STUDY OF THE PREVALENCE OF CHRONIC, NON-SPECIFIC LUNG DISEASE AND RELATED HEALTH PROBLEMS IN THE GRAIN HANDLING INDUSTRY

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BACKGROUND INFORMATION

"... Hence, whenever it is necessary to sift wheat and barley or other kinds of grain to be ground in the mill, or to measure it when corn-merchants convey it hither and thither, the men who sift and measure are so plagued by this kind of dust that when the work is finished they heap a thousand curses on their calling. The throat, lung, and eyes are keenly aware of serious damage; the throat is choked and dried up with dust, the pulmonary passages become coated with crust formed by the dust, and the result is a dry and obstinate cough; the eyes are much inflamed and watery; and almost all who make a living by sifting and measuring are short of breath and cachectic and rarely reach old age; in fact they are liable to lapse into orthopnea and finally dropsy. The dust moreover is so irritating that it excites intense itching over the whole body, of the sort that it is sometimes observed in nettle rash."

Thus, did Rammazini describe the health hazards of cereal grain workers in 1713[1]. Although pulmonary symptoms associated with exposure to grain dust have been known for centuries, the mechanism by which grain dust exerts its harmful effect is unknown. New insights into the nature and extent of the health problems created by grain dust have been provided by several epidemiologic[1-8] and clinical studies[9,11,12,14-23] of grain workers. The consequences of symptomatic, recurrent, long-term exposure, however, have not been established with certainty.

During exposure to grain dust up to 75 % of grain workers frequently experienced symptoms of cough, expectoration, wheezing, chest tightness, eye and nasal irritation[2-7]. From 6 to 33 % of grain workers also experienced one or more episodes of "grain fever" characterized by malaise, chills and fever occurring during or several hours following exposure[2-6]. With the exception of coughing and wheezing, which occurred significantly more frequently among smokers, these effects were independent of age, length of employment and smoking habits[6].

Symptoms of chronic respiratory disease were also common among grain workers[2-8]. These symptoms included persistent cough$^{27-40\%}$, phlegm$^{35-53\%}$, wheezing$^{14-31\%}$, or dyspnea on effort$^{16-46\%}$. Approximately one-third of the grain workers had chronic bronchitis or evidence[2-8] of airways obstruction as detected by spirometry. The MMF, $FEF_{25-75\%}$ were the most common abnormal individual tests of lung function, occurring in almost one-half of the workers who smoked and a quarter of the workers who had never smoked. Decreases in FEV_1 and FEV_1/FVC were found in approximately one-fourth of the workers who smoked and infrequently in workers who had never smoked. In all the studies reported, cigarette smoking was the predominant host factor in grain workers with obstructive lung disease. Moreover, the chronic bronchitis and chronic airways obstruction found in grain workers closely resembled that encountered in cigarette smokers. Because of the general lack of appropriately matched comparison populations in the reported epidemiologic studies, it is difficult to assess the contribution of grain dust to the obstructive lung disease seen in grain workers. The studies of Becklake[5], and more recent information by Dosman[9], and Broder[24] suggest that the effects of dust and smoking are additive, if not synergistic.

Grain dust is a complex mixture of husk particles, cellulose hairs and spikes, starch granules, spores of fungi, insect debris, pollens, rat hair, and approximately 5 % mineral particles[10]. The mean particle size of the airborne dusts may be less than 5m. Particles of this size can cause small airways and alveolar reactions, as well as upper airways injury.

In workers exposed to wheat dust a reduction in ventilatory capacity was observed within 30 minutes of starting work[11]. In addition, Warren, Cherniak and Tse[12] reported immediate and late asthmatic reactions in some subjects exposed to an inhalation challenge with grain dust extract. More recently, Chan-Yeung has confirmed these results and has further shown that disodium cromoglycate given before the challenge inhibited the immediate bronchial reaction; beclomethasone dipropionate failed to prevent the immediate bronchial reaction, but inhibited the late asthmatic reaction. Half of the workers studied had a marked degree of bronchial reactivity to methacholine. Chan-Yeung's findings[34] suggest that grain dust asthma may have an allergic basis. Results from several surveys[2,6] have shown that wheezing and abnormal lung function were more prevalent among atopic workers and workers with positive immediate skin tests to grain dusts. Thus, as with cigarette smoking, allergy and exposure to grain dust may operate as independent or interdependent factors in the development of respiratory disorders in grain workers. As in the case of grain workers[6], a survey of the general population in Arizona[13] revealed a significant correlation between wheezing in adults and cutaneous reactivity to a variety of common allergens, suggesting that atopic status might predispose the individual to the development of chronic obstructive airways disease[13]. Conversely, Gerard[8] demonstrated that non-atopic grain buyers who were nonsmokers from non-atopic families showed no increase in bronchial reactivity to extracts of cereal grains, their common fungal contaminants or histamine and are not likely to develop lung disease as a result of grain handling. However, evidence suggests that grain handlers are a self-selected group. The most sensitive individuals are likely to seek other employment early because of pulmonary symptoms.

Grain dust and its contaminants contain many allergens that are potent sensitizers in man[10,14-21]. Reactions to grain dust components have been described during many phases in the handling of grain, e.g., harvesting[22], local storage[17,19], grain elevators[4,6,12], and processed material[18,20,21]. In isolated instances, the agent in grain dust that was responsible for the reaction observed in individual workers appeared to be debris of a grain weevil (Sitophilus granarius)[15,16], a grain mite (Glycophagus destructor)[17], a specific fungus[14,19] or a specific component of grain (Appendix 23). In general, the role of these agents in the respiratory disease of grain workers is unknown.

Grain dust contains a wide variety of fungi and bacteria[25-27], including several species of Aspergillus, Penicillium, Mucor, Pullalaria and Thermophillic bacteria. These microbial agents can induce a variety of immunological reactions in the lung including a Type I (allergic) and a Type III (immune complex) reactions[14]. The clinical correlates of these reactions include asthma, allergic bronchopulmonary aspergillosis[28] and Farmer's Lung[29]. Except in isolated individuals, the immunological mechanism evoked by grain dust has not been identified. It was suggested[8] that grain fever is a Type III (immune complex) reaction similar to that seen in various forms of hypersensitivity pneumonitis. In the reported studies, hypersensitivity pneumonitis or its sequelae, chronic diffuse interstitial fibrosis of the type seen in Farmer's Lung, was not established with certainty. Also, doPico found no correlation between a history of grain fever and the presence of serum precipitins to fungi, grain or grain dust[6]. Whether or not hypersensitivity pneumonitis or its sequelae cause workers to leave the industry is unknown.

Emmanuel has described mycotoxicosis[30], a condition occurring in farmers exposed to massive concentrations of fungal spores. This syndrome resembles grain fever since there is no evidence of a Type III (immune complex) reaction and no chronic respiratory sequelae. Although the immunological mechanisms active in mycotoxicosis and grain fever are unknown, it was reported that airborne grain dusts activate complement by the alternative pathway, and that endotoxin can be recovered from all dust samples. Airborne grain dusts might be expected to elicit respiratory pathophysiology by a dose-dependent inflammatory response produced as a result of endotoxin or direct activation of the complement alternative pathway.

