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Allergic respiratory disease in grain workers: The role of storage mites

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One hundred thirty-three grain-store workers employed at a regional grain store in Essex, U.K., participated in a survey of respiratory symptoms, lung function, bronchial responsiveness to methacholine and skin tests, and specific IgE to occupational allergens, including extracts of five storage-mite (SM) species and grain extracts. Previously reported associations between occupational respiratory symptoms and cigarette smoking, and symptoms of bronchial hyperresponsiveness to methacholine were confirmed. This study also disclosed significant associations between work-related symptoms (WRS) and positive skin tests and/or specific IgE to SMs, but not between WRSs and positive skin tests or specific IgE to Dermatophagoides pteronyssinus, or between WRSs and positive skin tests to grain. These findings suggest that in United Kingdom grain workers, allergic responses to SMs may be another factor responsible for WRSs in grain-store workers. (J ALLERGY CLIN IMMUNOL 1989;84:296-303.)

It is well-known that workers occupationally exposed to grain dust have a high prevalence of respiratory symptoms,¹ but their pathogenesis remains obscure. Symptoms have been demonstrated to be associated with cigarette smoking² and with increased bronchial reactivity to histamine.³ Grain dust contains biologic contaminants, including mold spores, and insects, such as SMs,^{4,6} which could act as extrinsic

Abbreviations used

WRS: Work-related symptom
DP: *Dermatophagoides pteronyssinus*
GDs: *Glycyphagus destructor*
GDM: *Glycyphagus domesticus*
TP: *Tyrophagus putrescentiae*
AF: *Acarus farris*
AS: *Acarus siro*
Ch: *Cheyletus* species
SM: Storage mite
SPT: Skin prick tests
PD₂₀: Provocative dose of methacholine causing a 20% fall in FEV₁

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allergens. However, large surveys of grain-store workers reported from the United States or Canada have not suggested that allergic respiratory disease is a major cause of symptoms in grain workers.^{7,8}

In Europe and the United Kingdom, farm workers also develop respiratory symptoms when they are handling hay or grain contaminated with SMs.⁹⁻¹¹ Several studies have demonstrated that affected farm workers have specific IgE to SMs, indicating that these symptoms may result from allergy to these mites.¹² We have undertaken a survey of workers in a large dock-side grain store in the United Kingdom to determine whether SM allergy was an important determinant of respiratory symptoms in these workers.

SUBJECTS AND METHODS

The grain terminal

At the time of the survey, the terminal handled 1.6 million tons of grain each year; 90% was imported and unloaded directly from bulk-grain cargo vessels by means of hoppers and suction apparatus. Grain was stored in concrete storage towers until it was transferred to other vessels or road or rail transport (Fig. 1). English grain also passed through the terminal for export. This was delivered by road from the local grain-producing areas of East Anglia.

Subjects

One hundred forty individuals were working at the terminal; 104 of these workers were dock workers, and 36 workers were employed for cleaning and maintenance work. One hundred thirty-three workers (95% of the available work force) agreed to take part in the survey; 130 were male and three were female subjects. Age ranged from 18 to 65 years, mean age, 44.3 years. Thirty-eight workers (29%) were employed as manual laborers ("corn porters"), 39 (29%) as supervisors, 28 (21%) in maintenance or engineering, and 13 workers (10%) as cleaners. Fifteen workers (11%) had purely administrative responsibilities.

Grain exposure

It was not possible to measure grain-dust exposure directly for each category of occupation. Corn porters reported the most continuous exposure, but supervisors, maintenance staff, and cleaners were all liable to have significant exposure on occasions. Administrative staff were unlikely to experience high dust exposure at any time, although some of the staff had previously worked in areas in the grain store where exposure was higher.

Survey methods

All investigations were conducted on site at the grain terminal. All participants gave informed written consent.

Questionnaire. A computer-based questionnaire was used in this survey. The questions were administered directly to the subjects by a computer that also recorded the answers. With a program developed for the Commodore 8052 personal computer (Interact 3) (Bencard Allergy Units, Brentford, U.K.), a questionnaire was written consisting of 122 questions relating to cough, wheeze, and shortness of breath, and their allergic and occupational precipitants. Subjects were asked a stem question relating to each symptom.

