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Allergic Alveolitis in Swedish Farmers

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ABSTRACT

Allergic alveolitis due to mold dust inhalation in farmers is a severe but rare disease in Scandinavia. In this report 38 cases of the disease are presented. There were 31 men and 7 women, with mean ages of 46 and 38 years respectively. Strict diagnostic criteria were used, resulting in 21 definite, 12 probable and 5 possible cases. None of the patients were current smokers, but 10 of the men were ex-smokers. The great majority of the patients fell ill between October and April. The symptoms were dyspnea, cough, fatigue, episodes of fever, and in some cases loss of weight. The average duration of the disease was 6 months. The moldy material most commonly associated with the disease was straw, followed by hay, grain, and wood chips. For those tested serum lactate dehydrogenase was raised in 80% and the mean value for PaO_2 was 7.8 kPa. Precipitating antibodies to mold antigens were positive in 68%. In general, pulmonary function tests showed a restrictive pattern. Over half of the patients still had dyspnea on exercise after recovery. Three fourths of the patients were treated with antibiotics and thus clearly had been misjudged as having an infection.

INTRODUCTION

Allergic alveolitis due to mold dust is a rare disease in Scandinavia (9,21) but one which for the affected farmer can imply permanent invalidity due to impaired pulmonary function. The disease can be avoided if the exposure to moldy dust is prevented. The disease may have serious economic consequences and may force

the farmer to give up farming. When patients with this disease consult a physician, their symptoms are often inaccurately interpreted as an infectious disease, which may lead to unnecessary antibiotic treatment with its inherent side effects. It therefore seems to be of great importance to increase our knowledge about allergic alveolitis.

Apart from a few investigations (2,22) little attention has been paid to problems related to farmer's lung in Sweden until recent years. In the present report 38 cases of allergic alveolitis in Swedish farmers are presented. Symptoms and signs, laboratory findings and exposure characteristics are described.

MATERIAL AND METHODS

Selection of cases: The presented cases of allergic alveolitis were obtained from two studies previously performed in Sweden (9,10). The first one was performed in 1982 in the northern half of Sweden. A questionnaire devoted to symptoms characteristic of allergic alveolitis was sent to 6,267 farms and if allergic alveolitis was suspected, medical records were analyzed and the responder was invited to attend a personal interview. A second, prospective study was undertaken in 1984 to 1986 with the aim of measuring the exposure associated with allergic alveolitis; Swedish physicians were asked to report new cases of allergic alveolitis to the investigators and were offered assistance with a detailed environmental analysis, including measurements of microorganisms. In the first study 21 cases were found and in the second one 17 cases were identified.

Diagnosis: The medical records and the results of the interviews were evaluated by two independent physicians. The cases were judged according to the diagnostic criteria for allergic alveolitis proposed by an international work group in 1985 (4,20).

The main criteria were:
1) exposure
2) symptoms
3) chest radiographic changes.

Additional criteria were:

1) basal crepitant rales
2) impairment of pulmonary diffusion capacity
3) PaO_2 decrease at rest or exercise
4) restrictive pulmonary function impairment
5) lung biopsy histopathologic changes
6) positive provocation test.

All main criteria and at least two additional criteria had to be fulfilled. Other diseases with similar symptoms and clinical findings had to be ruled out. If the criteria were otherwise fulfilled, but the chest X-ray was normal, the diagnosis was considered confirmed if a lung biopsy showed changes compatible with allergic alveolitis.

In 21 definite cases the main criteria and at least two additional criteria were fulfilled (Table 1). In 12 probable cases the main criteria were met but the patients had not been completely investigated to determine whether the additional criteria were also fulfilled; allergic alveolitis was considered probable, however, since the patient had typical symptoms including dyspnea. In 5 further possible cases the history and symptoms were compatible with allergic alveolitis but some symptoms or laboratory findings indicated that other lung diseases with similar symptomatology could not be completely ruled out. For two of the possible cases sarcoidosis could not be completely ruled out, one patient had laboratory findings compatible with systemic lupus erythematosus, and in the remaining two patients there were details in the history which could suggest an episode of ODTS (organic dust toxic syndrome) (4) and infectious disease respectively. Consequently the study was based on 21 definite cases, 12 probable cases and 5 possible cases.

The symptoms, clinical signs, chest-radiographies and lung pulmonary function tests are described at the time, when the patient was admitted to hospital. In general, the patients then were in phase two according to Fuller's original classification (6).

