

Hypersensitivity reactions to grain dust

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Allergic and respiratory investigations were performed in 17 subjects with respiratory symptoms and occupational exposure to grain dust. Common symptoms included chronic cough and sputum production, grain fever, wheezing and dyspnea on exposure to grain dust. Results of pulmonary function tests demonstrated a pattern of obstructive airway disease. Immediate hypersensitivity to grain dust was common. Both immediate and late reactions were observed on inhalation challenge studies. There was a good correlation between the hypersensitivity reactions on skin testing and on bronchial provocation. Inhalation of crude grain dust extract may produce systemic symptoms of malaise, myalgia, headache, and leukocytosis even in normal subjects. There was no evidence of precipitin-mediated hypersensitivity.

HYPERSENSITIVITY REACTIONS TO GRAIN DUST

Pulmonary symptoms associated with exposure to grain dust have been recognized for several centuries, but the mechanism by which grain dust exerts its harmful effect is unknown.¹ Epidemiologic surveys have shown that chronic cough and sputum, dyspnea on exposure to grain dust, grain fever, and abnormalities in lung function are common in grain handlers.²⁻⁵ One study has attributed these findings to the effects of cigarette smoking,² while others³⁻⁵ have implicated the effects of grain dust exposure as an etiologic factor as well. Since grain dust contains a mixture of many organic materials such as seeds, pollens, insects, fungi, and dust, hypersensitivity reactions to these potential antigens might be important in the pathogenesis of the symptoms that develop in workers exposed to grain dust. The purpose of this paper is to report the nature of the pulmonary abnormalities resulting from occupational exposure to grain dust and the role of immunologic mechanisms in the production of these abnormalities.

MATERIALS AND METHODS

Subjects. Seventeen individuals, ranging in age from 28 to 64 years, were studied. These subjects were either symptomatic farmers who presented themselves to the Health Sciences Centre at the time of the present study, or symptomatic grain elevator agents from a previous study⁴ who had consented to participate in the present project. No special consideration was given to the nature of the symptoms of these subjects when they were chosen to be included in the project. Ten were smokers, 3 were ex-smokers, and 4 were nonsmokers.

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Special abbreviations used	
FEV ₁ :	forced expiratory volume in one second
FVC:	forced vital capacity
MEFR _{75, 50, 25} :	maximum expiratory flow rate at 75%, 50%, and 25% of vital capacity
MMF:	maximum midexpiratory flow rate
PBS:	phosphate-buffered saline
PEFR:	peak expiratory flow rate
TLC:	total lung capacity
VC:	vital capacity

Apart from 5 subjects who had been overseas for war service, all had lived in Manitoba, Canada, since birth.

Pulmonary function

Spirometry was measured using a wedge spirometer with a computerized calculator and digital print-out⁶ with which FVC, MMF, FEV₁, PEFR, and MEFR_{75, 50, 25} were determined. The FVC maneuver was repeated until two consecutive readings of FVC were within 5 per cent of each other, and the greater of the two readings was used. The static lung volumes were determined by the steady-state helium dilution technique,⁷ while the carbon monoxide diffusing capacity and percentage extraction were measured at rest by the steady-state end tidal methods. The measurements of lung function were compared with predicted values obtained from symptom-free nonsmoking males in Manitoba,^{6, 8} matched for age and height. Any value that differed from the predicted value by more than two standard deviations was considered abnormal. A bronchodilator, racemic epinephrine, administered by a hand nebulizer, was given and its effect on spirometry observed.

Immunologic studies

Skin testing. Hypersensitivity to specific allergens was assessed by prick skin tests on the forearm. The crude grain dust extract was prepared by shaking a grain dust sample collected from the subjects' own farm or grain elevator with PBS for 24 hours in the cold room (10 per cent w/v extract). This solution was then filtered, dialyzed against PBS, and sterilized by Millipore filter. A mixture of equal portions of individual crude grain dust extract was prepared for use in skin testing of normal control subjects. Other commercially available antigens* used for skin testing included grain mill dust, house dust, animal hairs (cat, cow, dog, hog, horse), grasses (Kentucky blue, brome, redtop, timothy), weeds (giant ragweed, western ragweed, Russian thistle, prairie sage, wormwood sage), and molds (*Alternaria*, *Aspergillus*, *Candida*, *Fusarium*, *Helminthosporium*, *Hormodendrum*, *Penicillium*, yeast, rust, smut). A wheal of 3 mm. or more in size was considered to indicate a positive reaction. In addition, intracutaneous skin testing was performed with approximately 0.02 ml. of 1:100 dilutions of the crude grain dust extract. The skin test sites were observed at 15 minutes for immediate wheal-and-flare reactions and at 4 to 6 hours for late reactions.

