickness, but a year earlier he had some contact with a workmate with active pulmonary tuberculosis.

He had been a sand-blaster for five years, working alone, and was self-taught. Before that he had been a milkman, a tram conductor, a part-time gardener, and a builder's laborer where his family thought he "made bricks" (probably concrete blocks, not kiln bricks).

All those who knew him as a sand-blaster remarked on his constant carelessness in taking safety precautions. He would often not bother to wear the regulation mask, and the one he owned was split down the side and almost useless. Visitors entering his workshop in between spells of blasting would be likely to find him unmasked in an atmosphere where one would immediately feel the teeth griting because of the suspended hard dust.

He blasted the following things (and probably many more): old paint, rusty scale from metal window frames, motor-car engine crank cases, plastic-dipped metal objects, baked enamel and chromium-plated chairs. He would sometimes clean a job with powdered caustic soda and then blast without washing it beforehand.

He was interested in cheap "cold-galvanizing," a process by which he could retouch galvanized metal which had been sent to him to have the rust blasted off at spoiled spots. His idea seems to have been to mix zinc dust with varnishes or...
resins and spray this out of a paint gun. He made his own mixtures and from the empty cans in his workshop he seems regularly to have used fine zinc dust and a varnish composed of vinyl chloride, chlorinated rubber, toluene and xylol. He was also using a commercial ready-cured cold epoxy resin mixed with zinc dust. It contained no setting agent. His daughter sometimes helped with this work. It was done in a different shed than the sand blasting. Neither she nor he used a mask when they sprayed. She never felt any ill effects and her chest was x-rayed and found to be clear in June, 1961, when she and the rest of the family were examined as his contacts. His last job before entering the hospital was cleaning off a large boat with a kerosene blow-torch and respraying with red, heavy marine paint.

He was first seen at the Chest Clinic, Royal Adelaide Hospital in May, 1961. On examination, he was sick-looking, dyspneic on slight exertion and rather emaciated. He had marked finger clubbing, but apart from scattered crepitations over both lung fields and a positive tuberculin test, other clinical findings were normal. A chest x-ray film showed fine nodular opacities through both lung fields (Fig. 1). He was admitted to the Royal Adelaide Hospital on May 8, 1961, with a provisional diagnosis of miliary tuberculosis and possible silicosis. At that stage, he was coughing up copious amounts of blood-stained sputum with an evening pyrexia of 104°F. Blood picture (WBC 7,800 per mm. with no eosinophils) urinalysis, blood chemistry, repeated sputum examinations for all organisms and proteinaceous material, also later cerebrospinal fluid examination, scalene node and liver biopsies were all negative. Normal or negative results were also obtained to serum electrolytes, L.E. cells, liver function and proctoscopy (carried out because of some episodes of diarrhea). An erythrocyte sedimentation rate was 116/126 and an electrophoretic pattern showed low albumin, all globulins (very high) and a strong "\( \beta\)-\( \gamma \) veil or filling in of the area between the beta and gamma globulins." Simple ventilatory function tests showed a vital capacity of 2.8 liters of which 2.2 were expired in the first second and maximum forced expiratory flow rate or peak flow was 350 liters per minute. (He was on heavy corticosteroid therapy at the time.)

He had been diagnosed on admission as probable tuberculosis and during the first three weeks, treatment consisted of streptomycin 2 to 4 gm. plus isoniazid 300 to 900 mg. daily. It became reasonably obvious, however, when first seen by us after that time, that this therapy was having little effect on the course of the disease and the more detailed investigations mentioned above were then initiated. However, a lung biopsy was deferred by the surgeons because of the patient's poor clinical condition. Later he received treatment with tetracycline, erythromycin, nystatin and large doses of iodides without relief and at one stage, prednisolone was increased to 80 mg. per day, but with little relief of symptoms. It can be said that despite the above intensive therapy, his condition steadily deteriorated (Fig. 2). He became restless, depressed, irritable and very dyspneic and died on August 7, 1961, some

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**FIGURE 1:** A chest x-ray film taken on May 5, 1961, a few days before admission to the hospital showing fine patchy opacities in each lung field particularly radiating from each hilum. **FIGURE 2:** A chest x-ray film taken ten weeks after admission to the hospital showing extensive spread of the disease process throughout both lung fields.
three months after admission and 14 months after the onset of his first symptoms.