It is possible that grain dust may cause acute and chronic respiratory abnormalities by a direct irritant effect. Irritant receptors have been identified in the mucosa of bronchial airways[31]. Stimulation of these receptors in experimental animals with impulses going through the vagal pathways, led to hyperpnea and bronchoconstriction[32]. Vagal stimulation has also been shown to cause increased secretion of the bronchial mucous glands. It is thus conceivable that chronic non-specific stimulation of the bronchial irritant receptors by grain dust may lead to pathologic changes in the bronchial airways and mucous glands which are the basis for the chronic respiratory symptoms and abnormalities present in the majority of grain workers. The picture of chronic cough and phlegm, obstructive airways disease, episodes of tightness in the chest, fever and bronchial reactivity to grain dust extracts are similar to byssinosis and mill fever. Other similarities to byssinosis were observed such as airflow limitation in nonsmoking grain workers which appeared to be detectable at the level of the small airways[4,5]. This suggests that the target for inhaled grain dust may be similar to inhaled cigarette smoke or cotton dusts. The MZ phenotype with intermediate $alpha_1$-antitrypsin deficiency did not seem to be a significant host factor for the chronic obstructive lung disease found in grain workers[8].

No information is available concerning cumulative dust exposures or dose-response relationships in any of the reported studies. Dust concentrations inside grain elevators vary greatly. Available measurements of dust[2,5-7] varied from 10 mg/m3 in some of the modern elevators in Vancouver[7] to 600 mg/m3 in some elevators in Montreal[5]. The reason for the wide range of dust concentrations is unclear. However, the terminal elevators in Vancouver generally handle grain that has been partly cleaned during its transport from the prairies. There may also be qualitative differences in the types of grain handled by each elevator. These quantitative and qualitative differences probably account for the generally lower prevalence of respiratory disease and grain fever reported by Chan-Yeung[7,34].

Population at risk. The exact number of workers exposed to grain dust is unknown since so many occupations are involved including farmers, grain elevator operators in small and large terminal elevators and workers in flour, feed and seed mills. The total population at risk in Canada was estimated at 100,000[34]. In the United States there are an estimated 500,000 grain elevator workers. The proportion of the more than 2 million farmers at risk is unknown. However, Wan and Wright[35] analyzed disability data from a survey conducted by the Bureau of Census and reported that U.S. farmers and farm managers had the highest prevalence of disabling respiratory diseases of any occupational group--a rate of 21.8/100,000.

Grain dust has also been identified as a community air pollutant capable of causing epidemics of asthma[36,37].

STUDY I. HEALTH STATUS OF A CROSS SECTION OF GRAIN HANDLERS WITHIN A SINGLE GEOGRAPHIC AREA.

The health status of grain handlers was evaluated by comparing the prevalence and characteristics of clinical, physiological, immunological, radiological, serological blood and urine parameters of 310 grain handlers with 239 city services workers (named controls) from the same geographic area.

1. MATERIALS AND METHODS

Population

1a. Grain Handlers

The 310 grain handlers that were studied represented 78% of the 397 total available working and acceptable workers (Table 1) from eight elevator companies, of Wisconsin and Minnesota State grain inspectors, and Wisconsin and of Minnesota longshoremen. Grain handlers from the elevator companies were members of Local 118 of the Grain Millers Association, the longshoremen were members of the International Longshore Association (ILA) and the state inspectors were members of the American Federation of State, County and Municipal Employees (AFSCME).

Workers were notified and asked to participate in the study by fliers, posted notices, union stewards, and general meetings with investigators. The purpose of the study was explained verbally and in writing. The management of each company was notified, the studies were explained to them and all agreed to permit their workers to participate without loss of personal income.

Companies absorbed the cost of temporary decreased manpower. Overall, the elevator operations and productivity did not appear to be significantly altered due to proper scheduling and coverage. For the cross sectional study, subjects were considered acceptable to participate if they were year round workers (defined as 9-12 months per year for grain handlers or 8 months per year for longshoremen); had worked for longer than one year; and were working at the time of the survey. The longshoremen accepted were those identified by the shiploading manpower companies as grain shiploaders exclusively. Workers on sick leave were studied, when possible, but their data was not included in the comparisons of group data analysis. Workers who refused to participate (N=51) on the first contact were contacted at least once more. Approximately 50% of the workers who initially refused, agreed to participate on the second contact. Thirty-nine workers agreed to participate but later, for reasons beyond their control, did not. One woman was studied but the data were not included in the group analysis.

1b. City Workers (Control Workers)

For the comparison population (called control population), subjects were recruited from outside workers of the cities of Superior and Duluth and from the Power and Light Company of Duluth, Minnesota. The arrangements were made with the cooperation of the mayors of these cities, city management officials, management of the Power and Light Company, and union (AFSCME) representatives.

Eligible workers were those whose work day was spent on outdoor functions at least 50% of the time. The job classifications included: engineers and bridge operators, street maintenance, water and gas (maintenance, meter readers, etc.), parks and zoo maintenance, sewage and sanitation maintenance and operations, building maintenance, airport mechanics and operators. Three hundred and eighty-six of 478 eligible city workers (Table 2) were contacted and informed of the nature of the study by fliers, general meetings, posters, or by department supervisors. Initial refusals were recontacted by supervisors and/or project coordinators. Two hundred and thirty-nine consented to participate and were studied (Table 2). The differences between the total eligible (N=478) and non-contacted (N=92) were explained by sex, vacation or sick leave, departments or divisions where management preferred services not be disturbed, failure to contact. The differences between those contacted (N=386) and not tested (N=147) were mostly due to refusals. The 239 city workers represent 62% of the contacted workers. This lower participation among city workers as compared to grain handlers may be explained by lack of motivation or other factors. Age, height, weight and smoking habit information were obtained from the non-participant workers. Their mean age was 44 % 12 years, height 172.3 % 6.5 cm, weight 83.3 % 13 kg, 49% smokers, 31% ex-smokers and 20% nonsmokers.

The characteristics of the test and control populations are presented in Table 3. All city workers and 99% of the grain workers were white males. Among grain workers there were one black, one hispanic and two American Indians. Table 3b shows the level of education in both groups. The distribution of smoking habit, height and weight by age groups are presented in Tables 4a and 4b. The characteristics of the smoking habits are presented in Table 5. Past histories of occupational exposure to pulmonary irritants are shown in Table 6. Because the Superior-Duluth city service workers are exposed to environmental city contamination with small amounts of grain dust that could sensitize them, it was decided to study the skin reactivity to aero-allergens and grains in 100 city service workers from a city where no grain dust exposure is known to occur, i.e., Madison, WI. One-hundred and three male volunteers were studied from the Madison Gas and Electric Company. The mean age of this group was 38 % 10 years.

