Farmer's Lung

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CAMPBELL[1] in 1932 described five farmers with a syndrome of fever, shortness of breath, tight feeling in the chest, cough with frothy or mucopurulent sputum and weight loss, together with rales and rhonchi scattered throughout the chest. Each had noted the onset of acute symptoms several hours after working with damp mouldy hay. Since that time there have been many reports and reviews of this condition, but little on the subject has appeared in the Canadian medical literature. Quinlan and Hiltz[2] reported five cases which they believed were examples of this syndrome. Three further cases from Nova Scotia were described by Gordon and Henderson[3] and the syndrome has been discussed on two further occasions.[11, 13]

This report summarizes four cases seen at the Royal Victoria Hospital, Montreal, from April 1967 to March 1968. None of the patients was seen during an acute episode but all were referred for investigation of dyspnea and pulmonary roentgenological changes.

TABLE I.—HEMATOLOGICAL STUDIES ON THE FOUR PATIENTS

Case No.	Patient	Sex	Hb. (g. %)	Hct. (%)	Sed. rate (mm. in 1 hr.)	WBC	Eos.	Alb. (g. %)	α1 (g. %)	α2 (g. %)	β (g. %)	γ (g. %)	IgG (mg. %)	IgA (mg. %)	IgM (mg. %)	β1C (mg. %)
1	T.L.	M	15.5	52	3	5100	206	3.39	.16	1.03	.95	2.77	1700	660	400	200
2	E.B.	F	14.4	46	24	9600	0	4.03	.8	.73	.73	2.34	1600	320	75	150
3	I.T.	F	15.0	45	18	8300	2	2.86	.23	1.03	.87	1.91	1000	200	175	250
4	D.T.	M	16.1	51	15	7000	10	3.55	.18	1.03	1.03	1.31	800	200	150	225

CASE REPORTS

CASE 1.—T.L., a 52-year-old man, complained of intermittent cough with purulent sputum and gradually increasing shortness of breath on decreasing exercise. These symptoms, which followed a prolonged attack of pneumonia with pleurisy at the age of 44, were more marked in the winter than during the summer, and were always exaggerated after working in his barn with mouldy hay and cows and pigs. During the evenings he frequently suffered from headaches and "the shivers", and for three months before admission he noticed anorexia and a 10- to 12-lb. weight loss. On examination he was thin, plethoric and dyspneic, with diminished chest expansion (¾"), hyperresonance on percussion, occasional rhonchi and many rales diffusely scattered throughout the lung fields but more pronounced at the bases. The pulmonary component of the second heart sound was accentuated and there was a soft early systolic murmur heard at the left sternal margin in the third intercostal space. The remainder of the findings were within normal limits except for a small thoracotomy scar from a previous lung biopsy.

CASE 2.—E.B., a 53-year-old woman, complained of cough with some purulent sputum and increasing shortness of breath on lessening amounts of exertion. She had enjoyed good health until age 50, when she developed a right lower lobe pneumonia. Subsequently she suffered from frequent acute respiratory infections and from wheezing during damp weather. She noticed that whenever she was in the barn, when old hay or straw was being shifted, she was troubled with cough and tightness of the chest with shortness of breath and some wheezing. When she left the barn the condition would improve, but several hours later she would experience a recurrence of her symptoms together with headache. The following morning she would raise a small amount of purulent sputum. Gradually she began to have symptoms daily and to cough each morning upon arising. This coincided with increased time spent in the barn during the early winter months. On examination she had a harsh cough and exhibited fine and medium rales at the base of both lungs. The remainder of the examination was normal.

