consideration, and likelihood of lead displacement. We believe that the benefits of atrioventricular coordination outweigh these theoretical disadvantages in a patient after treatment of transposition by Mustard’s technique. The problem of a relatively smooth-walled left atrium was solved with a tined lead that wedged tightly into the elongated left atrial appendage. Ventricular pacing in patients with intra-atrial appendage has often required the placement of epicardial electrodes because of the difficulty in securing catheter position in the smooth left ventricle.

The feasibility and advantage of atrial pacing must be thoroughly investigated in each patient by preoperative electrophysiologic catheterization studies. It is mandatory to demonstrate normal conduction through the atrioventricular node from impulses generated within the left atrial appendage. It is also important to confirm that conduction through the atrioventricular node will be successful at varying heart rates, including sinus tachycardia. In this particular patient with an intra-atrial baffle, it was most important to demonstrate adequate patency of the superior vena cava-baffle suture line to permit transvenous placement of the lead. Because this is a common site of significant obstruction with this operation, angiographic analysis of this area is important.

Although this patient was asymptomatic prior to pacemaker implant, there has been a subjective increase in activity and improvement in attitude noted by the family since the institution of atrial pacing. Twenty months of follow-up have demonstrated no change in lead position or loss of pacemaker function.

We submit this report to suggest the feasibility of transvenous left atrial pacing in children after the intra-atrial baffle operation. It should be emphasized that careful patient selection through electrophysiologic studies, selection of proper lead and pacemaker, and thorough follow-up all contribute to successful patient therapy.

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D-Penicillamine-induced Severe Pneumonitis
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We report the first histologically described case of severe D-penicillamine-induced pneumonitis. It occurred in a 73-year-old woman who suffered from rheumatoid arthritis and had previously demonstrated gold intolerance. Pathologic study disclosed marked interstitial and alveolar damage resembling that described with certain chemotherapeutic agents. We assess the drug’s responsibility, discuss possible pathogenetic pathways, and provide suggestions regarding the patient on a D-penicillamine schedule.

The use of D-penicillamine for the treatment of rheumatoid arthritis has been markedly restrained because of the frequent occurrence of various adverse reactions. Among these are pulmonary complications, including bronchiolitis obliterans and diffuse miliary lung opacities. The latter have never been described histologically. We report a case of D-penicillamine induced pneumonitis with a histopathologic study.

CASE REPORT
A 73-year-old woman was admitted on August 23, 1980 because of fever and dyspnea. She gave a history of rheumatoid arthritis since 1978 for which she received (in 1979) several courses of gold salts, which were discontinued because of skin rash. D-penicillamine, 300 mg daily orally, was started on July 1, 1980 for treatment of recurring joint symptoms. On August 15, after a total D-penicillamine dosage of 10.5 g, she noted she was dyspneic and febrile. She was given ampicillin by her physician and D-penicillamine was withheld, but her respiratory condition worsened and required her admission. Physical examination disclosed a tachypneic patient; temperature was 37.7°C and numerous fine inspiratory rales were heard over both lung fields. Cyanosis was present at rest, and arterial blood gases while the patient received 4 L/min oxygen via a nasal cannula were: PaO₂, 43 mm Hg, and PaCO₂, 35 mm Hg. Laboratory data showed normal red blood cell count, 20,000 leukocytes with normal differential count and no eosinophils; there was no proteinuria. A test for rheumatoid factor was negative and antinuclear antibodies titer was 1/1,024, but there were no anti-DNA antibodies. Complement fractions were within normal limits and no circulating immune complexes could be detected. Anteroposterior chest x-ray film (Fig 1) showed decreased lung volume, small bilateral pleural effusions, and diffuse opacities with a predominant interstitial pattern, although alveolar shadows could be observed in both lung bases.

Mycoplasma pneumonia and D-penicillamine reaction were considered and erythromycin, 2 g per day, was given. The respiratory condition remained stable, but the patient

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D-Penicillamine has been associated with two different pulmonary reactions, namely bronchiolitis obliterans and diffuse miliary opacities noted on x-ray film. \(^1,2,3\)

Bronchiolitis obliterans has been reported in several patients receiving D-penicillamine for connective tissue diseases, mainly rheumatoid arthritis. \(^4\) Clinically, these patients developed a rapidly progressive and severe airflow obstruction while taking the drug in various amounts. Roentgenographically, hyperinflation and normal chest x-ray film findings have been observed, but diffuse interstitial or alveolar shadows are also reported. Microscopically, the disease results from the growth of granulation and subsequent scar tissue into the bronchiolar lumen, but the great majority of the alveoli remain normal. \(^4\) This pathologic picture differs from that of our patient in which marked alveolar damage was present, while the bronchioles were nearly unaffected.