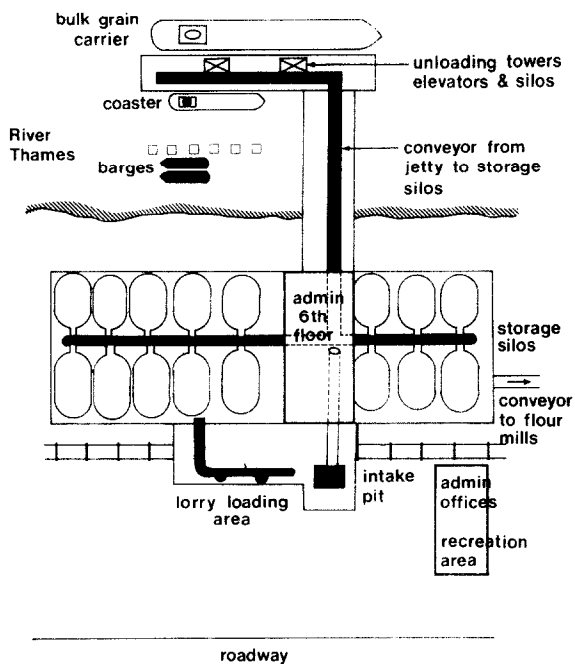


FIG. 1. Plan of the grain terminal.

Further details concerning each symptom were recorded only if a positive answer was received to the stem question. Internally inconsistent replies were eliminated (0.2% of all questions). Subjects who gave a history of more than one attack of cough, wheeze, or breathlessness within the last year were regarded as having current respiratory symptoms. Subjects who reported one or more of the above, and symptoms which deteriorated at work and improved away from work, at weekends, or holidays, were regarded as having WRSs.

The reproducibility of this questionnaire has been assessed in 75 grain workers tested on two occasions. Concordance (the proportion of identical responses on the two occasions) was 73% for cough attacks, 75% for attacks of wheezing, 80% for attacks of breathlessness, and 81% for WRSs.

The validity of the questionnaire has been assessed by correlation with objective measures of lung function. In this work force, there was a close correlation between all respiratory symptoms and FEV₁ as percent predicted ($p < 0.01$ for all symptoms). Attacks of wheeze and breathlessness, but not cough attacks, were also significantly correlated with PD₂₀ FEV₁ ($p < 0.001$ for both). The smoking history obtained from the computer questionnaire was compared with history obtained by direct interview in 75 subjects; concordance was 96.4%. Further evaluation of this questionnaire has been obtained from comparison of the responses made by normal subjects and subjects with asthma, and it has been demonstrated that almost all questions discriminate well between the two groups of subjects.¹³

Lung function. FEV₁ and FVC were recorded in all subjects in triplicate with a Vitalograph dry-bellows spirometer

TABLE I. Characteristics of study population in relation to WRS

	WRS positive (n = 43)	WRS negative (n = 90)
Age (yr)	43.12 ± 1.41	43.88 ± 1.11
Duration of employment (yr)	11.1 ± 0.92	9.46 ± 0.9
FEV ₁ , % predicted	94.5 ± 2.79*	110.8 ± 2.34
PD ₂₀ FEV ₁ †		
<8 µmol	13‡	11
>8 µmol	21	71
Smoking		
Current	30‡	36
Ex	7	6
Non	6	24
Occupational category		
CP	20	28
S/E	20	46
Admin	3	16

CP, Corn porter; S/E, supervisor/engineer; Admin, administrative.

*Significant difference between WRSs and no WRSs, $p < 0.01$.

†n = 116 (17 exclusions from methacholine challenge; 9 WRS positive, 8 WRS negative).

‡Significantly more prevalent positive WRSs than negative WRSs, $p < 0.01$.

(Vitalograph Medical Instrumentation, Bucks, U.K.). The highest value for FEV₁ and FVC was recorded in ambient temperature and pressure, saturated, and related to predicted values derived from regression equations as listed by Cotes.¹⁴ Mini-Wright portable peak flow meters (Clement Clarke International, Harlow, U.K.) were issued to all subjects with instructions in their use.

Methacholine provocation tests. Bronchial responsiveness to methacholine was measured with a standard tidal breathing technique¹⁵ with a De Vilbiss 646 nebulizer (DeVilbiss Co., Somerset, Pa.) driven by compressed air that delivered an output of 0.3866 ± 0.076 ml/min⁻¹. PD₂₀ was determined from this test. Subjects responding to 8 µmol of methacholine or less were regarded as having a level of hyperresponsiveness consistent with symptomatic asthma.¹⁶ Subjects were excluded from methacholine challenge if FEV₁ was >2 SD below the predicted value (n = 5), if they reported a respiratory infection within the last 4 weeks (n = 6), or if they reported severe intercurrent illness (n = 2). Four subjects refused methacholine challenge; all the methacholine challenges were performed in 116/133 participants.