	Number	Exposure	Sympt.	X-ray	Main criteria fulfilled	Other disease	Crepit.	PaO2	Lung function Restr.	Lung function Obstr.*	DLCO	Biopsy	Provoc.	Add. criteria fulfilled
Definite cases	21	21/21	21/21	21/21	21/21		21/21	13/16	18/20	0/20	12/12	2/2	2/2	21/21
Probable cases	12	12/12	12/12	12/12	12/12		8/12	..	2/2	0/2	..	..	..	0/12
Possible cases	5	5/5	5/5	4/5	4/5	2 sarcoidosis?	2/2	1/1	1/2	1/2	1/1	1/1	..	1/2
						1 SLE? °	1/1	1/1	0/1	1/1	1/1	1/1	..	1/1
						1 infection?	0/1	..	..		..	..	..	0/1
						1 ODTS?	1/1	..	..		..	..	..	0/1
All cases	**38**	**38/38**	**38/38**	**37/38**	**37/38**	**5/38**	**33/38**	**15/18**	**21/25**		**14/14**	**4/4**	**2/2**	**23/38**

* Obstructive but not restrictive. ° This patients chest x-ray was normal, but he had a pathological lung biopsy. .. = data not avaible

Table 1: Diagnostic criteria for allergic alveolitis (38 cases).

The first figure indicates how many patients had pathological findings and the second on how many patients the test or procedure was done.

RESULTS

Sex, age, and smoking habits: Of 38 cases with a definite, probable, or possible allergic alveolitis, 31 were men and 7 were women. The mean age of the men was 46 years (range 22 - 69) and of the women 38 years (range 22 - 52). Of the men, 21 were non-smokers and the rest were ex-smokers. All women were non-smokers. The majority of the farmers were dairy farmers.

Seasonal variations: The cases of allergic alveolitis occurred mainly during October to April, only three cases occurring during May to September (Fig.1).

Symptoms: Episodes of fever were noted by 34 out of the 38 patients (in the following such figures will be referred to as 34/38). As high a temperature as 40 °C was noted by 9 of the farmers. All but one complained of severe dyspnea and fatigue. An equal number had cough, 14/38 with expectoration. Four patients had even noted blood in their sputa. 16 observed loss of weight - four lost more than 10 kg and one 15 kg. In 8/38 cases headache occurred and in 7/38 diffuse chest pain. Muscular pain or arthralgia was experienced by 6/38. Two had noted wheezing in their chest (Fig.2). 33 out of the 38 patients had both progressive dyspnea, cough and recurrent episodes of fever. One patient had an acute form of the disease, but a prolonged attack of organic dust toxic syndrome could not be completely ruled out.

Short episodes of fever after mold exposure (organic dust toxic syndrome) (4) were reported by 6/38 to have occurred before the allergic alveolitis and by two patients after the recovery from allergic alveolitis.

Duration: The duration of the disease varied from 1.5 months to several years. The median duration was 6 months. The duration of the disease was defined as the time from the onset of the disease until such time as the patient was able to work again.

Material associated with the disease: The material most likely associated with allergic alveolitis was moldy straw (37%), followed by moldy hay (29%), moldy grain (20%), and moldy wood chips (17%).