History
The history was obtained by a standard self-administered questionnaire (Appendix IV), reviewed for completeness by two trained interviewers who also assisted in the completion of the questionnaire when required. Additional histories were obtained by the physicians who reviewed the questionnaire and obtained a detailed history of grain fever and any other relevant health information.

Work history was filed using a job coding (Appendix III) which classified jobs by the type of hazard, site where job was performed and descriptive job title.

It became immediately apparent that not enough information could be obtained on grain fever because of the structure of questions Q46 and Q47. The answers to these two questions were therefore not entered in the workers files. Instead, an interpretation of the answers to questions 46 and 47 was made by the examining physician, with additional information as explained in Appendix V.

Examination
Physical examinations were performed by one of three physicians following a standard procedure for heart and lung auscultation and liver palpation (Appendix VII).

Pulmonary Function Studies
Pulmonary function studies were performed using standard equipment and following acceptable clinical procedures as described in Appendix VIII. Included were FEV_1, FVC, MMF, $Vmax_{50}$, $Vmax_{75}$, CV N2/L, D_{LCO}, V50HeO2 and VisoV. These tests were considered abnormal when: $FEV_1/FVC<70\%$; FEV_1 and D_{LCO} <80% of predicted; MMF, $Vmax_{50}$ and

$Vmax_{75}$<1.65 SD; and N2/L and CV <1.65 SD. (1.65 SD was chosen since the abnormality on these tests is undirectional.)

Immunologic Evaluation

a) Antigen preparation (Appendix X).

b) Immediate skin reactivity to common allergens: fungal antigens, mites, insects, grain extracts, airborne grain dust extracts and settled dust extracts were done by a prick test using commercial antigens or antigens prepared in our laboratory as explained in Appendix X and Appendix XI. These were considered positive if a wheal of 3 mm or greater developed 20 minutes following the prick.

c) Delayed hypersensitivity to PPD, mumps, Candida, Streptokinase-Streptodornase and Trichophyton was determined using commercially available antigens injected intradermally (.02 cc). Intradermal skin tests were considered positive when: PPD, 5TU was 10 mm or greater induration; SKSD, Trichophyton and Candida were 5 mm or greater induration and mumps 15 mm or greater erythema.

d) Serum precipitating antibodies were analyzed by techniques described in Appendix XII.

e) Immunoglobulins IgE, IgG, IgA and IgM were determined by techniques described in Appendix XIII.

Hemoglobulin, hematocrit, urinalysis and blood chemistries

Methods for the determination of pseudocholinesterase, serum SGPT, serum creatinine and gamma GT are described in Appendix IX and for $Alpha_1$-antitrypsin levels in Appendix XIII.

Chest Roentgenograms

Roentgenographic examinations of the chest complied with the specifications published in the Federal Registry, Vol. 28, No. 144, July 27, 1973. The posterior-anterior views were taken at Memorial Hospital, Radiology Department, Superior, Wisconsin. At the end of each testing day one of the principal investigators (GdP) reviewed all of the radiographs for quality and abnormalities that would require re-examination or recommendation to the patient of the need for further medical attention, e.g., bilaterial hilar adenopathy in subject #719. Workers with severe kyphoscoliosis or cardiomegaly would have been excluded in the group pulmonary function analysis. The PA chest roentgenographs were later read and interpreted independently by two physicians (a radiologist (M.E.P.) and a pulmonologist (H.D.). There was 95% agreement in the readings. The disagreements were on minor issues of questionable clinical or physiological significance, e.g., whether a single nodule was calcified or not, etc. When disagreements occurred, the roentgenographs were re-examined and the final readings agreed to by the two readers and a principal co-investigator (GdP.). The reading form for the chest roentgenograms is contained in Appendix XVI.

The levels of circulating immunoglobulins (G,A,M,E) were determined by the standard timed Mancini technique (Appendix IX) using frozen serum samples from 307 grain workers and 237 city services workers.

The reproducibility of the immunodiffusion system was insured by the following protocol: The same lot of immunodiffusion plates was used to test both grain workers and controls for IgG, IgA, IgM and IgE levels. Accuracy control (internal standard) was included on each plate and a three point protein reference curve was included on every third plate.

Quality control data indicated a 2.5% variation in the values of the internal control from plate to plate. Plots of the squared diameter of the precipitin rings (ordinate) obtained from the protein references against their respective concentrations (abscissa) on linear graph paper yielded an intercept ordinate of 11 % 2.5 mm3.

2. RESULTS

2a SYMPTOMS (ANALYSIS OF QUESTIONNAIRE)

The analysis of symptoms or symptom complexes was made with the following objectives in mind:

1) To determine if the prevalence of acute and chronic respiratory symptoms; eye, nose, throat, skin and joint symptoms; diseases or conditions diagnosed by a physician; and family histories of certain diseases among grain handlers were different than expected for people residing in the same geographic area with similar labor backgrounds, age, sex, smoking habits and socioeconomic status.

2) To determine the relative importance of the effects of cigarette smoking and grain handling on the prevalence of respiratory symptoms.

3) To determine if the prevalence of symptoms in grain handlers was related to job classification, place or length of employment.

4) To determine the prevalence and characteristics of the symptom complexes presented by grain handlers on exposure to grain dust and to pesticides.

5) To determine the relationship, if any, of acute and chronic symptoms with lung function or immunologic parameters of the individual (see Section I-2a b c Correlations).

Definitions

Determination of chronic bronchitis followed the currently accepted definition of chronic expectoration for two or more years. Using this definition the diagnosis of chronic bronchitis can be made from the answers to the questionnaire. The combination of answers that may represent this definition, however, has not been standardized We used primarily question 14E-- qreater than two years--as an indication of chronic bronchitis. In addition, we have used other combinations that may define the presence of chronic bronchitis and these are presented in Table 7.

Occupational asthma may be defined as wheezing and/or chest tightness when exposed to the working environment or the result of or aggravated by, exposure to the work environment. One may add to the definition: the association of cough and/or dyspnea also brought on or aggravated by exposure to the work environment, and/or the relief or improvement of these symptoms when away from work or when on vacation. Answers to questions that may be used to categorize four definitions of occupational asthma are explained in Table 8. Dyspnea on exertion. Grade 1: when hurrying on level ground or walking up a slight hill. Grade 2: when walking on level ground with people of own age. Grade 3: having to stop walking when walking on level ground at others pace. Grade 4: having to stop walking when walking at own pace.

Objective 1. (refer to Tables 9-11 and Appendix VI)

Overall respiratory symptoms and symptom complexes, as well as symptoms of eye, nasal and throat irritations on exposure to the working environment were higher among grain handlers than controls (Table 9 and Appendix VI). Personal histories of pulmonary, cardiovascular, kidney and liver disease, diabetes or dermatitis diagnosed by a doctor and a family history of pulmonary disease were similar in the two occupational groups (Tables 10 and 11).

Usual cough and expectoration (Q 13 and 14).