Necropsy: The body showed some muscular wasting. Both lungs were consolidated and together weighed 3,300 gm. and sank in water; they felt nodular when palpated and a thin fibrinous pleurisy covered all surfaces; there was one small adhesion in the mid-axillary line on the right side. The rest of the organs of the body showed no gross change, except for the pancreas where there were two minute white opaque areas (0.5 mm.) on the anterior surface suggesting fat necrosis. The following organs were examined at the time of the necropsy, with periarteritis, neoplasm, and non-specific inflammations or fibrosis in mind, and were macroscopically normal; entire gastrointestinal tract, liver, spleen, adrenal glands, kidneys, ureters, urinary bladder, testes, gall bladder and biliary passages, retroperitoneal space, tongue and pharynx, thyroid gland and brain.

Microscopic examination showed abnormalities only in the pancreas, liver and lungs. The pancreas contained two small areas of typical fat necrosis, which were confirmed to the places seen macroscopically, and would not have been a remarkable finding in any necropsy.

The liver showed some fatty change. This was widely present, but to some extent focal, being more often periportal than centrilobular. There was minimal fibrosis in periportal areas near the liver capsule with a mild lymphocytic infiltration. Also, some very occasional small areas of focal necrosis with no special lobular distribution were found.

The lungs showed numerous areas where the alveoli were filled with caseous eosinophil material which was periodic acid-Schiff positive, and stained blue with Mallory and green with Masson trichrome (Fig. 3). There was no acute inflammatory reaction in the alveolar walls, and no infiltration with lymphocytes or plasma cells in these areas. Many alveolar cells were swollen and appeared to be multiplying. Here and there in the lungs were a few fibrous nodules suggestive of early silicosis, but compared to the gross changes within the alveoli, these were minor.

Over small areas, the lungs varied from having almost a normal air entry into a few alveoli, to their being filled with the caseous material or with alveolar cells. The coagulum contained numerous clefts, which were seen to contain doubly refractile crystals in frozen sections. The intra-alveolar material seemed to have some relationship with the multiplication of alveolar cells, for there were areas where there was an apparent transition from cell aggregations to cell necrosis to amorphous coagulum.

The appearances were those which have been described as "pulmonary alveolar proteinosis."

**DISCUSSION**

The patient presents the characteristic pattern of pulmonary alveolar proteinosis in symptomatology and radiologic and pathologic changes. He was exposed to occupational inhalation hazards, he received intensive treatment with antibiotics and in addition, corticosteroid therapy, three factors which have been possibly incriminated in the disease process. It became apparent after two or three weeks of treatment with specific antituberculosis therapy plus antibiotics and prednisolone, that the man was not suffering from tuberculosis unless it was caused by organisms of a highly drug-resistant character. Indeed, his disease appeared unlikely to be any other acute inflammatory or allergic process on account

![Figure 3](https://example.com/figure3.jpg)

**Figure 3:** Microphotograph enlargement (x100) to show pulmonary alveoli filled with periodic acid-Schiff-positive proteinaceous material.
of the lack of response to corticosteroids; for the same reason, such conditions as the collagen group of diseases of even the Hamman-Rich syndrome could possibly have been excluded. As all other investigations, including sputum examinations and liver and scallene node biopsies, were negative, and in the absence of lung biopsy, the diagnosis was necessarily speculative. It included the reticuloses, secondary neoplasms, sarcoidosis, pulmonary alveolar proteinosis, stannosis, etc. In the end, it was left to the necropsy to establish the nature of the disease.