Serum precipitins. Serum was examined for precipitins against the subjects' own crude grain dust extract and other commercially available antigens* including *Micropolyspora faeni*, *Thermopolyspora vulgaris*, *Strophilus granarius*, *Aspergillus fumigatus*, *Alternaria*, and *Penicillium* by immunodiffusion in 1 per cent agar. Each agar plate consisted of a center well (4 mm. in diameter) and 6 peripheral wells (2, 4, 6, 8, 10, and 12 mm. in diameter, respectively). The distance between the center and peripheral wells was 4 mm. An individual antigen was placed in the center well and the serum from an individual subject was placed in all six peripheral wells. The agar plates were kept in a moisture chamber at 25° C. and

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examined for the presence of precipitin daily. If no precipitin developed at the end of 7 days, the serum was regarded to be negative.

Fungal culture of the grain dust samples was not done in the present study, and serum precipitin test against the specific cultured organisms has not been carried out.

Inhalation challenge. Bronchial inhalation challenge with the crude grain dust extract was performed in 15 subjects. Five symptom-free individuals with normal lung function were chosen as control subjects and were also challenged with grain dust. Two of these control subjects had a history of hay fever. Reproducible measurements of lung function and the effect of the inhalation of saline were recorded 12 hours before and again just prior to inhalation challenge with the grain dust extract. If there was no reaction to saline inhalation, the subjects then inhaled increasing concentrations of the diluted 10 per cent grain dust extract (w/v) from a DeVilbiss No. 42 nebulizer driven by an air compressor until symptoms developed or a maximum dose of 5 ml. of 1:10 dilution of the extract had been administered. The subsequent changes in symptoms, signs, temperature, and white blood count were noted. Lung function was assessed at 5, 15, 30, and 60 minutes, then hourly for up to 6 hours, and, finally, at 24 hours after challenge. The FVC, FEV₁, PEFR, and a trace of the flow-volume curve were recorded utilizing a Monaghan M403 pulmonary analyzer* attached to an X-Y recorder. Each measurement was repeated until two flow-volume curves were consistent. The blood leukocyte and total eosinophil counts were measured prior to inhalation challenge, and at 1 and 5 hours postchallenge. The oral temperature was recorded at 1 to 2 hour intervals during the day. The serum C3 complement level was determined by radioimmunodiffusion† before challenge and 6 and 24 hours after challenge.

RESULTS

Clinical data. All the seventeen workers had respiratory symptoms. These included a chronic productive cough in 12 (1 a nonsmoker), dyspnea on exertion in 7, and dyspnea on exposure to grain dust in 13 subjects. The latter symptom was manifested by frank wheezing in 3 subjects, but in the other 10 it was less dramatic and consisted only of tightness or congestion in the chest. The wheezing would occur soon after contact with grain dust. The tightness in the chest developed slowly during the day's work and was most severe in the evening. The latter was usually accompanied by cough and sputum. In addition, 12 of the workers developed systemic symptoms of headache, myalgia, malaise, and even chills and fever several hours after contact with grain dust. These symptoms are those of "grain fever," which has been described by other investigators.²⁻⁴ Grain fever did not necessarily accompany respiratory symptoms. Radiographic examination revealed hyperinflation of the lungs in 2 subjects, while the examination was normal in the remainder.

None of the subjects had a history of hay fever or asthma when young, but there was a family history of allergic diseases in 5 subjects. Most of the subjects had been born on farms and exposed to grain dust all their lives. All considered that old or moldy grain affected them most, and that barley was the worst seed for producing symptoms.