There were significant differences between grain workers and controls ($P \leq .001$) in the prevalence of cough and expectoration: first thing in the morning, at other times during the day, four to six times a day at least four days a week (Q 13 & 14 a,b,c), at least three months of the year and for greater than two years (Q13 & 14 d,e). Of the 194 that had some type of cough, 175 had it for more than two years. There were 116 who did not have "usual" cough. Two hundred and sixty-six of the 310 grain workers had some type of expectoration; 151 had it for more than two years. The prevalence of chronic bronchitis as defined in Table 8 was significantly higher among the grain workers than the controls. The prevalence of chronic bronchitis I was 46% in grain handlers and 18% among city workers. The incidence of chronic bronchitis was 35% in nonsmoking grain workers.

Cough and/or expectoration in relation to work (Q 15-18)

The cough or expectoration was worse on work days in a greater percentage of the grain workers (73%) than in controls (18%) ($P < .001$). Seventy-nine % of the controls noted no difference in cough or expectoration between work days and weekends. Only 27% of the grain workers noticed no difference between work days and weekends (Q 15).

Eighty-two % of grain workers felt their cough and/or phlegm was better on vacation (Q 16), whereas only 28% of controls reported improvements in cough or phlegm ($P < .01$).

Cough and/or expectoration brought on or aggravated by exposure to grain dust, other dusts, gases or fumes at work (Q 18) was also significantly higher among the grain workers than controls. The aggravation of cough and/or expectoration by barn dust was also higher among the grain workers than controls ($P < .001$). There was no difference in the prevalence of symptoms aggravated by house dust, weather or other factors.

Wheezing and/or chest tightness (Q 21-36).

The prevalence of wheezing and/or chest tightness (Q 21a) was higher ($P < .001$) in the grain workers (65%) than among controls (42%). These significant differences were also apparent in all smoking categories between grain workers and controls and between smokers and nonsmokers in both occupational categories. Note that 57% of the nonsmoker grain workers complained of wheezing and/or chest tightness.

The controls appeared to have a greater prevalence of "only wheezing" and "mainly wheezing" (Q 22) than the grain workers, who had a greater prevalence of "both wheezing and/or chest tightness." However, the prevalence of "only chest tightness" or "mainly chest tightness" was not different between the two occupational groups.

The onset of wheezing during 0-15 years of age was greater among controls than among grain workers. Among the other age groups the onset of wheezing was not significantly different (Q 23).

Wheezing and/or chest tightness related to work exposure.
The prevalence of wheezing at work while performing their job (Q 25) was higher among grain workers (82.5%) than among controls (50%) ($P < .001$). The average frequency of wheezing and/or chest tightness during work appeared to be higher among the grain workers than controls. The prevalence of wheezing "at least once a day" and "a few times a month" was significantly higher ($P < .001$) among the grain workers than controls. The prevalence of wheezing "a few times a week" was significantly higher among controls (26% vs. 21%) ($P < .05$). The prevalence of wheezing and/or chest tightness occurring "a few times a year" or "ever" was not different between the two occupational groups. It would appear that smokers in both groups (grain and controls) were more likely to have more frequent wheezing than the nonsmokers. That is, they were more likely to have it "daily" rather than "a few times a month." There was only a small percentage (5% of the grain workers and 14% of the controls) that had wheezing only "once."

Among the grain workers who had wheezing at work, 60% reported wheezing was usually worse any day of the week at work, 15% reported wheezing the first day of the work week and 25% claimed no difference between the first day or any day of the week. None of the grain workers felt worse on the weekend. Among the controls, 76% answered that the day of the week made no difference, 20% claimed that wheezing was worse any day at work and 4% reported wheezing on the first day of work. None of the controls answered that wheezing was worse on weekends (Q 27).

The prevalence of wheezing and chest tightness that was better while on vacation or off work was significantly different and higher in grain workers (88%) than controls (20%) ($P < .001$). Most of the controls (78%) felt that their wheezing remained the same on vacation or when not working ($P < .001$). There were two controls who felt worse on vacation.

The prevalence of occupational asthma, wheezing and/or chest tightness brought on or made worse by exposure to grain dust, other dusts, fumes or gases at work was significantly higher among grain workers than controls ($P < .001$). The differences were also significant between grain workers and controls in the three smoking categories. Significant differences were also observed when other combinations of questions were used to indicate occupational asthma (Table 8b).

Nocturnal dyspnea (Q 33)

The prevalence of wheezing (Q 33a) that awakened a subject from sleep was higher in grain workers (20%) than controls (10%). There was no difference in the prevalence of this symptom among the three smoking categories of each occupational group (Q 33a). The frequency of individual episodes of nocturnal wheezing (Q 33b) was not different between grain workers and controls.

Wheezing and/or chest tightness relation to time of the year (Q 34)

The prevalence of wheezing with no specific relation to the time of the year was similar in grain workers and controls. Controls who noticed seasonal variation reported the predominance of wheezing in January (28/40 or 70%). In the grain workers, the highest prevalence was found during January (32%) followed by April (16%), May (11%), June (11%), August and September.

Wheezing with dyspnea (Q 36)

The prevalence of attacks of wheezing with shortness of breath was higher among grain workers than controls ($P < 0.001$) (Q 36).

Dyspnea (Q 37-42)

The prevalence of ever having shortness of breath (Q 37), Grade 1 (Q 38) or Grade 2 (Q 39) dyspnea was significantly higher in grain workers than controls ($P < 0.001$, $P < 0.01$, $P < 0.05$, respectively). There were no differences for dyspnea on exertion for Grade 3 (Q 40) and Grade 4 (Q 41). The number of years they had shortness of breath was not different between the two occupational groups (Q 42).

Dyspnea while performing work (Q 43-44)

The prevalence of shortness of breath while performing work (Q 43) was higher in grain workers (36%) than controls (11%).

Chest illnesses (Q 63)

The frequency of chest illnesses and their interference with normal activities was similar in grain workers and controls (Q 63a, b).

Disease or conditions diagnosed by a doctor (Q 64-67)

Except for the prevalence of allergic rhinitis, which was higher in the controls than grain workers, the prevalence for the diseases or conditions indicated in Table 10 was not different between the groups.

Family history (immediate blood relatives) (Q 74)

The prevalence of lung diseases shown in Table 11 in blood relatives of the grain workers and controls were not different.

<u>Objective 2</u>

Role of cigarette smoking.

A. Analysis of prevalence of symptoms by smoking categories.

Considering that the proportion of smokers, ex-smokers and nonsmokers was similar in grain workers and controls, the significantly higher prevalence of respiratory symptoms in grain handlers must be due to a significant effect of grain handling independent of smoking. To confirm this assertion and further evaluate the effects and possible interaction of cigarette smoking on symptom prevalence, we compared and analyzed the prevalence of symptoms or symptom complexes between grain workers and controls for each smoking category and between smokers and ex-smokers, ex-smokers and non-smokers, and non-smokers and smokers for each occupational group. (Table 9 and Appendix XI).