CASE 3.—I.T., a 51-year-old woman, was well until March 1962, when, at the age of 46, she developed fever, chills, cough with yellow sputum and shortness of breath aggravated by exertion. Symptoms were severe enough to require hospitalization for two months and she was not completely well until July of that year. A similar syndrome developed during the following winters after symptom-free summers. Her symptoms always occurred after working in the barn for more than half an hour; she would experience choking and a stiff feeling in the chest. Upon leaving the barn she would quickly feel better, but several hours later the chills accompanied by headache would occur. Between November 1967 and January 1968 she experienced anorexia

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TABLE II.—IMMUNOLOGICAL STUDIES ON THE FOUR PATIENTS

Case No.	Patient	Skin tests			Precipitins
		Group A*	O.T. 1/100	Other	
1	T.L.....	Neg.	Neg.	Dust 4+	*T. polyspora, M. vulgaris M. plumbeus*
2	E.B.....	Neg.	Neg.	*A. fumigatus*, dual reaction Dust 2+ Feathers 2+ 4 other moulds +	*T. polyspora, M. vulgaris A. fumigatus*
3	I.T.....	Neg.	Neg.	*A. fumigatus*, dual reaction	*T. polyspora, M. vulgaris A. fumigatus*
4	D.T.....	Neg.	Neg.	*A. fumigatus*, dual reaction Dust 4 + Cow 2 +	*A. fumigatus*

*Group A — Histoplasmin, blastomycin, coccidioidin.

and a weight loss of 10 lbs. On examination the only abnormal findings were rales throughout the chest and occasional wheezing on forced expiration.

CASE 4.—D.T., a 55-year-old man (husband of I.T.), complained of a chronic cough productive of small amounts of whitish sputum, rhinitis with clear fluid discharge, and wheezing while in any of his barns and when around the cows. Several years earlier he noticed that every time he went into the barn where the old hay was stored he would experience a choking feeling. This sensation would settle quickly when he left the building but several hours later, usually when relaxing in the evenings, he noticed shortness of breath, diaphoresis and a general feeling of malaise. By the next day he would feel better, but he would not be completely well for several days. This phase of his illness was not associated with any wheezing. He suspected that his barn had a role to play and he refused to enter it, his wife taking over its management. He has had no similar episode since that time. On examination there were diffusely scattered rhonchi and fine crepitations at both lung bases; the remainder of the physical examination was normal.

Table I shows the results of many of the blood tests performed on these patients. Hemoglobins and hematocrits were in the higher normal range while the leukocyte and eosinophil counts were in the range of mid-normal. The erythrocyte sedimentation rates were slightly elevated. Serum electrophoresis showed lowered albumin in two patients, elevated α_2 globulin in three and elevated γ globulin in a polyclonal distribution in the three patients who had had a recent exacerbation of their illness. Immunoglobulin quantitation showed elevations in all three fractions in one patient, in IgA in one and in IgM in the other two patients. β_{1C} levels were within normal limits in all.

Table II shows that none of the four patients responded to the routine screening tests for fungal infiltrative diseases and that all were negative also to old tuberculin in a strength of 1/100. Other antigens did, however, elicit significant responses. One patient (T.L.) showed a marked reaction to dust and another (D.T.) to dust and cow dander. In both these cases their symptoms had originally been attributed to allergy to these substances. Case 2 showed mild reactions to extract of *A. fumigatus*, elicited by the intradermal injection of 0.02 ml. of 0.7 mg. per ml. concentration. The first component of this reaction was the normal immediate wheal and flare, reaginic antibody-mediated. This phase usually faded within an hour to be followed by a second reaction characterized by a soft, diffuse but discrete swelling with variable amounts of erythema, maximal after four to eight hours and lasting about 24 hours.

Skin tests using *T. polyspora* and *M. vulgaris* antigens were not performed, as these are too irritating to give meaningful reactions. Biopsies of two of the six-hour reactions showed edema and infiltration with polymorphonuclear neutrophil leukocytes and eosinophils typical of the Arthus phenomenon (Fig. 1). Staining by