Pulmonary function. Pulmonary function was completely normal in 3 subjects. The remainder had at least one abnormal spirometric measurement. The total lung capacity was increased in 5 subjects and the residual volume in 9.

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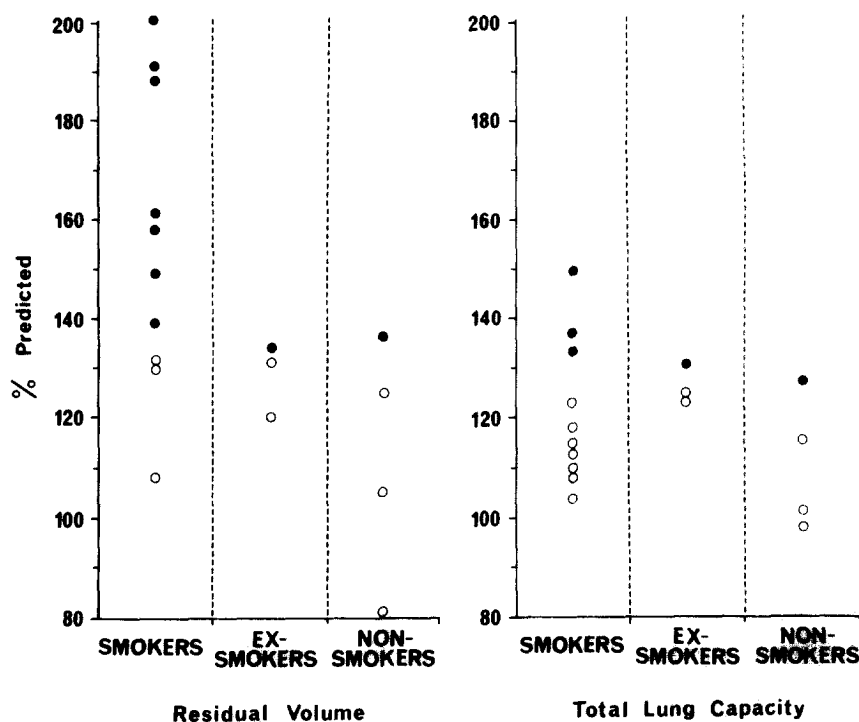


FIG. 1. Lung volumes in 17 grain handlers. Subjects with values greater than 2 s.d. from the mean predicted value are indicated by a closed circle.

These static lung volumes expressed as a percentage of the predicted value for the individuals are shown in Fig. 1. The sensitive spirometric tests of airway obstruction were the $MEFR_{25}$, which was abnormal in 14 subjects, and the MMF, which was abnormal in 13. The results of these two parameters also expressed as a percentage of the predicted are shown in Fig. 2. The vital capacity was reduced in 2 subjects. The carbon monoxide diffusing capacity was abnormal in 3 subjects, but only 1 had an abnormal percentage extraction. In 5 subjects, there was some lessening in airways obstruction after nebulized bronchodilator.

Skin tests. The incidence of positive immediate skin reactions to the different antigens is shown in Table I. Seven of the 17 subjects had negative skin reactions to all the antigens, including the extract of crude grain dust obtained from their place of work. Of the 8 subjects with a positive skin reaction to the autogenous crude grain dust extract, only half reacted to a commercial grain mill dust. Two subjects who had no skin reaction to grain dust had isolated skin hypersensitivity to *Candida albicans*. Only 1 subject (Subject 5, Table I) had a late skin reaction to crude grain dust extract when observed at 4 to 6 hours.

No reaction was seen on skin testing with the crude grain dust extract at a dilution of 1:100 in 12 control subjects who had no history of allergy or contact with grain dust.