The significant differences were analyzed by chi-square analysis. Overall the symptoms were more prevalent among grain workers than controls in every smoking category (Table 9). For example (Table 12), the prevalence of chronic bronchitis among grain workers who smoke was higher than controls who smoke (57% vs. 30%) (P < .001), and higher among nonsmoking grain workers than nonsmoking controls (35% vs. 10%) (P < .001). Actually the prevalence of chronic bronchitis in nonsmoking grain workers was higher (35%) than in controls (30%) who smoked.

The prevalence of "occupational asthma I" was also higher among grain workers who smoke (67%) than smoking controls (13%) and higher in nonsmoking grain workers (50%) than nonsmoking controls (11%). The prevalence of symptoms among nonsmoking grain workers was higher than among controls who smoke.

In grain workers, the prevalence of chronic cough and expectoration, chronic bronchitis, wheezing and/or chest tightness was higher in smokers than nonsmokers or ex-smokers, but there were no differences in symptoms between nonsmokers or ex-smokers. The prevalence of nocturnal wheezing, dyspnea on exertion and "chest illness" was not significantly different between smoking categories (Table 12).

In grain handlers the prevalence of wheezing and/or chest tightness and cough and/or expectoration on exposure to the work environment ("occupational asthma II") was significantly higher among smokers than nonsmokers and ex-smokers. The prevalence of dyspnea at work and grain fever was not different in smoking categories.

2b. A quantitative analysis of the relative effects of smoking and grain handling on symptom prevalence.

In order to quantitate the effects of smoking during grain dust exposures we analyzed the data using a log-linear model. We found that the effects of smoking and grain handling were both highly statistically significant and independent. Factors, or quantities, by which grain handling or smoking increased the odds (risk) of having a specific symptom or symptom complex are presented in Table 13. Overall, the effects of grain handling were greater than the effects of smoking. For example, the grain handler had four and a half times greater risk of having chronic bronchitis than a non-grain handler regardless of the smoking habit. Smoking, independent of grain handling, increased the odds of having chronic bronchitis by a factor of three. Grain handling also increased the odds of having occupational asthma II by a factor of five to 10, regardless of the smoking habit and smoking by a factor of three regardless of grain handling.

<u>Objective 3</u>

To study the effects of job categories and length and place of employment on symptom prevalence among grain handlers, we used logistic regression analysis adjusting for age, smoking habit and length of employment. Prevalence by smoking habits have been presented in Table 9 and by age groups in Table 14. Only eye and nasal symptoms were related to age. We found that wheezing, dyspnea, nasal symptoms on exposure to grain dust and usual cough first thing in the morning were positively related to length of employment (Table 15). Eye symptoms on exposure, chronic bronchitis as previously defined and grain fever were not related to length of employment (Table 15). In Table 15, the percent of prevalence was not adjusted for age or smoking. The P value indicates the significance of the relation between length of employment and prevalence of symptoms obtained from the used in the log-linear model adjusting for age and smoking. The job categories used in the analysis are presented in Table 16. Overall there were no significant differences in the prevalence of symptoms among the various job categories adjusting for age, smoking and length of employment (Table 17). Table 18 shows those symptoms in which there were significant differences in prevalence between jobs ranked using the z values from the regression analysis. We found the highest prevalence among weighers and longshoremen and the lowest among inspectors.

The prevalence of wheezing and dyspnea on exposure was significantly different among elevator companies, but other symptoms were not different (Table 19). We ranked the relative prevalence of symptoms adjusting for age, smoking, and length of employment among the companies from one to eight (Table 20). One corresponded to the company with the lowest prevalence; eight to the highest. The score value resulted from adding all the rank values for each symptom. Companies 1, 7, 5 and 4 appeared to have the highest prevalence, whereas 2 and 8 had the lowest. When we analyzed all other symptoms or symptom complexes and ranked them, we obtained similar results. The overall ranking, considering symptoms which were found to be significantly different or not found to be significantly different among the companies is indicated in parenthesis. The relatively more symptomatic populations appeared to be in companies 1, 7, 5 and 4 who had fewer symptoms than in companies 8 and 2.

Objective 4

The characteristics of the symptoms and symptom complexes (Table 9, 8, and Appendix VI) developed by the grain workers on exposure to grain dust were as follows:

Respiratory symptoms on exposure

Cough and/or expectoration brought on or aggravated by exposure to grain dust was present (Q 18a) in 200 of 310 grain workers or 65%, and it was significantly higher among smokers (75%) than nonsmokers (52%); the symptoms were equally prevalent among ex-smokers and nonsmokers. The grain dusts that were most likely to bring on or aggravate cough and/or expectoration were durum wheat (55%) and barley (48%). Next were spring wheat (25%), rye (27%) and oat (21%). Least likely were corn (4%), soybean (5%), sunflower and others (1.6%). The frequency of cough and/or expectoration on exposure to grain dust, regardless of the smoking category, was daily (77%), a few times a week (18%) and a few times a month or a few times a year (3.2%).

The frequency of wheezing at work was determined in grain workers.

Most subjects (59%) reported that wheezing occurred once a day, a few times a week or a few times each month; another 16% reported that wheezing occurred once a year.

Wheezing/or chest tightness brought on or made worse by exposure to grain dust was reported by 59% of the grain workers. Durum wheat and barley were reported to be the most common inducer of symptoms followed by spring wheat, rye and oats. The onset of wheezing and/or chest tightness was reported to occur: during work (70.5%), after work (11.5%) or during and after work (16%). Only three workers claimed wheezing before going to work. Of those who felt that wheezing started or got worse during work, 19% of 156 reported that it started immediately and 81% of 156 reported that wheezing started a few hours later. In the latter group, the workers reported that wheezing developed: 2 hours after starting work (42%), 4 hours after starting work (16%), the first hour of a work shift (14%) and 3 hours after starting work (14%). Only 6% of the workers felt the symptom develop during the fifth or sixth hour of work.

Some grain workers did report that wheezing and/or chest tightness occurred after the work shift. The symptom was likely to occur during the first hour after work (34%) or in the second hour (20%). However, some individuals had reactions 5, 6, 8, 9, 10 or more hours later.

Shortness of breath during or after exposure to grain dust was claimed by 49% of the grain workers. The prevalence of this symptom was higher among smokers than nonsmokers. The dusts that were most likely to bring on this symptom were durum wheat, barley, spring wheat, rye and oats. The dusts least likely to induce shortness of breath were soybean, corn, linseed, sunflower and beets. The workers reported that shortness of breath occurred: during work (82%), either during or after work (12%) or after work (6%). Of the subjects who reported shortness of breath at work, the onset occurred: 5 hours after starting work (66%), within 2 hours after starting work (50%) or immediately after starting work (33%). The few workers who developed shortness of this breath after work reportedly noticed it between one and three hours after work.