The cause of pulmonary alveolar proteinosis so far obscure. A similarity has been shown, particularly in European reports, to pneumocystis carinii pneumonia, but no such parasites in the proved cases have been demonstrated. It has been suggested that it may be an immune response to either exogenous or endogenous antigenic substances. It may even be related to a condition called thesaurosis, reported by Bergmann and others, which appears to be due to inhalation of hair sprays containing certain epoxy resins. This was in close careless contact with such substances and they may well have been responsible for initiating an early phase of his disease. Quite a number of the cases of pulmonary alveolar proteinosis described had some occupational inhalation hazard prior to illness. Although infective processes have been suspected, no positive organisms have been isolated so far; certain fungi such as Nocardia and Candida have been present in some cases. The patients concerned had received antibiotic (particularly penicillin) therapy early in their sickness and most of those who received corticosteroid therapy died. Rosen has pointed out that the pathology is so characteristic that the disease could scarcely have escaped description previously and that as lesions are confined to the lungs, the causative agent was most likely to be inhaled as an organism, irritant or antigen. Speculatively, a simple explanation could be that in certain susceptible people, the inhalation of a modern synthetic substance initiates symptoms and later antibiotic therapy encourages progression of the disease process with superimposed fungal invasion; corticosteroids further complicate this picture, perhaps by modifying the response in the alveoli. It may well be that where a combination of these factors does not exist, only transient symptoms occur, the disease never coming to recognition.

Several patients have been diagnosed by finding proteinaceous material in their sputum. The methods used have been the periodic acid-Schiff stain test and also material obtained by endobronchial heparin infusions. In the cases reported by Ramirez and his co-workers a marked elevation of serum lactic acid dehydrogenase and low pH in the sputum was observed. These returned to normal with progressive radiologic improvement.

This case emphasizes the need for early lung biopsy if sputum findings are negative because antibiotic and corticosteroid therapy may be useless or even contraindicated. The patient reported by McDowell and others in New Zealand recovered completely with the simplest of symptomatic treatment, yet he apparently, at one stage, was in a most critical condition.

Pulmonary alveolar proteinosis is being reported from several countries and now from Australia. It would appear to be a modern disease and should be suspected in any patient with undiagnosed radiologic evidence of diffuse pulmonary infiltration, particularly with a history of respiratory symptoms gradually worsening over a period of some months.

REFERENCES


CARCINOMA OF ESOPHAGUS

Sixty-three consecutive cases of treatment of carcinoma of the esophagus at a university hospital have been reviewed. A selective program of therapy combining supervoltage radiation and surgery has been described. Eighteen consecutive patients received supervoltage radiation in preparation for surgery and only 12 of these underwent colon transplantation and esophagectomy with only three survivors. In two of 12 cases of operation, there was no gross or microscopic evidence of residual tumor in the surgically excised esophagus.

CARCINOMA OF TRACHEA

Five basal cell carcinomas of the trachea, all in women whose ages ranged from 21 to 63 years at the time of diagnosis, are reported. The variations in patterns of growth that may occur are stressed. Four patients were treated initially by endoscopic resection followed by irradiation; the fifth patient was treated by resection only. The three ultimately fatal neoplasms were characterized by slow progressive growth and local recurrences and there was one instance of pulmonary metastases. Three patients died as a result of extensive locally recurrent and infiltrative neoplasm 8, 12 1/2 and 13 years after treatment; two are alive 6 1/2 and 8 years after treatment.

RADIOGRAPHIC PULMONARY CHANGES IN NEAR-DROWNING

The roentgenographic features of ten cases of near-drowning, one case of sea-water aspiration, and two of acute death from drowning have been presented. This series tends to support previous opinion that the most frequent radiographic appearance is that of a diffuse, fuzzy, nodular infiltration throughout both lung fields, somewhat sparing the bases, apices and extreme lateral portions of the lungs and more concentrated in the perihilar and medial areas. The spectrum may vary, however, from this more frequent presentation to that of a fairly homogeneously diffuse infiltration with small, fuzzy nodules covering almost the entire lung field, but with minimal involvement of the extreme bases and apices. The process may also be more accentuated in either the right or the left lung. The infiltration tends to clear almost entirely in the uncomplicated case in 12 hours to six days, but occasionally not until eight to ten days.

The authors feel that the radiographic findings represent pulmonary edema and hemorrhage. There is probably a minimal component of pneumonitis which usually never evolves further because of the general use of antibiotics. Also, considering the usually rather rapid resolution of the densities in these cases, it is probable that those in which the infiltrations have not cleared almost completely by ten days, or in which they become noticeably increased in three to four days, represent a superimposed pneumonitis of major proportions.


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