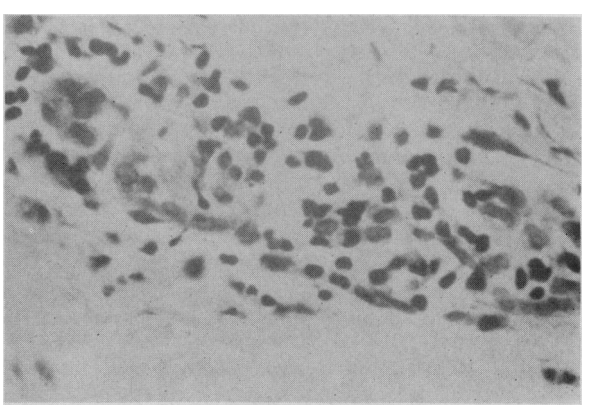

Fig. 1—Six-hour skin biopsy of an Arthus phenomenon showing vascular infiltration with polymorphonuclear neutrophil leukocytes and eosinophils. (Original magnification × 400, May-Grünwald-Giemsa stain.)

Fig. 2.—Immunofluorescence of skin biopsy of an Arthus phenomenon similar to that seen in Fig. 1. Section stained with rabbit anti-human β_{1C} showing localization in and around the vessel wall. (Original magnification × 400.)

immunofluorescent techniques using rabbit anti-human IgG and β_{1C} suggested deposition of IgG and β_{1C} in the involved vessel wall (Fig. 2).

A search was made for circulating antibodies of the precipitating variety to *Aspergillus fumigatus*[4] by double diffusion in agar gel. In addition, extracts of *Thermopolyspora polyspora* (*Micropolyspora polyspora*) and *Micromonospora vulgaris* (*Thermoactinomyces vulgaris*) were obtained. These were chosen because the work of Pepys and his colleagues[5-8] has shown them to be the most significant. Three of the four patients showed precipitin bands against *T. polyspora* and *M. vulgaris*, and three sera also gave lines against *A. fumigatus* (Table II). The precipitin lines on two patients are shown in Figs. 3a

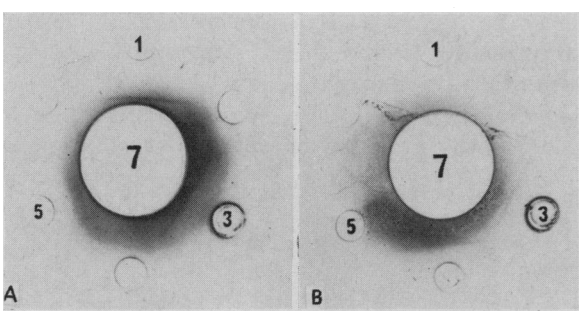

Fig. 3a and b.—1. *T. polyspora*. 2. *M. vulgaris*. 3. *A. fumigatus* (R.V.H. No. 2). 4. *A. fumigatus* (R.V.H. No. 3). 5. *A. fumigatus* (Bencard Laboratories No. 2). 6. *A. fumigatus* (Bencard Laboratories No. 1). 7. Serum (left) I.T. (right) D.T. (a) Case 3. Lines demonstrating presence of precipitating antibodies to 1, 2, 3 with partial identity between antigens. (b) Case 4. Line of identity against two extracts of *A. fumigatus*.

and 3b. Case 3 (Fig. 3a) shows lines of partial identity with the three fungi tested, whereas Case 4 (Fig. 3b), who no longer visits the barn, had lines against only *A. fumigatus*.