SPTs. SPTs were performed according to the method of Pepys.¹⁷ Six commercial extracts of domestic inhalant allergens (DP, B2 grasses, *Aspergillus fumigatus*, house dust, cat, and dog) (Bencard Allergy Unit) were used. Phenol

saline was used as a negative control. SPT wheal areas were recorded as previously described.¹² Wheals with a diameter of 2 mm or more greater than the wheal of the control solution were regarded as positive, and subjects who had one or more positive SPTs to the above allergens were regarded as atopic.

SPTs with occupational allergens were performed in an identical manner with four commercial grain extracts (wheat, barley, maize, and rye) (Bencard Allergy), and extracts of SMs belonging to five species, *GDm*, *GDs*, *AF*, *AS*, and *TP*. One percent extracts of these five species and extracts of the culture medium on which they were grown were prepared as previously described.¹²

Total and specific IgE. Total IgE was measured with the Phadebas PRIST kit (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions. Allergen extracts for RAST to storage mites and *DP* were prepared, and allergen was coupled to CNBr-activated paper disks, as previously described.¹² Cord serum was used as a negative control and was included in each assay run and with each allergen disk type. The mean percent binding for cord serum was $0.35\% \pm 0.12\%$ (n = 63). Binding greater than the mean percent binding to cord serum plus two and one-half times the SD was accepted as indicating the presence of allergen-specific IgE (a positive RAST). In this survey, specific IgE was measured against all five species of SM individually.

Mite content. The mite content of stored grain was recorded by members of the Pest Infestation Control Laboratory of the Ministry of Agriculture, Cambridge, England. Samples of grain were taken from grain silos and the intake pit where U.K. grain was received. Moisture content of the grain was measured, and mite species were identified visually.

Bronchial challenge with extract of SM. One individual employed at the grain terminal agreed to attend the laboratory for specific bronchial challenge with SM extracts. An SM mix consisting of 1% extracts of *GD*, *AF*, and *TP* was prepared as described, dialyzed against phenol saline for 24 hours, and passed through a Millipore filter (Millipore Corp., Bedford, Mass.). SPTs with 0.01%, 0.1%, and 1% dilutions of this extract were performed in this subject as described above. The lowest concentration producing a 3 mm wheal was used as the starting concentration for bronchial challenge.

Recordings of FEV₁ and FVC were made, as described above, in triplicate. Allergen was nebulized according to a standard protocol with the Rosenthal-French dosimeter (The Johns Hopkins University, Baltimore, Md.).¹⁸ FEV₁ and FVC were recorded at 1.5, 5, and 10 minutes after each challenge until the maximum concentration was reached or PD₂₀. FEV₁ and FVC were recorded for 8 hours after challenge at 15-minute intervals. On a separate day, a placebo challenge was undertaken with phenol saline only. Baseline FEV₁ was within 15% on each occasion.

Statistical methods. Comparisons between proportions have been made with chi-square or Fishers exact test; cor-

TABLE II. Skin tests and specific IgE to mites in grain workers

Species	No. of positive SPTs	Geometric mean wheal area (mm ²)	No. of positive RAST	Correlation* coefficient
				DP vs SM
<i>GDs</i>	13	5.5	12	0.665†
<i>GDm</i>	12	4.7	12	0.532†
<i>TP</i>	21	5.72	21	0.689†
<i>AF</i>	4	—	15	0.582†
<i>AS</i>	20	5.11	9	0.617†
<i>DP</i>	39	6.9	30	—

*Correlation for RAST between each SM species and *DP*.† $p < 0.05$.

relation has been assessed with linear or ranking methods, depending on the distribution of the results.¹⁹ Odds ratios and their approximate 95% confidence limits have been calculated to display the relationship between factors influencing WRSs according to the method described by Fleiss.²⁰

RESULTS

Symptoms

Current WRSs, more than one attack of cough, wheeze, or breathlessness, improving away from work, at weekends, or holidays, as defined above, were reported by 43/133 subjects (33%) (Table I).