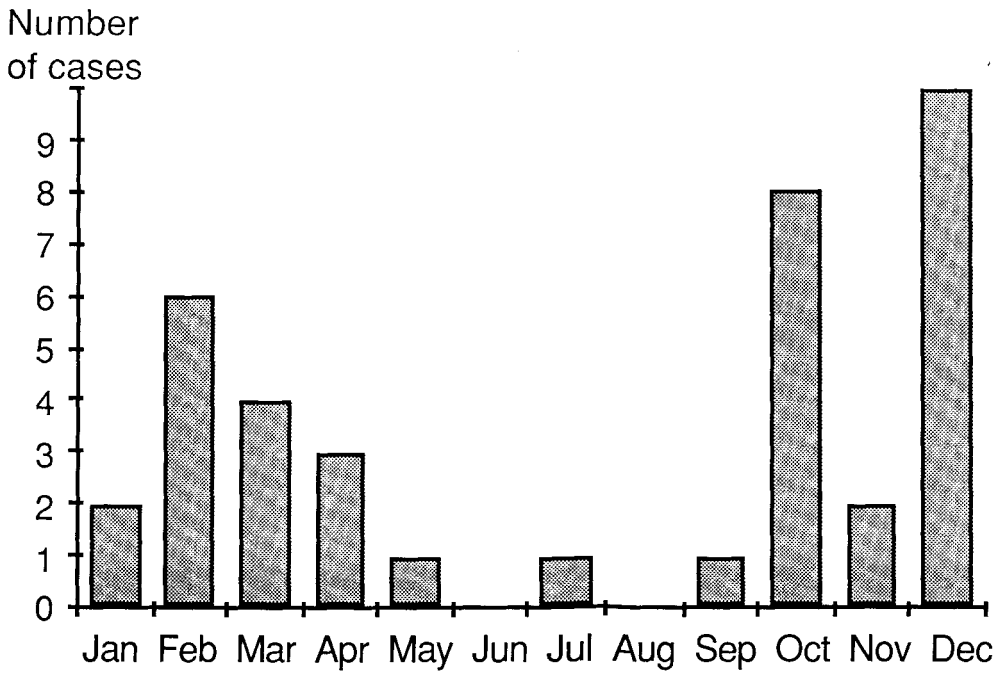

Fig. 1: Seasonal variation of allergic alveolitis based on 38 cases.

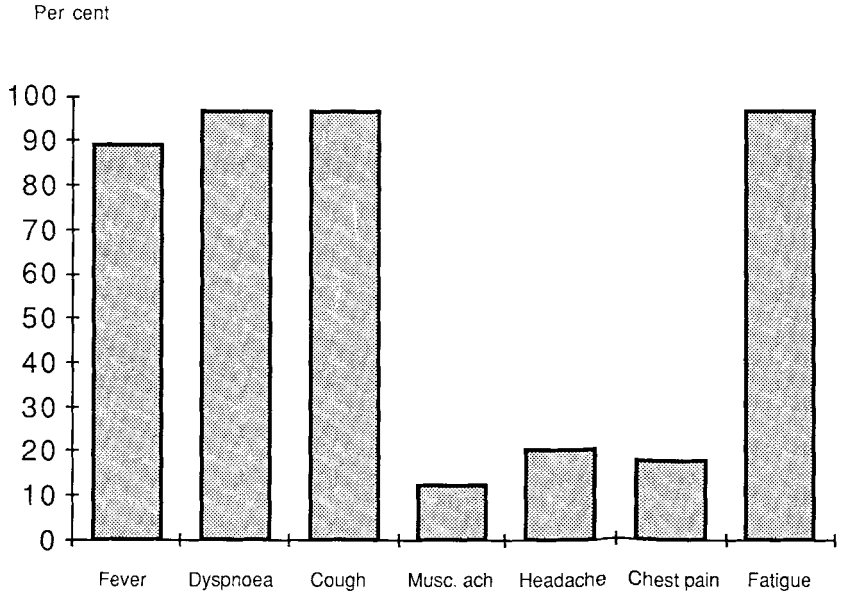

Fig. 2: Symptoms in the 38 patients with allergic alveolitis.

Clinical findings: Crepitating rales were heard on auscultation in 33/38. Dyspnea at rest was noted in 5/38 and when undressing in 8/38. Lip cyanosis was observed in 7/38 and 4/38 had tachypnea. Three patients had tachycardia.

Laboratory findings: The mean sedimentation rate was 42 mm/h (range 7 - 121). The hemoglobin values were normal. The white blood cell count was often increased, with a left shift. The lactate dehydrogenase activity (S-LD)in serum was measured in 15, and in 12 of them an abnormally high value was found (more than 7.0 μkat/l). The average was 9.8 μkat/l and highest value 23.6 μkat/l. This was noted during the second day in hospital in a 33-year-old man who on admission to the hospital had a value of 12.9 μkat/l. One patient had hypercalciuria. Electrophoresis of serum proteins showed signs of slight inflammatory activity. Rheumatoid factor was analyzed in 7 patients and was positive in two of them. An antinuclear factor was noted in 1/10. The same patient also showed a positive titer against native DNA. Another patient had a positive antibody titer against smooth muscle. Total IgE was increased in one out of 5 patients. A skin-prick test was performed in 5 patients and all were negative. Arterial oxygen tension was measured in 18/38 patients and was normal in 3 of them. The mean value was 7.8 kPa and the lowest value 5.1.

Precipitin tests: Precipitating antibodies to mold antigens were measured in 25 patients with an immunodiffusion method (the double diffusion-in-gel method of Ouchterlony) (1). 17/25 were positive. The tests were not carried out with the same batches of antigens, since the cases appeared during a period of 20 years. Each patient was on the average positive to four different kind of mold antigens. There was no clear over-representation of any of the mold species (Figure 3).