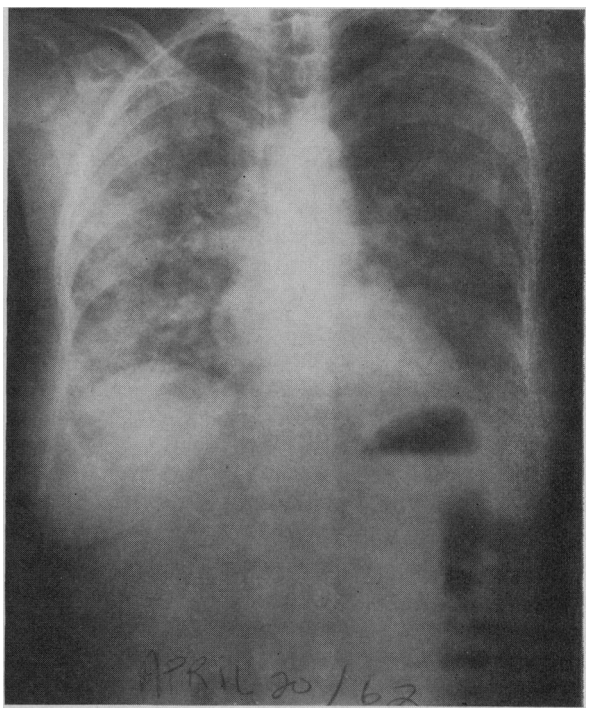

Fig. 4.—Case 3. Radiograph showing diffuse bilateral interstitial disease with some nodularity.

Chest radiographs showed diffuse bilateral interstitial disease in all patients, together with a reticulonodular pattern. The basal areas showed the greatest degree of involvement, and the size of the nodules varied from patient to patient in serial radiographs. Figs. 4, 5, 6 and 7 illustrate four such examinations in one patient. Case 1 showed a degree of hilar adenopathy.

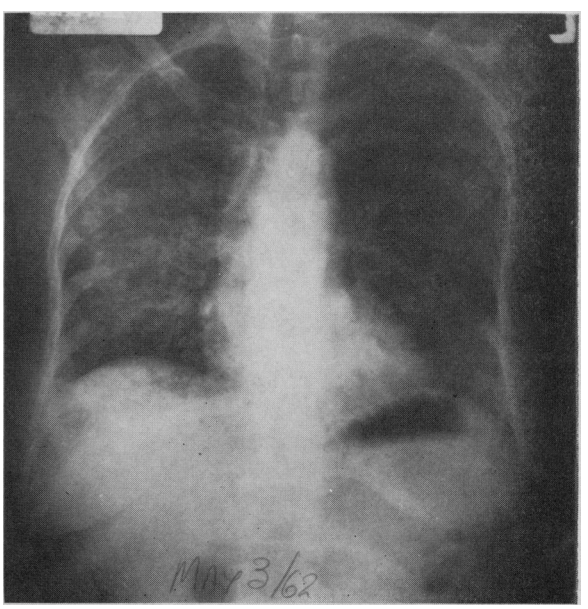

Fig. 5.—Case 3. Radiograph showing considerable clearing during a period of hospitalization away from antigenic exposure.

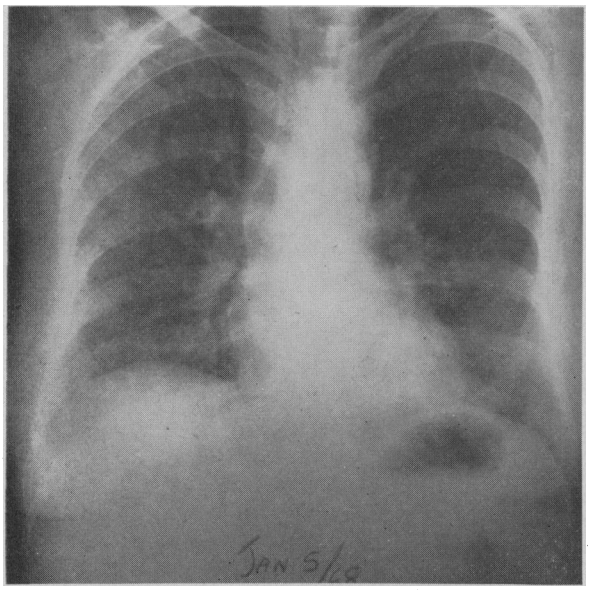

Fig. 6.—Case 3. Radiograph several years later, after recurrent winter illnesses.