Sixty-six subjects were current cigarette, cigar, or pipe smokers or had smoked within the last year; 37 had not smoked for more than 1 year (exsmokers), and 30 subjects had smoked less than one cigarette a day and were lifelong nonsmokers.

Duration of employment in grain-storage occupations ranged from 5 weeks to 33 years (mean, 10 years). None of the workers surveyed reported significant occupational exposure to environmental hazards other than grain dust.

Spirometric tests

FEV₁ and FVC were both normally distributed in this work force with a mean value for FEV₁ of 105.5% predicted, and for FVC, of 100.1% predicted. There were five subjects with FEV₁ >2 SD below predicted values and six subjects with FVC below this limit.

Methacholine provocation testing

Seventeen subjects were excluded from methacholine provocation testing for the reasons presented above. Of the remaining subjects (116 subjects), 24 (21%) reacted to a methacholine dose of 8 µmol or less, 13 (11%) had PD₂₀ between 8 µmol and 32 µmol, and 79 subjects (68%) reacted only to doses of >32

µmol or did not react. The distribution of bronchial responsiveness to methacholine in relation to WRSs is illustrated in Table I.

Peak expiratory flow rate meters

Only 62% of the mini-Wright peak flow meters with diary cards were returned. This proportion is too low for adequate analysis and will not be considered further.

SPTs

One subject was excluded from skin prick testing because of severe intercurrent illness, and two subjects produced equivalent skin wheal responses to negative control and allergen solutions. These two subjects were considered to have dermatographism and were excluded from further analysis.

Thirty-nine subjects (30%) had a positive SPT to *DP*, 32 (25%) had a positive SPT to one or more extracts of SMs, and 13 subjects (10%) had a positive SPT to one or more grain extracts. Skin test responses to individual SM extracts are presented in Table II. Wheal diameters to at least one SM extract were >4 mm in 23/32 subjects with positive SPTs to one or more SMs, 3 to 4 mm in seven subjects, and 2 to 3 mm in two subjects.

Total and specific IgE

Total and specific IgE was measured in 128 subjects; five subjects refused venepuncture. Total IgE was significantly higher in atopic subjects and in subjects with WRSs than in nonatopic subjects and in subjects without WRS (Fig. 2).

Thirty subjects were positive to one or more SM species, and 29 subjects were positive to *DP*. The distribution of positive RAST to SMs and *DP* is presented in Table II.

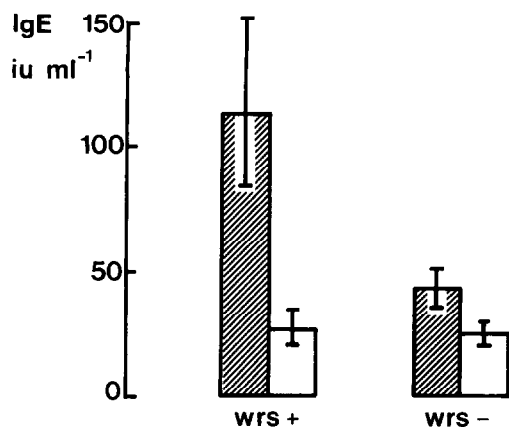


FIG. 2. Total IgE, atopy, and WRSs in grain workers, atopic (▨); nonatopic, (□).

There were 11 positive RAST to the culture medium on which the mites were grown. For 10 of these 11 sera, it was possible to measure RAST with medium-free mite extract as the allergen. (Mites largely free of medium were a gift of the Slough laboratory of the Ministry of Agriculture.) Only one subject demonstrated a negative RAST with this extract but a positive RAST with the crude extract. This subject may have been reacting simply to the culture medium, but his inclusion does not influence the results of the study.

Factors associated with WRSs

That subjects with WRSs were not different in age, employment duration, or category of occupation from subjects without WRSs is presented in Table I. Subjects were significantly more likely to be current cigarette smokers and to have increased bronchial reactivity to methacholine (PC_{20} , $<8 \mu\text{mol}$) than subjects without WRSs. FEV_1 was slightly but significantly lower in subjects with WRSs, although only five subjects (two with and three subjects without WRSs) had an FEV_1 >2 SD below predicted values.

The distribution of SPTs and RAST to environmental allergens in relation to WRSs demonstrated that positive SPT and RAST to SMs, but not *DP* or grain, were significantly more frequent in subjects with WRSs than in subjects without (Table III).²¹ Twenty-one subjects with WRSs had positive SPTs to one or more SM extract. In three subjects in whom SPT wheal diameter was 2 to 4 mm, RAST to SM extract was strongly positive. In the five subjects with positive SPTs to one or more SMs and negative WRSs, RAST to SMs was weakly positive to two and negative in three subjects.