Serum precipitins. Precipitins against crude grain dust were demonstrated

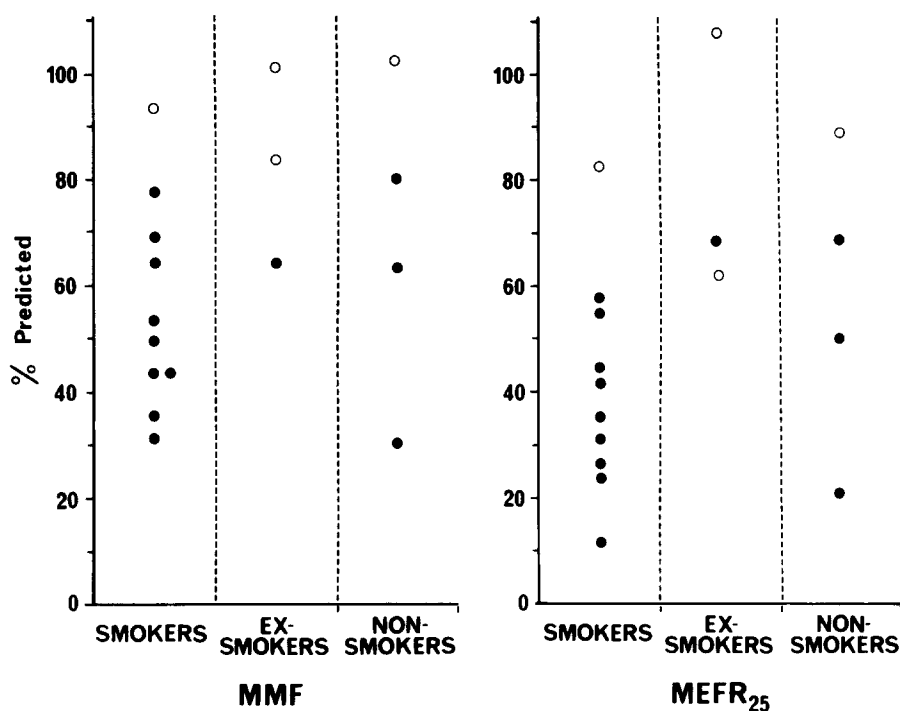


FIG. 2. MMF and MEFR at 25% of the vital capacity in 17 grain handlers. Subjects with values greater than 2 s.d. from the mean predicted value are indicated by a closed circle.

TABLE I. Positive skin reactions in 10 subjects

Subject	Antigens that elicited positive immediate reaction
1	Crude grain dust,* house dust, cow hair, dog hair, horse hair, wormwood sage, smut
2	Crude grain dust, grain mill dust, Kentucky blue grass, giant ragweed, Hormodendrum, Helminthosporium
3	Crude grain dust, grain mill dust, redtop grass, giant ragweed, western ragweed
4	Crude grain dust, grain mill dust, wormwood sage, Candida, smut
5	Crude grain dust, grain mill dust, mixed Aspergillus sp., Candida
6	Crude grain dust, house dust, cat hair, western ragweed
7	Crude grain dust, dog hair, horse hair
8	Crude grain dust, smut
9	Candida
10	Candida

*Crude grain dust antigen was prepared from grain dust samples collected from the subjects' place of work. All others were commercially available antigens.

in 2 subjects, against *M. faeni* in 2 subjects, and against both in 1. One of the 3 subjects with serum precipitins against grain dust also had an immediate reaction on skin testing, but none of the three had a late skin reaction to the same antigen. No precipitins were detected against other actinomycetes, *S. granarius*, or molds.

Inhalation challenge. After bronchial inhalation challenge, respiratory symptoms developed in 7 of the 8 subjects with skin hypersensitivity to grain

TABLE II. Relationship between skin hypersensitivity and respiratory symptoms following bronchial challenge in 15 subjects and 5 controls

Skin reaction to grain dust	No. of subjects	Symptoms following inhalation challenge		
		No symptoms	Immediate wheezing	Immediate and late dyspnea
Positive immediate reaction	7	0	3	4
Negative	7	6	0	1
Immediate and late reactions	1	1	0	0
Negative (controls)	5	5	0	0

TABLE III. Relationship between the development of respiratory and systemic symptoms in 15 subjects and 5 controls following bronchial challenge