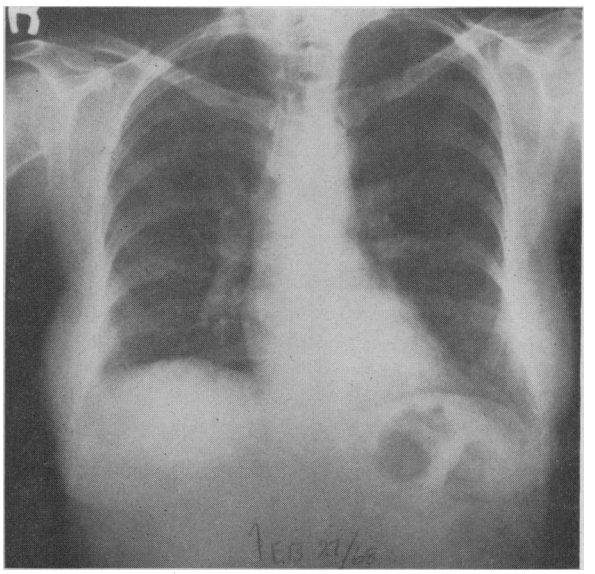

Fig. 7.—Case 3. Radiograph showing considerable clearing but some residual increased lung markings most marked at the bases.

Pulmonary function tests[9] as recorded in Table III showed that three patients exhibited lowered diffusing capacity, CO extraction, vital capacity, per cent mixing and ventilatory flow rates. These results indicate mainly restrictive lung disease with loss of diffusing surface within the lung parenchyma. Lung mechanics studies on two of these patients confirmed the presence of restrictive disease. A degree of airway obstruction was found in each of the patients. Arterial blood gas studies revealed lowered P_{O_2} in all cases and an elevated P_{CO_2} in Case 1.

DISCUSSION

The clinical course of this condition has been divided by Fuller[10] into three stages. The first phase occurs after a massive exposure to the fungi, often in a barn with old damp, mouldy hay. Several hours later patients complain of headache together with rigors, fever, a dry irritating cough and production of a small amount of mucopurulent sputum with occasional hemoptysis. Examination of the chest shows crepitations over both lung bases. In a few days the entire condition clears and is usually attributed to an attack of influenza.

The subacute or middle phase commonly arises after repeated exposure to the mouldy hay and is more insidious in its onset; however, it may follow immediately after the initial attack. A slight evening fever and some headache, anorexia and increasing shortness of breath on less and less exertion are characteristic. A dry cough with scanty sputum is usually present, and if there is severe dyspnea, central cyanosis may be observed. It is during this stage that the mottling of the chest radiograph is obvious, especially in the middle and lower zones. Recovery from this phase may occur in three to six months provided there is no further expo-

TABLE III.—PULMONARY FUNCTION STUDIES[9] ON THE FOUR PATIENTS

		Vital capacity (l.)	*Functional residual capacity (l.)*	*Residual volume (l.)*	*Total lung capacity (l.)*	*Mixing %*	*Maximal voluntary ventilation (l./min.)*	*$FEV_{0.75}$ x 40 (l./min.)*	*Maximal mid-expiratory flow (l./sec.)*	*Diffusing capacity*	*CO extraction (%)*	*H+ μEq.*	*P_{CO_2} mm. Hg*	*HCO mM/l.*	*P_{O_2} mm. Hg*	*O_2 % Sat.*
T.L.	Predicted	3.62	3.24	1.95	5.57	54	100		3.19	13.7	43					
	Observed	2.65	4.27	2.90	5.54	39	53		0.66	8.0	30	42	53	29.5	63	88
		2.87	4.51	3.02	5.89	44	78		1.62	7.8	30	38	49	32	69	69
E.B.	Predicted	3.27	2.90	1.86	5.13	53		78	2.49	12.0	43					
	Observed	1.94	2.45	1.76	3.70	33		73	2.57	6.9 (17.8)*	21	33	34	24.4	74	95
										9.1 (15.6)						
I.T.	Predicted	2.78	2.42	1.56	4.34	54		72	2.41	11.8	45					
	Observed	1.79	2.12	1.53	3.32	39		61	2.81	6.0 (7.0)	30	38	36.5	23.0	77	94
D.T.	Predicted	3.85	3.50	2.15	6.00	52	100		3.17	13.3						
	Observed	3.35	4.21	3.48	6.33	36	53		1.03	10.4		38	40	25	72	94