Chest X-ray findings: All but one patient displayed chest X-ray changes. Characteristic features were the presence of bilateral patchy nodular infiltrations, which often persisted for several months. One patient showed bilateral hilar lymphoma one year before the onset of the disease. This patient had a negative Kveim's test. In several cases the first chest X-ray was considered normal. On the next chest X-ray a few weeks later typical patchy infiltrations were seen and on reviewing the first

chest film discrete changes were also discovered there.

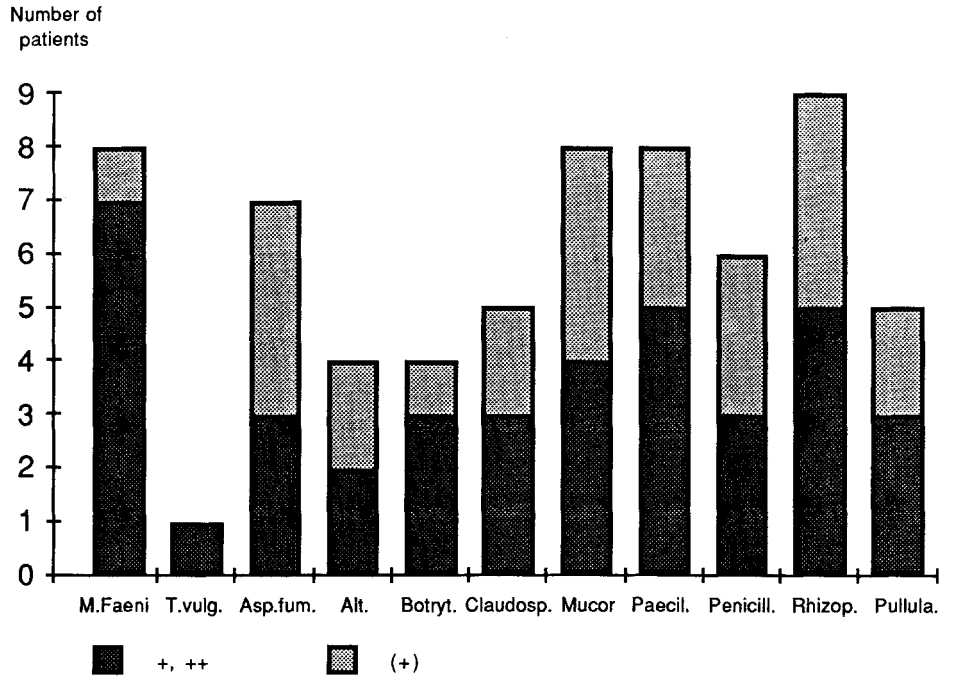

Fig. 3: Precipitating antibodies to mold antigens in 17 patients.

M.faeni = Microspolyspora faeni, T.vulg. = Thermoactinomyces vulgaris, Asp.fum. = Aspergillus fumigatus, Alt. = Alternaria, Botryt. = Botrytis, Claudosp. = Claudosporium, Paecil. = Paecilomyces, Penicill. = Penicillium, Rhizop. = Rhizopus, Pullula. = Pullularia.

ECG, exercise tests: ECG was recorded in 22 patients. In one of them the ST segment was elevated. This patient was not further investigated. Two showed depression of the ST segment, but the others were normal. Four patients performed an exercise test. Their exercise capacity was found to be impaired to varying degrees by their decreased lung function.

Lung function tests: Lung physiological tests were performed in 25 patients. The average vital capacity was 69% of the predicted value. A restrictive pattern, defined as a TLC (total lung capacity) of less than 85% of the predicted value or a vital capacity of less than 80% of the predicted value on dynamic spirometry, was found in 21/25 patients. The reason for using less than 85% of the TLC was because an earlier study showed that Swedish farmers as a group have higher TLC than the predictive values used. Combined lung-physiological impairment with both restrictive and obstructive changes was found in 3 of these patients and purely obstructive impairment, defined as FEV1/FVC%

(percent of forced vital capacity expired in one second) of less than 70 with normal TLC was found in another two. The two latter were in the patient with hypercalciuria and the one with a positive titer against native DNA. Diffusing capacity of carbon monoxide was measured in 14 patients. In all cases this showed a decrease, defined as less than 80 % of the predicted value. The lowest value noted was 33 % of the predicted and the mean value 60 %. However 3 of these patients had normal spirometries. In some patients the diffusing capacity was followed during the different stages of the disease. Even when the patients had recovered and were at work, the diffusing capacity in many cases was still decreased (mean value 88 % of the predicted) although it was higher than at the climax of the disease. The mean value of the VC (vital capacity) after recovery was 87 %. In 6 patients a nitrogen washout test was performed, and 5 of them showed an elevated slope of the alveolar plateau as a sign of an uneven distribution of gases. A methacholine test was performed in three patients and was negative in all cases.