Respiratory symptoms	No. of subjects	No. of subjects with systemic symptoms	Mean rise in W.B.C. (cells/cu. mm.)	Mean rise in temperature (°C.)
Acute wheezing	3	0	5,450	0.7
Immediate and late dyspnea	5	4	5,460	1.8
None	7	2	3,750	1.0
None (controls)	5	2	5,730	1.1

dust and in 1 of the 7 subjects without skin hypersensitivity to grain dust (Table II). They did not occur in any of the 5 control subjects. The 3 individuals (one a nonsmoker) with a history of wheezing at work developed acute dyspnea and wheezing following bronchial provocation. The wheezing cleared spontaneously over the next 2 hours in 2 subjects, but in the third it was relieved only by the administration of isoproterenol. The 5 other subjects (one a nonsmoker) developed chest tightness immediately after challenge, which improved at 1 to 2 hours, recurred more severely at 4 to 6 hours, and then disappeared overnight. However, wheezing did not occur and was not detected by auscultation. This feeling of chest tightness was similar to the symptoms experienced by them at work.

Following inhalation challenge, systemic symptoms of malaise, myalgia, headache, and fever occurred in 4 of the workers who developed late respiratory symptoms, 2 of the workers without respiratory symptoms, and in 2 control subjects. The white blood count rose to a similar extent in the control subjects and the workers (Table III). The initial total eosinophil count was normal in all the subjects and did not alter following challenge. There was no significant change in C3 complement levels in any subject after challenge.

There were changes in VC, FEV₁, and the flow-volume loops following bronchial challenge in the symptomatic subjects. An example of the effect of inhalation of grain dust extract on the flow-volume relationship resulting in the development of airways obstruction is shown in Fig. 3. It can be seen that there was a parallel shift to the left of the flow-volume curve. In order to quantitate the changes in the flow-volume relationship, the MEF_R was determined at a lung volume equivalent to 50 per cent of the initial VC (MEF_{R50}). The interpretation of the effect of inhalation challenge on the expiratory flow rate is based

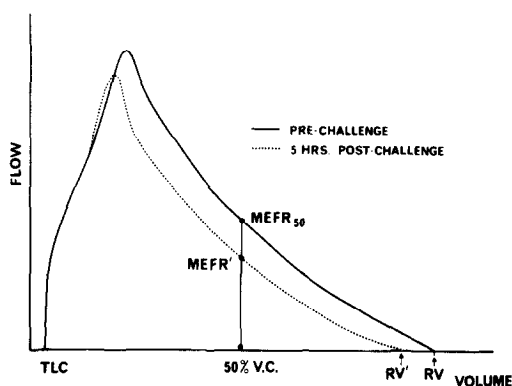


Fig. 3. Effect of inhalation of grain dust on the flow-volume relationship in a grain handler.

on the assumption that the TLC did not increase after challenge. However, if the TLC had increased following challenge, then the flow-volume curve would have shifted further to the left and the change in observed $MEFR_{50}$ was underestimated. Studies on the lung volumes after inhalation of methacholine⁹ and pollen¹⁰ in asthma have shown that TLC was either unchanged or actually increased during the subsequently induced bronchoconstriction. The progression of the $MEFR_{50}$ after challenge is summarized in Figs. 4 and 5 where the $MEFR_{50}$ is expressed as a percentage of the mean of the prechallenge values. A result less than 80 per cent of the prechallenge values was considered abnormal. The $MEFR_{50}$ did not fall below 88 per cent of the prechallenge values in the control subjects. In the 3 subjects who developed acute wheezing during challenge, there was a marked fall in the $MEFR_{50}$ that returned to normal in 1 to 2 hours and did not fall again. In 5 other subjects, the $MEFR_{50}$ fell initially, improved, and then fell further at 4 to 6 hours. Administration of isoproterenol to 3 subjects reversed both the immediate and the late reactions. The immediate and late changes in respiratory function observed in these 5 subjects corresponded to the biphasic pattern of their respiratory symptoms induced by inhalation challenge.

DISCUSSION

In the present study, cough and sputum were present in 85 per cent of the subjects who had smoked, but in only 1 nonsmoker. However, earlier surveys of grain elevator agents^{3, 4} have found that about one-quarter of the nonsmokers complained of cough and sputum. This would indicate that both cigarette smoking and exposure to grain dust might result in bronchial gland hyperplasia and chronic bronchitis.