*Numbers in parentheses refer to values on exercise.

sure to the fungi. After each attack the recovery period is more extended until finally the third stage of the illness is entered. In this phase there is permanent damage to the lungs which takes the form of a widespread fine fibrosis and honeycomb type of bronchiectasis. There is no recovery from this end-stage, and the patient eventually becomes a respiratory cripple with all the usual disabilities.

Each of the patients studied here reported the stages of symptoms as described above. All noticed that their first major difficulties occurred during winter months when their barns were kept closed and they were handling the older mouldy hay. Subsequently they noted some difficulty in summer but much less than in winter. These historical findings were also noted by Fuller[10, 11] and by Emanuel *et al.*[12]

Many fungi are found in mouldy hay and can be incriminated as the possible etiologic agents; the studies by Pepys and his colleagues[5-8] have shown that the two major ones are *Thermopolyspora polyspora* and *Micromonospora vulgaris*. Aspergillus species are also present and may play a role, especially in the immediate dyspnea which occasionally is seen. Precipitating antibodies to these fungi were found in the sera of all patients. The line of identity between *T. polyspora* and *M. vulgaris* and the line of partial identity between these and *A. fumigatus* suggest that a similar antigen is shared by *A. fumigatus* and the former two. Emanuel *et al.*[12] were unable to obtain precipitin lines to extracts of mouldy hay in patients with a clinical diagnosis of farmer's lung if more than five years had elapsed since the last exacerbation; for about six years these patients showed precipitating antibodies only against *A. fumigatus*. This fungus alone can cause bronchopulmonary disease, as has been well described, and possibly is responsible for some of the asthma D.T. currently experiences after working in his other barns.

The findings on chest radiographs mirror the stage of the illness. The acute interstitial pneumonitis seen in patients who have been exposed to mouldy hay is almost pathognomonic when demonstrable; however, the absence of roentgenological evidence of this pneumonitis does not exclude the diagnosis. Rankin *et al.*[13] found considerable disease by lung biopsy at times when the radiographs were considered normal. Emanuel *et al.*[12] frequently found fine nodular densities measuring 3 to 5 mm. in the lower two-thirds of the peripheral lung field. They occasionally found larger areas of pneumonitis, and with extensive disease, areas of fibrous and peribronchial accentuation were more apparent. Frank[14] found that if progression of the illness takes place, coalescence of the fine nodules may occur with formation of large conglomerate lesions and an interstitial reaction which obscures much of the lung parenchyma. In our series, clearing was gradual, and although return to apparently normal chest occurs after the acute attack, mild emphysema and scattered fibrotic strands were not infrequently seen on the films (Figs. 4, 5, 6 and 7).

The pulmonary function tests in patients with recent exacerbations of symptoms uniformly gave a picture of lowered diffusing capacity, thus mirroring the disturbed ventilation-perfusion ratios. Case 2 demonstrated that in the earlier stages of the illness there is a degree of reversibility, as there was a definite rise in the Dco value when two measurements were taken 10 days apart after avoidance of the antigenic stimulus. Case 1 on the other hand, with an illness of longer duration, demonstrated a later phase with irreversibility at the alveolar-capillary level; however, his accompanying bronchospasm did show reversibility during a period of hospitalization. This latter feature is not an important feature of the farmer's lung pathophysiology.

The pathophysiology of this condition seems to be dependent upon an immunological reaction occurring at the alveolar level. It appears that the susceptible person inhales the tiny spores from the mouldy hay and they are admitted to the most peripheral portions of the lung where interaction of the fungal antigen and precipitating antibody occurs. Following antigen-antibody interaction, complement is fixed with subsequent release of anaphylotoxins, which in turn cause attraction of polymorphonuclear leukocytes and release of cathepsins, leading to a destructive reaction, systemic symptoms and local loss of function of the alveolar capillary units. Once the process has been initiated, the healing of the inflammatory aspect takes longer each time and there is more fibrous tissue deposition.