<u>Grain fever syndrome</u> (Table 21)
A detailed history was obtained on the 121 workers who reported fever and/or chills on exposure to grain dust. We concluded that a syndrome compatible with grain fever was present in 99 of the grain workers who complained of fever on exposure (82%). Although the history was questionable, an additional 16 workers may have had grain fever. In the remaining 6 workers, we could not exclude the possibility that the symptoms of grain fever were evoked by an upper respiratory tract viral infection or other infectious processes.

The prevalence of grain fever was similar in the three smoking categories. All subjects included in the grain fever group (N=115) had episodes of "a flu-like" syndrome with the sensation of fever, chills or chilliness, myalgia, arthralgias, malaise, warmth in the face with or without respiratory symptoms. Most of the workers (73%) recalled no associated respiratory symptoms with the grain fever and a smaller proportion of workers recalled cough, wheezing, or dyspnea associated with the grain fever. In subjects who developed respiratory symptoms, the symptoms developed during or after work and improved in a few hours or by the next working day. These episodes were usually associated with heavy exposure to grain dust on that day. In 96 of the 115 workers, the number of grain fever episodes was ascertained. Forty-two percent of the workers had fewer than 10 episodes, whereas a small number of workers (16%) reported numerous episodes (Table 21). Workers reported that the grain fever usually occurred during work (32%), after work (35%), or during and after work (33%). Most of the workers (83%) indicated that grain fever occurred on any day of the week, whereas 17% indicated that grain fever occurred the first day at work after a weekend or vacation. When grain fever occurred on the first day of work, the symptoms were usually worse.

Eye, nose and throat symptoms on exposure at work (Q 48a, b, c - Appendix XI)

Grain workers (98%) reported symptoms of eye irritation on exposure to grain dust. After exposure, grain workers also reported a stuffy nose (99%) or a sore throat (52%). Durum wheat and barley were the most likely inducers of these symptoms, followed by rye, spring wheat and oats.

Skin pruritus (Q49 - Appendix XI)

On exposure to grain dust, pruritis (itching of skin) was reported by 63% of the grain workers. The most common inducer of skin pruritis was barley, followed by wheat, oats and rye dust.

Health problems caused by pesticide exposure at work (Table 22)

One hundred and sixty-eight of the 294 grain workers who reported being exposed to pesticides at one time or another during their work life, reported health problems associated with pesticide exposure (Table 22). The most common symptoms were: headache (37%), dizziness (28%), weakness (21%), nausea (21%) and trouble breathing (16%). Blurred vision, stomach pains, diarrhea, fainting and cramps occurred in fewer than 5% of the workers. Nineteen of the 167 (11%) who answered Q 61 and Q 62 had to seek medical attention, and twenty-eight (17%) could not continue regular work assignments on the day of exposure. Exposure to phostoxin, carbon tetrachloride, malathion and methyl bromide were reported by the workers. There were, however, many instances in which the workers could not identify the pesticide. 72% had fewer than 10 symptomatic exposures to pesticides. A small number (16%) reported 20 to 100 symptomatic exposures to pesticides.

2a. RESULTS OF PHYSICAL EXAMINATION (Tables 23 and 24)

Physical examination revealed no chest configuration differences between grain workers and controls (Table 23). There was no significant difference between grain workers and controls in auscultation of the heart or in the presence of hepatomegaly. However, the liver was more frequently palpable in the grain workers than controls.

Auscultation of the chest detected rhonchi or wheezes diffuse or localized, in 43% of the grain workers and 16% of the city workers ($p < .005$). The differences were also significant in each smoking category (Table 24). Once again, one should notice that 35% of the nonsmokers among the grain handlers had expiratory wheezes.

There was no difference in the incidence of abnormal diastolic blood pressures in grain workers and controls. Thirty-nine (13%) grain workers and 25 (10%) controls had diastolic pressures higher than 90 mmHg; 4 (1%) grain workers and 6 (3%) controls had diastolic pressures above 100 mmHg. Systolic pressures above 150 mmHg were found in 8% of grain workers and 13% of controls.

CONCLUSIONS

1) Clinical findings

Grain handlers had a higher prevalence of respiratory symptoms and signs (rhonchi) than comparable non-grain handling city service workers from the same geographic area (Table 7-9, 12, 24) whether or not they smoked. The effects of grain handling on prevalence of respiratory symptoms were highly significant, independent and usually greater than those of smoking (Table 13). The prevalence of work related respiratory symptoms adjusted for age and smoking habit was also positively related to place (Tables 19, 20) and length of employment (Table 15). The data suggested variable environmental working conditions among elevators and perhaps an accumulative respiratory effect due to recurring exposures to grain dust.

Grain workers suffer from:

a) acute and chronic airways reactions (occupational asthma and chronic bronchitis) induced by exposure to grain dust with varying degrees of cough, expectoration, wheezing and/or chest tightness and shortness of breath. Durum wheat and barley grain dust were the most common inducers of symptoms. During the work shift, wheezing and/or chest tightness occurred immediately after starting work or within two hours. In late reactors, wheezing occurred within two hours after leaving work. Very late reactions were not reported.

Wheezing and dyspnea on exposure were related to length of employment. This may indicate either increased sensitization to the allergens present in the environment or the bronchial mucosa being rendered more hyperactive by the recurrent non-specific inflammatory reactions of the airways by grain dust. The place of employment was found to affect the prevalence of symptoms. The highest prevalence of symptoms were found in companies 1, 7, 5 and 4 and the lowest in companies 2 and 8.

b) A grain fever syndrome (Table 21) is characterized by a short-term febrile illness (flu-like syndrome) that may be associated with respiratory symptoms. It usually occurs during work or shortly after work. It is related to exposure to high concentrations of dust any day of the work week and not necessarily the first day at work or the first day of the week. There was, however, a small percentage of workers who had a single episode of grain fever the very first time at work and not again. The workers stated that in the last three years, because of the improvement in the working conditions, grain fever occurred less frequently. Some workers had grain fever a few hours after work, compatible with allergic pneumonitis. However, none of these episodes were severe enough to require medical attention, and we lack radiographic proof of allergic pneumonitis. Furthermore, the symptoms tended not to recur unless very high concentrations of dust were again present. Although we cannot deny that in some instances the grain fever syndrome may be a manifestation of allergic alveolitis, we have not found the typical history and radiographic changes of allergic alveolitis in these workers.

c) Acute recurrent conjunctivitis and rhinitis during exposure to grain dust occurred in most grain workers.

d) Skin pruritis occurred mostly on exposure to barley dust.

e) Pesticide exposure caused temporary disabling symptoms.

The long-term effects of recurrent symptomatic or asymptomatic exposures to pesticides are unknown. But we have encountered several former grain handlers with chronic neurological defects attributable to pesticide exposure.

Section I - Results 2b

2b. PULMONARY FUNCTION STUDIES

Lung function evaluations served the following purposes:

1) To determine if there was a difference in pulmonary function between grain handlers and people residing in the same geographic area with similar labor backgrounds, age, sex, smoking habits and socioeconomic status.

