begin two hours to 10 days after the initial dose of the drug and consist of fever of acute onset, chills, cought and dyspnea. Sollaccio and his associates (20) were the first to point out that the pulmonary reaction can be delayed, occurring after the drug has been taken during a prolonged period (one year), and that the symptoms may persist for a "subacute" period (four weeks) without causing the patient to be acutely ill, as in the usual case. David et al., (21) from our clinic, have described a seven-year-old child with chronic pulmonary symptoms of one year's duration who had taken the drug for three years before the reaction developed.

Strauss and Griffin (11) summarized the eight cases reported up to 1967 and added two of their own. In all 10 cases, the onset of pulmonary symptoms was acute, beginning two hours to nine days after the initial dose of nitrofurantoin. Of the 10 patients, six were women, with an age range of 31 to 61 years. The pulmonary infiltrates were in the lower lobes and usually in both lower lobes. Three of the 10 patients had associated pleural effusion. Symptoms consisted of fever, cought and dyspnea, and all patients had symptoms that disappeared 24 to 48 hours after the use of the drug was discontinued. Four of the 10 patients had eosinophilia. In all cases the diagnosis was substantiated by the disappearance of symptoms and the rapid clearing of the roentgenographic findings after the use of the drug was discontinued. None of their patients underwent lung biopsy, but in most, a provocatory test was confirmatory. Steroids were not used.

The onset of pulmonary symptoms was gradual in the five patients discussed in this report. The duration of pulmonary symptoms varied from seven weeks to six years before the nitrofurantoin therapy was stopped. Only one patient (Case 2) had a history of febrile reaction associated with the onset or occurring during the course of the pulmonary symptoms, as has been characteristically present in patients with the acute-onset variety. The interval between the initial dose of nitrofurantoin and the onset of pulmonary symptoms ranged from six months to six years.

The five cases presented above suggest that nitrofurantoin can be taken for a prolonged time (six months to six years) before pulmonary side effects occur, and that pulmonary symptoms may be chronic (seven weeks to six years) rather than acute, which has been the most commonly recognized manifestation of nitrofurantoin pulmonary reaction.

In all cases the roentgenogram of the chest gave evidence of a nonspecific, diffuse, bilateral interstitial pulmonary infiltrate that frequently was most severe at the bases. Roentgenographically, the lung bases have also been most frequently involved in the cases of acute onset. Pleural effusion was not seen in any of our patients.

Pulmonary function was abnormal in all five patients and was typical of restrictive disease with an impairment of the carbon monoxide diffusing capacity. Two of the three patients who were retested showed great improvement. No patient had cosinophilia. The level of lactic dehydrogenase enzyme was elevated in the three patients tested. De-Remee (22) has reported that this test is a reliable indicator of active interstitial pulmonary disease and frequently correlates with the clinical course. The level of this enzyme, rechecked in the follow-up study of two of the three patients, correlated with improvement in the clinical course.

A transbronchoscopic lung biopsy (23) was done on four patients, and an open lung biopsy on the fifth. In all five patients, both types of biopsy revealed chronic interstitial pneumonitis or fibrosis or both. The histologic appearance was not diagnostic, and was not unlike that seen in idiopathic, chronic, diffuse interstitial pneumonitis.

All patients were traced, and four of the five had moderate to definite improvement after the use of nitrofurantoin was discontinued and after administration of steroids. Only one patient (Case 1) did not improve significantly after withdrawal of the nitrofurantoin. She had had pulmonary symptoms for six years, in contrast to the other four patients, who had pumonary symptoms for seven weeks to one and one-fourth years. A few months after the onset of the symptoms, She was seen at another institution, where chronic Hamman-Rich syndrome was diagnosed on the basis of an open lung biopsy. Therapy was started with steroids, but the nitrofurantoin dosage of 50 mg twice a day was continued (for a total of eight years). In a study of patients with chronic interstitial pneumonitis and fibrosis, Sheridan et al. (24) have shown that the degree of fibrosis present determines whether the condition can be reversed by steroids. The patient who does not improve with withdrawal of nitrofurantoin and with