It should be stressed that the association of connective tissue disease and bronchiolitis obliterans has also been described in the absence of D-penicillamine exposure, and thus, the respective responsibility of the drug and that of the underlying disease in the pathogenesis of the airway obstruction remain to be clarified. \(^4\)

A diffuse miliary lung pattern similar to that in our patient has been described in very few cases who were receiving D-penicillamine for rheumatoid arthritis. \(^1,2,3\) These opacities were transient, \(^1,2,3\) and well tolerated; they did not require any lung biopsy procedure. It is thus very difficult to assess the pathologic background of these patients inasmuch as comparable x-ray film changes may be observed during the course of bronchiolitis obliterans. \(^4\) However, in Eastmond's \(^1\) case, the restrictive ventilatory defect and the FEV\(_1\)/VC of 76 percent are not likely to be related to bronchiolar obstruction.

The criteria required for the establishment of an adverse drug reaction (ADR) have been reviewed by Irey. \(^3\) In the present case, three alternative diagnoses for this acute lung damage had to be discussed. Rheumatoid arthritis may be associated with pulmonary fibrosis. However, it is reported to develop rather slowly and affected patients frequently demonstrate sero-

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**DISCUSSION**

**Figure 1.** Anteroposterior chest x-ray film demonstrates diffuse interstitial shadows predominating in the lung bases where an alveolar pattern with bronchograms can be seen. The patient died abruptly from a cerebrovascular accident on the 13th hospital day.

Postmortem examination was limited to the lung and a sample was obtained from the right middle lobe. Microscopic examination (Fig 2) showed marked interstitial fibrosis and edema, numerous lymphocytes and plasma cells scattered throughout the interstitial space. Alveoli were severely narrowed and contained desquamated alveolar cells and lipid-laden macrophages. Alveolar pneumocytes frequently demonstrated a marked hyperplasia with a racket-shaped appearance, and were protruding into the alveolar lumen. Slight bronchiolitis without obliteration was also observed; the vessels were normal. Electron microscopy showed that the fibrosis was made of collagen, elastic and muscular fibers and that the septa contained numerous histiocytes, fibroblasts and less numerous mast-cells. Moreover, dysplastic changes of the alveolar epithelium involved mainly the type 2 pneumocytes. Direct immunofluorescence failed to disclose immunoglobulins A, D, E, G, M, or complement fractions within the lung parenchyma.

**Figure 2.** Upper panel shows at low power view a severe interstitial fibrosis with cellular infiltrate and narrowed alveoli containing desquamated cells. (Hemalum-phloxin-safranin staining, \(\times 10\)). Lower panel shows at higher magnification and alveolus lined with markedly dysplastic pneumocytes protruding into the alveolar lumen, the latter appearing filled with desquamated pneumocytes and lipid-laden macrophages (same staining as above, \(\times 125\)).

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positivity and subcutaneous nodules. All these features were lacking in our case. A careful questioning failed to demonstrate any exposure to inhalants or toxic agents capable of producing an acute lung reaction. Mycoplasma or viral pneumonia may progress rapidly to lung fibrosis, but the negativity of repeat serologic studies for Myxovirus influenzae, parainfluenzae 2 and 3, Herpes virus, cytomegalovirus, Mycoplasma pneumoniae and Legionella pneumophila give no support to an infectious etiology. We therefore consider that this acute lung damage can reasonably be ascribed to D-penicillamine.

The main pathologic features in our patient were the extent of the interstitial fibrosis and the severity of dysplasia of the alveolar pneumocytes. To date, the combination of these changes has been mainly described in lung disease induced by some chemotherapeutic agents and has led some authors to consider them as "characteristic of drug-induced and radiation pneumonitis." This statement gives further support to D-penicillamine as the causative agent in our patient.

The pathogenesis of the D-penicillamine-induced lung damage in our patient remains unclear. The negative search for immune complexes either in the serum or within the lung parenchyma provides no support to their intervention which has been suggested in D-penicillamine nephropathy. There is no evidence such as eosinophilia or granuloma formation suggesting a hypersensitivity mechanism, which has been put forward in methotrexate and procarbazine pneumonitis. Given the similar pathologic pattern, the drug might behave as antineoplastic agents do, and have a toxic effect upon the lung. Furthermore, it remains possible that the interference of D-penicillamine into collagen and elastin synthesis may have influenced the time course of the fibrotic process.

Gold salts and D-penicillamine may be used sequentially for the treatment of rheumatoid arthritis. Recent reports have drawn attention to the occurrence of adverse drug reactions to both drugs, the target organ of the reaction to either drug being the same or different. Moreover, all patients, including the patient presented here, who developed a miliary pattern while on D-penicillamine and for whom mention is given, previously suffered from gold-induced skin rash. Possible connections may therefore exist between D-penicillamine-induced pneumonitis and earlier gold intolerance; this hypothesis requires further study.

From a practical point of view, we think that D-penicillamine has to be added to the list of drugs capable of producing severe interstitial and alveolar damage. If this drug is scheduled in a patient who previously received gold salts, a careful search for gold intolerance should be performed. As pointed out by Epler et al., pulmonary function tests and chest x-ray examination should be included in the follow-up of patients who are given this drug.

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