2) To determine the relative effects of cigarette smoking and grain handling on lung function.

3) To determine the prevalence of abnormal lung function and the patterns of dysfunction among grain handlers.

4) To determine if job category, place or length of employment had an effect on lung functions among grain handlers.

5) To determine the prevalence, if any, of abnormal lung function and patterns of dysfunction among grain handlers.

Objectives 1 and 2

The results of the pulmonary function studies by age and smoking groups are presented in Table 25 for the grain workers and Table 26 for the controls. The mean values for all lung functions (Table 27) were significantly different when grain handlers and city workers were compared by the unpaired t-test. There were no differences in the mean FEV_1 and FVC of workers tested either on the same day of exposure one or more than 2 days after the last exposure. MMF means were different ($P < .05$) between those tested the same day and those tested more than two days from the last exposure (Table 28).

The effects of grain handling, age, height and smoking habits on lung function were analyzed by multiple regression analyses (Table 29). Age had a significant effect on all lung functions except $Vmax_{50}$. The effects of grain handling were significant on all measures except CV. Smoking had an effect on all lung functions. The combined effects of grain handling and smoking were additive, but not synergistic when tested for interaction.

Objective 3

The prevalence of abnormal lung functions, except FVC, was higher among grain workers than controls using chi-square analysis (Table 30). Airway obstruction, defined as $FEV_1/FVC < 70\%$, was present in 16% of grain workers and 7% of control workers. If abnormal MMF, $Vmax_{50}$ and $Vmax_{75}$ are considered to indicate airways obstruction, then MMF detected airways obstruction as often as FEV_1/FVC, whereas, $Vmax_{50}$ and $Vmax_{75}$ detected a higher proportion of abnormalities in both grain workers and controls. Abnormality in the distribution of ventilation (CV, N2/L) may also reflect airways dysfunction but is affected by the parenchymal recoil status. Grain workers had a higher prevalence of abnormality in distribution of ventilation (CV, N2/L) than controls. N2/L, although it detected a higher percentage of workers with dysfunction than FEV_1/FVC, also detected a higher percentage of abnormalities among the controls. The prevalence of abnormal D_{LCO} was higher in controls than grain workers and higher in smoker controls than smoker grain workers. The percentage of abnormal function tests other than D_{LCO} in nonsmoker grain workers tended to be higher than that of nonsmoker controls, however, the differences were statistically significant only for MMF and $Vmax_{50}$. The prevalence of abnormal functions was consistently higher among smoking grain workers than non-workers and reached statistical significance for MMF, $Vmax_{50}$, $Vmax_{75}$, N2/L. More severe airways obstruction, indicated by an $FEV_1/FVC < 60\%$ was not more prevalent among grain handlers (4%) than among controls (3%) and there were only 3 grain and 3 control workers with FEV_1/FVC less than <50%.

To determine the relative importance of cigarette smoking and grain dust exposure on lung function, we analyzed the ratios of their regression coefficients from the regression analysis (Table 31). A ratio of 1 indicates that smoking and grain exposure had the same effect on lung function. Values greater than 1 indicate a greater effect of smoking. For example, smoking had a 44% greater effect on FEV_1 than grain handling. Smoking had a much greater effect on D_{lco} and CV whereas flows at low lung volumes were close to 1 or even lower. Hence, the effects of smoking were the same or greater than grain exposure for all lung functions except $Vmax_{50}$. The reasons for the latter are not clear.

In addition, to further quantitate the effects of smoking and grain dust exposure, we analyzed these data using a log-linear model. Both grain handling and smoking significantly and independently increased the odds of having airways obstruction by two and one-half times (odds factor = 2.6 for grain handling and 2.7 for smoking). That is, a grain handler had two and a half times greater risk of having airways obstruction than a non-grain handler regardless of their smoking habit. Smoking, independent of grain handling, also increased the odds of airways obstruction 2.5 times.

<u>Objective 4</u>

Lastly, to study the effects of type, place and length of employment, we also used multiple regression analysis to adjust for age and smoking. We found no significant differences in lung functions between the six job categories, places of employment and length of employment (Tables 32 and 33).

CONCLUSIONS

Grain dust exposure had an adverse effect on lung function (Tables 25-27, 29-31). The effects of grain dust on airways function was highly significant, and the overall effect was the same or of a smaller magnitude than that of smoking. Although there were more grain workers with mild airways obstruction than controls, moderately severe or severe airways obstruction was equally prevalent in both. The effect of grain handling appeared to be on the airways and not on the parenchyma. However, the high prevalence of abnormal N2/L which may reflect parenchymal injury needs further evaluation. There was no correlation between lung function and job category, place or length of employment (Tables 32 and 33).

Section I - Results 2c

2c. SKIN TESTS-IMMEDIATE HYPERSENSITIVITY

A. Analysis of Prevalence of Positive Reactions in the Grain Workers and Control from Duluth Metropolitan Area and Controls from the Madison, Wisconsin Area (Tables 34 and 35).

Common Allergens

The prevalence of positive skin tests to oak pollen or timothy grass in the grain handling population was lower than observed in the control population from the same geographic area. Moreover, the prevalence of 1 or more positive skin tests to common allergens was lower in the grain handling population (Tables 34 and 35) than in the Superior-Duluth city workers.

Superior-Duluth city workers had a higher prevalence of positive skin tests to oak pollen than Madison workers. Moreover, more of the subjects from the Superior-Duluth area had positive skin tests to 1 or more common allergens.

Conclusion

The lower prevalence of atopy in grain workers (1 or more positive skin tests) than city workers from the same geographic area suggests that the more "allergic" individuals tend to avoid the grain dust environment or leave the industry.

Fungal Antigens

There was a very low prevalence of positive skin tests reactions to fungal extracts. No differences were found between the occupational groups. However, the skin test reagents were not representative of the fungi and flora we found in the airborne dust of grain elevators (See Dr. Smalley's subcontract report).

Insects and Mites

There was a higher prevalence of skin test reactivity to mixed grain mites and mixed grain beetles in grain workers when compared to Duluth city workers. Skin test reactivity to grain beetles among the grain workers was higher than in the Madison workers.

Conclusion

As expected, a higher proportion of grain workers reacted to grain mites and insects commonly found to contaminate cereal grain. The prevalence of reactivity is similar to that we found in 1974 with common house insect extracts.

Grain Antigens

The prevalence of positive skin tests to whole grain antigens was low in the test and control populations. The prevalence of positive skin tests to small seeds was different when the city workers were compared to Madison workers or when the Madison workers were compared to grain workers. There was, however, no difference in skin test reactivity to small seeds when grain workers were compared to city workers.

Conclusions

The low prevalence of positive reactions may be due to low antigenicity of grain, extracts tested at sub-optimal concentrations, or the loss of antigenic components during extraction procedure.