The respiratory symptoms that developed after exposure to grain dust were either immediate wheezing or tightness in the chest of a slower onset, which became worse after some hours. The immediate symptom of asthma was consistent with a reaginic-mediated hypersensitivity reaction to grain dust. The mechanism of the late respiratory symptoms was less clear. This latter symptom was similar to that seen in some subjects with asthma due to hypersensitivity to house dust,¹¹

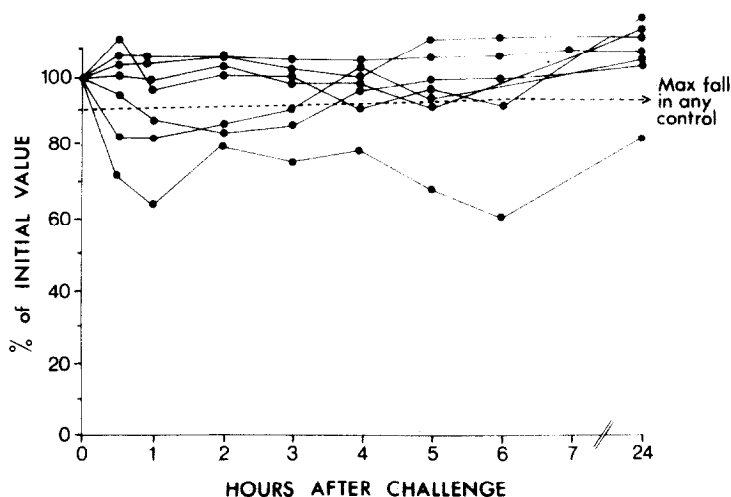


FIG. 4. Change in MEFR₅₀ following inhalation of grain dust in 7 subjects with a negative skin test.

or *Aspergillus fumigatus*.¹² It also corresponded to some extent with the pattern seen in hypersensitivity pneumonitis, such as farmer's lung or bird fancier's lung. The late component of the symptoms in *A. fumigatus* hypersensitivity and hypersensitivity pneumonitis has been postulated to be mediated by precipitating antibodies.

Lung function tests showed that airways obstruction was common in the subjects, and it was often associated with an increase in static lung volumes. Lung function was normal in 1 of the 3 subjects who developed clinical asthma on exposure to grain dust and was reversible in the other 2. There was slight reversibility in only 3 of the other 11 subjects with abnormal lung function. Airways obstruction may have been the result of cigarette smoking in most of the workers, but its presence in 3 nonsmokers implies that other factors such as the effects of grain dust exposure were involved. In this group of subjects there was no evidence of restrictive lung disease that would have been expected if hypersensitivity pneumonitis had occurred. Similarly, the chest radiographs were either normal or showed hyperinflation. There was no evidence of pulmonary fibrosis or nodular shadowing. The latter radiographic changes have been reported in dockers unloading grain¹³ and were attributed to the inhalation of silica in the grain dust.

Fifty-two per cent of the subjects demonstrated immediate hypersensitivity on skin testing with the extract of crude grain dust collected from their place of work. This is consistent with the findings of Skoulas, Williams, and Merriman¹⁴ that up to 61 per cent of symptomatic workers had skin hypersensitivity to grain dust collected from their elevators. Both in the present study and in that of Skoulas, Williams, and Merriman,¹⁴ skin reactions to commercially available milled grain dust extract were less common, and this may explain why skin hypersensitivity to grain dust was found to be uncommon in our previous survey of elevator agents in Manitoba⁴ when the commercial extract was used for skin