Subjects with two or more positive RAST were significantly more likely to have WRSs (65.6%) than

TABLE III. WRSs in subjects with positive SPTs and RAST

	No.	% With* WRSs
Environmental allergen		
Positive SPT to		
>1 SM	32	65.6
<i>DP</i>	39	43.6
Grain	13	30.8
Positive RAST to		
>1 SM	30	50.0
<i>DP</i>	29	44.8

*Proportion of subjects with positive SPTs or RAST who had WRSs.

subjects with one positive RAST, only 21% of whom had WRSs.

Odds ratios for WRSs in relation to SM and *DP* skin tests and RAST, bronchial hyperresponsiveness to methacholine, and cigarette smoking are presented in Table IV. Where the lower 95% confidence limits are >1 , an association between the factors is implied.

Bronchial challenge with SM extract

One symptomatic subject agreed to attend the laboratory for bronchial provocation testing with SM extract. This subject developed a 28% fall in FEV_1 within 15 minutes of challenge with 0.1% extract, which returned to baseline during the next 2 to 3 hours (Fig. 3). There was no change in FEV_1 on challenge with placebo.

Mite contents

The analysis of mite contents of grain in storage silos and the intake pit (which was the receiving point for U.K. grain) is presented in Table V.

DISCUSSION

The present study confirms previous findings that a high prevalence of grain-store workers (33%) reported WRSs. As in previous surveys,² symptoms were significantly more common in current cigarette smokers and were associated with bronchial hyperresponsiveness to methacholine.³

A minor reduction in airway caliber (FEV_1) was also found in symptomatic grain workers, compared to grain workers without symptoms. It is unlikely that reduced airway caliber was itself responsible for the association between symptoms and bronchial hyperresponsiveness because all subjects tested with methacholine had normal lung function and because subjects

TABLE IV. Factors associated with WRSs—Odds ratios and 95% confidence limits

Factor	% With WRSs	Odds ratio	95% Confidence limits
Cigarette smoking	45.5	3.461*	1.494-17.97
Bronchial hyper-reactivity	54.1	7.574*	1.421-10.72
Positive skin test to storage mites (>1)	65.6	7.837*	3.297-32.44
Positive skin test to <i>DP</i>	43.6	2.251	0.947-17.89
Positive skin test to grain	30.8	1.286	0.765-12.32
Positive RAST to <i>GDm</i>	67.7	4.97*	1.239-31.02
Positive RAST to <i>GDs</i>	67.7	4.97*	1.239-31.02
Positive RAST to <i>TPs</i>	57.1	3.54*	1.227-21.69
Positive RAST to <i>AS</i>	77.8	8.65*	1.527-49.13
Positive RAST to <i>AF</i>	75	2.44	0.816-26.07
Positive RAST to <i>DP</i>	44.8	2.45	0.860-5.62

* $p < 0.05$ for association between factor and WRS.

with abnormal FEV₁ were excluded from methacholine challenge.

An alternative explanation for increased bronchial hyperresponsiveness in some symptomatic grain workers could be extrinsic allergic asthma. The findings reported above of increased total IgE and a higher prevalence of positive SPTs and IgE to SMs in grain workers with WRSs, as well as the presence of SMs in the occupational environment, support this conclusion. A positive response to specific bronchial challenge with SMs in one affected subject confirms that SMs do cause asthma in these workers. It is likely that a significant proportion of the affected grain workers in this survey had developed asthma because of occupational exposure to SMs.

Allergic responses to SMs have been widely reported in European, Scottish, and Canadian farm workers⁹⁻¹² who handle stored hay and grain. Surveys of grain-store workers, in contrast, have not, in general, found evidence of allergic asthma, and the prevalence of atopy is often lower than in matched control subjects.⁷ No other survey of grain-store workers has reported evidence of allergic responses to SMs.