Lung biopsy: Lung biopsy was performed in four patients. In specimens from two patients infiltration of lymphocytes and plasma cells in the alveolar membrane was observed. One of these patients had a normal chest X-ray. Two patients - one of them the patient with hypercalciuria - showed granuloma with fibrous changes and lymphocytes.

Provocation: Two patients underwent a provocation test with moldy material. One of them was provoked with moldy grain and reacted with fever (38 °C) and muscular aching four hours later. Forced vital capacity decreased from 2.6 to 2.0 l. Another farmer was provoked with moldy hay, and fever and other symptoms developed some hours later. This patient himself associated the disease with exposure to moldy straw.

Hospital care: Thirty of the 38 patients first consulted a general practitioner. Thirty patients were admitted to hospital, on the average for two weeks. Twenty-eight patients were treated in departments of pulmonary medicine. Initially 5 were treated in departments of internal medicine and three in departments of infectious disease.

Treatment: Twenty-nine out of the 38 patients were treated with antibiotics, most frequently penicillin or tetracycline, but erythromycin or cephalosporins were also used as well as sulfonamides. In many cases the same patient was treated with several different antibiotics. In the beginning the illness was often misjudged as pneumonia and the doctor first tried penicillin and perhaps later changed to erythromycin or tetracycline. One patient was treated with four different types of antibiotics before the correct diagnosis was made. Some were treated with digitalis and diuretics for a period. Twenty-two of the 38 patients were treated with cortisone, in general in a high initial dose that was reduced according to the effect on the symptoms and X-ray findings, generally the patients were on cortisone for several months. Twenty-six patients were sick-listed, on the average for 7 months.

Secondary prevention: Nine of the 38 patients started using a breathing mask and in this way were able to continue their work as farmers. Four of the 38 reconstructed their equipment so that the grain, straw and hay would be better dried. Two patients stopped using wood chips and three stopped using large bales for their straw. Two of the 38 patients received a half-time retirement pension and three had to change their occupation.

Symptoms after recovery: The patients were followed for 3 months to 20 years (median value 3.5 years). At follow up 18 of the 38 patients still had dyspnea on effort even several years after the acute attack. Eight of the 38 had cough but only a few with expectoration. Wheezing in the chest was reported by 6/38. One third had noticed an increased general sensitivity to dust after recovery from their disease.

DISCUSSION

Allergic alveolitis can strike both sexes at any age. In this study men were found to be more often affected, probably reflecting differences in working tasks. In Finland, however, women predominate among patients with allergic alveolitis, presumably for the reason that the farmers' wives take care of the cattle (21). None of the patients of the present study were

current smokers. Allergic alveolitis has been called "a disease of non-smokers" (23). This is assumed to be attributable to local immunological changes in the lungs of smokers.

The incidence of allergic alveolitis was increased during the winter time also in this study, in accordance with earlier findings (19). During the cold period of the year the cattle are kept inside. This often means working in poorly ventilated cow-sheds, which increases the risk of extreme exposure to moldy dust. Among our 38 patients with allergic alveolitis there were two examples of both the farmer and the farmer's wife falling ill. This may indicate that the degree of exposure and the environmental conditions are important factors, besides a certain degree of individual susceptibility.

The material that most commonly caused the disease among our patients was moldy straw. In other countries moldy hay is the main cause of allergic alveolitis (12,18). Moldy hay only caused one fourth of the cases in our study, reflecting the fact that the method of drying hay in Sweden is usually adequate. Grain and straw are harvested in the autumn when it often rains or even snows, resulting in difficulties of getting the materials sufficiently dry. In addition innovative farming methods with new technology, for example the use of large bales for straw, may give rise to new problems. The use of wood chips for heating purposes is also an example of new techniques, and if too large piles are chopped up they can get moldy.