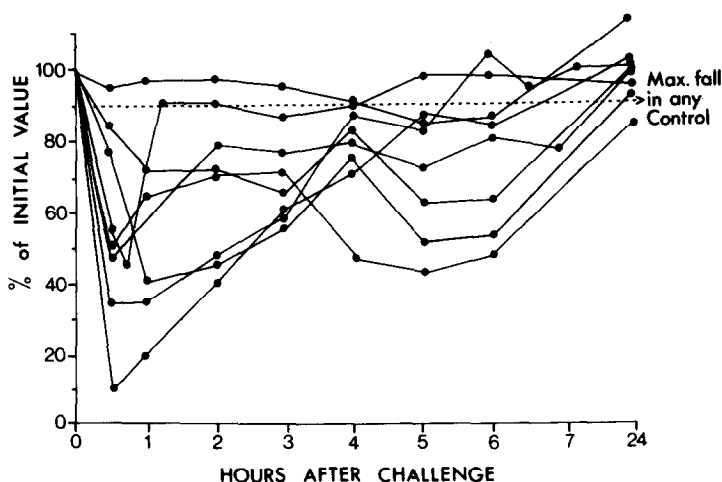


FIG. 5. Change in MEFR₅₀ following inhalation of grain dust in 8 subjects with a positive skin test.

testing. Although grain dust contains many fungi including *Alternaria*, *Aspergillus* species, *Penicillium*, and *Cladosporium*,¹⁵ hypersensitivity to molds was uncommon in these subjects when they were examined by prick testing. This was in contrast to the findings of Skoulas, Williams, and Merriman,¹⁴ who found skin hypersensitivity to fungi to be surprisingly common. It has been suggested that their findings may have been due to the use of intracutaneous testing that resulted in a high incidence of positive reactions.¹⁶

Bronchial inhalation challenge confirmed that the immediate hypersensitivity to grain dust as demonstrated by skin testing was relevant to the symptoms experienced by the subjects at work. Seven of the 8 subjects with skin hypersensitivity to grain dust developed respiratory symptoms after inhaling it. The development of airway obstruction was confirmed by the changes in lung function observed following inhalation challenge. Grain fever appearing after challenge did not correlate with the presence of skin hypersensitivity to grain dust or the development of respiratory symptoms. There was no correlation between the presence of serum precipitins to grain dust or *M. faeni* and the occurrence of respiratory and systemic symptoms following challenge. This would agree with the observation that precipitins may only indicate exposure to the dust.¹⁷ In fact, the systemic symptoms that evolved in 2 control subjects and the leukocytosis that was found in most subjects following inhalation of grain dust imply that grain fever is a nonspecific result of exposure to grain dust. It may be due to the presence of bacterial endotoxins in the dust,¹⁸ and it is not evidence for the late respiratory reactions being precipitin-mediated. The mechanism of the late bronchial reaction to antigen exposure when precipitins are not detectable is unclear, but it has been observed following bronchial challenge with house dust and house dust mites,¹¹ pollens,¹⁹ and western red cedar.²⁰ This late bronchial reaction is also often associated with a late reaction on skin testing. Recently, Kerigan and associates¹⁹ have related these late bronchial and skin

reactions in ragweed-allergic patients to the high levels of serum IgE antibodies. The only subject in this study with a late skin reaction to grain dust extract had no reaction on inhalation challenge.

It is still unclear which constituent of grain dust might be the main antigen causing the hypersensitivity. Molds, grass, and weed pollens are unlikely to be the source because skin hypersensitivity to them did not correlate with hypersensitivity to the grain dust. Grain dust also contains many arthropods.¹⁵ Lung disease due to hypersensitivity to the grain weevil (*S. granarius*) has been described,²⁰ but precipitins against this were not detected in the subjects in the present study. Grain dust also contains many mites such as *Glyciphagus destructor*.¹⁵ Since mites are now known to be an important antigen of house dust,¹¹ they may be the important antigenic component of grain dust as well. In 1713, Ramazzini²² first described lung disease in workers exposed to grain dust and attributed it to lice recently detected in grain dust by Leuwenhoek's microscope. The pathogenic mechanism of the pulmonary symptoms associated with exposure to grain dust is slightly clearer today, but the exact cause is still as obscure as when it was first described.

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Select the ONE best answer for the following question from the Allergy Foundation of America Self-Assessment Program:

Question 1. Proof of the existence of a food allergy can best be established by

- (A) positive scratch or intradermal tests
- (B) repeated precipitation and relief of clinical symptoms as the suspected food is added and withdrawn from the diet under controlled conditions
- (C) response to parenteral hyposensitization with foods
- (D) in vitro immunologic techniques
- (E) roentgenographic study of the gastrointestinal tract

The correct answer and bibliographic reference will be found on page 188 of this Journal.