The lung pathology in the subacute phase is that of an interstitial pneumonitis with several types of giant cells, epithelioid cells and peripheral lymphocytes, suggesting granuloma formation.[11-13] In several cases a degree of central necrosis, in one case simulating caseous necrosis, was found.[12] T.L. had had a lung biopsy after his prolonged pneumonia eight years previously and the histology was similar to the above patterns.

Williams,[16] in an attempt to define *in vivo* immunological methods for diagnosing this condition, studied the relationship between symptoms, skin tests and inhalation tests. He found

that inhalation of aerosols of water-soluble Seitz-filtered extracts of mouldy hay, but not of clean hay, evoked reactions in 12 out of 15 patients with the clinical diagnosis of farmer's lung, but in none of 20 control subjects. These reactions were characterized by a delay of several hours before onset, a marked fall in compliance, a less marked but definite fall in ventilatory function, a fall in pulmonary diffusing capacity, an increase in minute volume and no significant evidence of airway obstruction. A functional defect in the alveoli and respiratory bronchioles was suggested by these findings. This may be contrasted with the results of inhalation tests on 38 allergic asthmatics using appropriate antigens, in whom the immediate onset of bronchospasm appeared. Williams also found that prednisolone protected the patient from a reaction and that skin tests by themselves were not of significant value in the direct diagnosis of farmer's lung.

Infected farmers must be encouraged to stop working with mouldy hay, thus avoiding the allergen, and to dispose of hay which is so affected. When this is impossible, the use of facial masks, dampened over the air filter area, will help to a degree. These should fit snugly and be dampened regularly in an effort to trap the spores. Because of their small size, however, many spores will pass through the filters and will still reach terminal bronchioles. When simple measures fail, corticosteroids may be indicated. These suppress the disease[16] and they are of use at least in preventing progression of the illness on further contact with the allergens, and by their anti-inflammatory properties they help in the partial reversal of the interstitial inflammation. Other supportive measures such as expectorants and bronchodilators, when indicated, are of benefit.

Summary Four patients with clinical histories compatible with farmer's lung were evaluated by immunological and respiratory function methods. These patients were found to have circulating precipitating antibodies to specific purified fungal extracts utilizing double diffusion in agar. When two of these patients were skin-tested with the appropriate fungal antigen, the positive four-hour skin reactions were biopsied. By light and immunofluorescent microscopy, these reactions were compatible with Arthus reactions. The pulmonary function tests revealed predominantly a restrictive type of disease. The pathophysiology of this disease is discussed and its immunological nature indicated. Therapy is directed towards the utilization of simple face masks, avoidance of antigen and the use of corticosteroids to suppress the inflammatory response.

Résumé Nous avons étudié par la méthode immunologique et par l'épreuve de la fonction respiratoire quatre malades dont l'histoire clinique évoquait le syndrome connu sous le nom de poumon de fermier. On a découvert dans la circulation de ces malades des anticorps précipitant des extraits purifiés de champignons spécifiques donnant lieu à une double diffusion dans l'agar. Après avoir chez deux de ces malades procédé à une cutiréaction avec l'antigène fongique approprié, on a fait une biopsie cutanée de la réaction cutanée après quatre heures. Au microscope optique et au microscope sous lumière immunofluorescente, ces réactions étaient compatibles avec les réactions d'Arthus. Les épreuves de la fonction pulmonaire ont mis en évidence une pathologie de type avant tout restrictif. Les auteurs discutent la physiopathologie de cette maladie et précisent sa nature immunologique. On peut tenter d'éviter cette maladie en conseillant à la personne de porter un simple masque facial, d'éviter le contact avec l'antigène et on peut la traiter par la corticothérapie en vue de supprimer la réaction inflammatoire.

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