Almost all patients had a combination of dyspnea, which could be very severe, cough, and fatigue. Often there also were periods of fever and sometimes loss of weight. A prominent clinical feature was bilateral basal crepitations. The laboratory findings were in accordance with those in earlier studies with an increased sedimentation rate and white blood cell count, with a predominance of polynuclear neutrophils (5).

An interesting finding was the abnormally high serum levels of lactate dehydrogenase in 80 % of the 15 patients in whom it was measured. Unfortunately the iso-enzymes of LD were not measured. Increased levels of LD have been observed earlier in patients with pulmonary embolism, pulmonary edema, small cell lung cancer (13),

and in AIDS-patients with Pneumocystis carinii pneumonia (16), but not in allergic alveolitis. Among workers exposed to cotton dust in a study in India, a significant increase in LD_1 and a decrease in LD_3 (the iso-enzyme primarily deriving from the lung) were found both in a group with byssinosis and in an asymptomatic group: but the total LD was normal (8).

The positive rheumatoid factor found in some patients seems to constitute an unspecific finding, which is probably caused by the inflammatory reaction of the allergic alveolitis (7). One patient had positive antinuclear factor and also a positive titer against native DNA, a laboratory finding highly specific of systemic lupus erythematosus; but there were no other symptoms or signs of this disease. The changes in lung function in this patient, however, were not typically restrictive but obstructive. In another patient with hypercalciuria, the lung function impairment was also obstructive. These two patients belonged to the group with possible allergic alveolitis and other disease could not be excluded. Obstructive changes have been described in patients with farmer's lung (14). Apart from differences in lung function, there were no differences in symptoms, signs or laboratory findings between the different groups of patients (certain, probable and possible).

In the majority of the cases in this study the changes in lung function were restrictive. Often the TLC returned to normal when the patient recovered. A more sensitive test appears to be the diffusing capacity, which was abnormal in all 12 patients investigated. The sensitivity of this parameter in allergic alveolitis has also been noted by other investigators (11). As the patients recovered the diffusing capacity increased, but it was often still lower than normal. This test can be recommended for following recovery. The nitrogen washout curve showed signs of uneven distribution of gases as described earlier (17). Some patients displayed pronounced dyspnea - some were unable to walk a few steps. A PaO_2 value as low as 5.1 kPa was noted. In accordance with earlier reports a high frequency of positive precipitin tests was found (68 %) (15).

The disease often extended over several months to some years necessitating considerable financial expenditure with both social

and health consequences. There were long periods of sick-listing, with expenses for the sickness insurance besides the farmer's loss of income, especially in cases where they had to change their occupation.

Many of the patients of this study were treated in small hospitals with no facilities for performing advanced laboratory investigations or lung function tests. The laboratory tests were not systematically performed, since this study was retrospective. It was therefore sometimes not possible to be categoric about the diagnosis allergic alveolitis, but in the majority of cases this diagnosis could be settled with a high degree of certainty. Some of the patients, however, were investigated with advanced methods, for example 8 patients underwent bronchoalveolar lavage, 6 of these having been reported on elsewhere (3). The typical finding of an increase in lymphocytes, macrophages and mast cells as well as the surface phenotype of lymphocytes offers additional support to the diagnosis, but, like lung biopsy and provocation tests, these examinations are not routine diagnostic procedures in patients with possible allergic alveolitis (4).

The difficulties in diagnosing allergic alveolitis are illustrated by the fact that three fourths of the patients in this study were treated with antibiotics, often of several different kinds. This shows that the patients were considered to suffer from an infectious lung disease, which means that they would not have been given information about the danger of continuous exposure to mold. If the farmer was able to get a deputy to take care of the cattle, he or she got some days' rest and the exposure to mold was interrupted. Perhaps then he recovered but then returned to the same mold exposure and got worse again. The lack of a correct diagnosis at an early stage of the disease probably resulted in repeated exposure and may have increased the risk of permanent lung damage. Actually more than half of the patients of this study (18/38) were still dyspneic on exertion some months to years after the disease. It is therefore of great importance to seek for exposure to mould dust in a farmer with fever, dyspnea, cough, perhaps loss of weight, bilateral basal crepitations and bilateral patchy nodular infiltrations on a chest X-ray. In persons with symptoms suggesting allergic alveolitis and a normal chest X-ray, there may be reason to repeat the X-ray, since the radiographic

changes may be very discrete at an early stage of the disease. By doing so, it is possible to prevent permanently impaired lung function and longstanding suffering for the patient by interrupting the exposure to moldy dust.

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