Stored grain does contain other potential allergens, including grain itself and a wide variety of fungal spores.⁴ Allergic responses to grain have been reported

in grain workers²¹ and responses to fungal spores in farmers.²² The present survey provides no evidence that grain itself was an important allergen to these subjects. The prevalence of positive skin tests to grains was low, and these were not associated with WRSs. A detailed environmental survey of mold spores in the grain terminal and skin tests and RAST to the relevant antigens was beyond the resources of the present study; therefore, it remains possible that mold spores could be responsible for allergic symptoms in some grain workers. However, mold spore-induced asthma has only previously been reported in farm workers exposed to grain during the harvest.²² Stored hay and grain with a high water content is widely recognized as a cause of extrinsic allergic alveolitis rather than asthma²³ because of its contaminants.

If, as this study suggests, SMs are an important cause of occupational respiratory symptoms in grain-store workers, the failure of previous surveys to find evidence for the role of these mites requires explanation. It is likely that the higher moisture content of grain grown in the United Kingdom provides the answer. SM growth is dependent on humidity,²⁴ and indeed only grain grown in the United Kingdom was found to contain SMs; drier imported grain had none. A separate survey of farm workers in the United King-

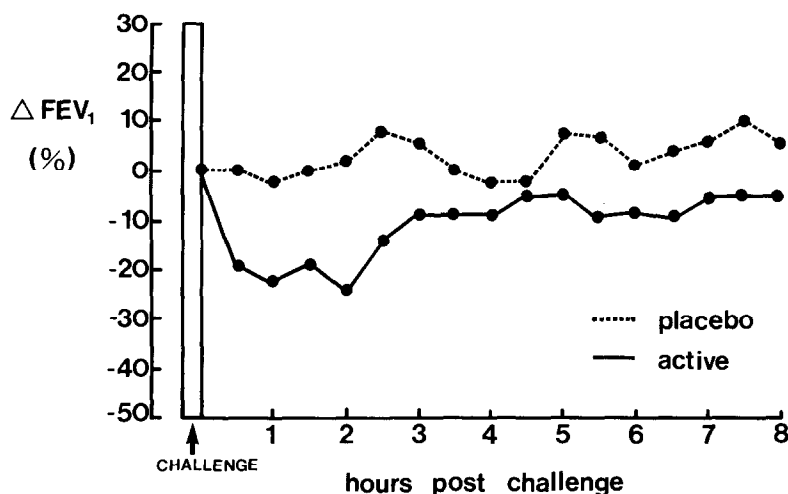


FIG. 3. Results of bronchial provocation testing with SM extract and placebo in a symptomatic grain worker.

TABLE V. Mite content of stored grain in the grain terminal

Grain	Site	Moisture content (%)	Mites found
Canadian DNS	Storage silo	12.5	None
Canadian wheat	Storage silo	13	None
U.K. grain	Loading bay	16	TP, AS
U.K. grain	Intake pit	16	GDs, Ch spp
Dust samples	Intake towers	—	None
	on quay		
Dust samples	Silo basement	—	TP, AF

DNS, Dark Northern Spring.

dom growing grain in the same area as the grain store also demonstrated a close relationship between occupational respiratory symptoms and specific IgE to SMs.¹²

The findings of the present study raises the possibility that respiratory symptoms in some U.K. grain workers may be preventable by reducing the SM population of stored grain, perhaps by reducing its water content before storage. This would obviously be of only limited value, if symptoms were perpetuated by a close relationship between allergens derived from SMs and allergens derived from the house dust mite, DP.

Information concerning allergen cross-reactivity between SMs and DP is limited.^{6, 25} In some surveys, as in the present survey, epidemiologic evidence suggests some degree of relationship in that significant correlations have been found between specific IgE binding to SMs and to DP. However, this could equally well be explained by the finding that positive skin tests and RAST to any allergen are more likely to occur in atopic subjects. Clearly, detailed immu-

nologic studies on selected subjects are required to evaluate relationship between allergens from SMs and DP. A study of RAST inhibition and cross-reactivity in some of the grain workers reported here has demonstrated that the relationship between allergens derived from DP and SMs is complex. Different degrees of RAST inhibition by DP, and different degrees of cross-reactivity, coexist in different subjects.²⁶

In conclusion, the present study has confirmed an association between respiratory symptoms in U.K. grain workers and cigarette smoking and bronchial hyperresponsiveness. Immunologic studies in the same subjects suggest that SMs may be responsible for occupational respiratory allergy in some of these grain workers. The higher water content of grain grown in the United Kingdom may account for the presence of SMs in U.K. grain, and it is possible that reducing the water content of stored grain may reduce the prevalence of occupational respiratory symptoms in U.K. grain workers.

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