Airborne Dust

The prevalence of positive skin tests to durum and spring wheat dusts was higher in the grain workers when compared to the city workers and the Madison workers. The city workers had a higher prevalence of positive reactions to durum wheat, corn, rye, oats and sunflower seeds when compared to Madison workers. The prevalence of the skin reactivity to barley was not different in the grain workers and city workers. However, the grain workers had a higher prevalence of skin test reactivity to barley than the Madison workers. When considering the prevalence of skin test reactions to one or more of the dust antigens, there was no difference between grain workers and city workers. There was, however, a significant difference between Duluth-Superior city workers and Madison workers. Similar differences were observed when the grain workers were compared to Madison workers.

Conclusions

The increased frequency in skin test reactivity to wheat dust extracts reflects the higher exposure of grain workers to wheat dusts. City workers, however, also seem to be exposed to environmental contamination with several types of grain dusts based upon comparisons with the Madison workers.

Settled Dust

The prevalence of skin test reactivity to settled dust was similar in grain worker and Duluth/Superior city workers but both were significantly higher than Madison workers.

B. Analysis of the Intensity and Degree of Skin Hypersensitivity in the Three Occupational Groups using the Total Sum of Wheal Reactions (Fig. 1).

Figure 1 presents the distribution of sums of all wheal reactions for each group of antigens. The mean wheal reaction for each group is indicated with a horizontal bar. The mean wheal reaction for common atopic allergens in control workers was greater than in grain workers. There were no significant differences in mean wheal reactions to the other antigens between the three occupational groups.

C. Prevalence of Grain Dust and Insect-Mite Reactivity among Atopic Grain Workers and Controls (Table 37).

The prevalence of skin reactions to grain dusts and insects or mites was significantly higher among atopic individuals (grain or control) than among non-atopic individuals.

Conclusions

Not surprisingly, atopic workers are more likely to become sensitized to antigens extracted from grain dust and the insects or mites which are commonly found in cereal grains.

2a, b, c RELATIONSHIPS BETWEEN SYMPTOMS, PULMONARY FUNCTIONS AND SKIN REACTIVITY.

2a, b. RELATIONSHIPS BETWEEN SYMPTOMS AND PULMONARY FUNCTION.

The relationships were analyzed by: i) multiple regression analyses using the lung function value as the dependent variable and selected independent variables: symptoms, symptoms complexes, age, height, and smoking habit; and ii) comparisons of abnormal lung function in symptomatic and asymptomatic grain workers.

i) Results of Multiple Regression Analysis

The relationships between acute and chronic symptoms or symptom complexes are presented in Table 38. There was a significant negative relationship between symptoms on exposure to grain dust and tests of ventilatory function (FEV_1/FVC, MMF, $Vmax_{50}$, $Vmax_{75}$). There was also a significant and negative relationship between chronic cough first thing in the morning and the FEV_1/FVC and MMF. Chronic bronchitis phlegm the first thing in the morning, wheezing at night, grain fever, and chest illness did not correlate with pulmonary functions as tested.

Among controls, there was a negative relationship between FEV^1/FVC and chronic bronchitis, wheezing at night and dyspnea on exertion.

ii) Results of Relationship between Symptoms and Abnormal Pulmonary Functions. The Prevalence of Abnormal Lung Function in Grain Workers with and without Selected Symptoms (Table 39).

A higher proportion of workers with chronic bronchitis had airways obstruction as measured by FEV_1, FVC, MMF and $Vmax_{50}$. A higher proportion of workers with respiratory symptoms (cough, wheezing or dyspnea) on exposure to grain dust had abnormal FEV_1/FVC, MMF, $Vmax_{50}$ and $Vmax_{75}$ N2/L and DL_{CO}. There was no correlation between the history of grain fever or wheezing at night and abnormal pulmonary function. Workers with dyspnea on exertion had a higher prevalence of abnormal FEV_1/FVC, MMF, $Vmax_{50}$, FVC and D_{LCO}.

Conclusions

Clinico-physiological correlation. Grain workers with symptoms on exposure to dust had lower values of ventilatory function than workers without symptoms on exposure regardless of smoking habits (Table 38, 39). This suggests that such symptomatic workers are at a higher risk of developing airways dysfunction and possibly non-specific bronchial hypereactivity. The prevalence of chronic bronchitis with airways obstruction was higher in grain workers than controls, regardless of smoking habits. In addition, chronic bronchitis with airways obstruction was related to length of employment. These findings suggest that chronic grain dust exposure may result in chronic obstructive pulmonary disease.

2b, c. RELATION BETWEEN PULMONARY FUNCTION AND SKIN TESTS.

This analysis was done by: i) multiple regression analysis adjusting for age, height and smoking habit (Tables 40a and 40b), and ii) comparing prevalence of abnormal lung function tests in positive and negative skin reactors (Table 41a and 41b).

i) Multiple Regression Analysis - Grain Workers.- (Table 40a).

There were negative relationships between the total mean wheal diameter for common allergens and grain dust antigens and FEV_1/FVC, FEV_1, FVC, MMF, $Vmax_{50}$ and $Vmax_{75}$. Using skin tests in the categorical way (positive or negative skin tests), there were also negative relationships between reactivity to common atopic allergens (CAA), airborne dust extract, durum wheat, fungi and settled dust extracts and FEV_1, MMF, $Vmax_{50}$ and $Vmax_{75}$ (Table 40a). We found no consistent relationship between reactivity to insects and mites, and barley or to one or more grain antigens and pulmonary function. There was no relationship between skin test reactivity and pulmonary function in the control group (Table 40b), except for vital capacity with total wheal for common allergens and total wheal for grain and grain dust antigens and with reactivity to barley, grain and settled dust antigens.

ii) The prevalence of abnormal lung function in positive and negative skin reactors is shown in Tables 41a-b. The prevalence of abnormal FEV_1/FVC, MMR, $Vmax_{50}$ and N2/L were not different between atopic and non-atopic grain workers or between reactors and non-reactors to insect and mite antigens. There was, however, a difference in the prevalence of abnormal lung functions in reactors and non-reactors to fungal antigens. An abnormal $Vmax_{50}$ was more prevalent in reactions to airborne grain dust. Among the controls (Table 41b), there were no significant differences between reactors and non-reactors.

Conclusions

The results of the regression analysis indicate that grain workers with atopy or skin reactivity to grain dust antigens are more likely to have lower lung function values than non-reactors to common allergens or grain dust antigens. The clinical significance of these findings is not clear since abnormal lung function is not more prevalent among atopic individuals or skin reactors.

2a, c. RELATIONSHIP BETWEEN SYMPTOMS AND SKIN REACTIVITY.

The relationship between the prevalence of symptoms on exposure to grain dust and chronic symptoms and skin reactivity to allergens are presented in Table 42.

The data demonstrated that: 1) dyspnea on exposure to grain dust was more frequent among those grain workers with positive skin reactivity to fungal antigens and to grain antigens, and 2) nasal symptoms on exposure to grain dust were more frequent among those workers with positive skin reactivity to grain antigens, barley and oats antigens. Overall, there were no significant correlations between acute symptoms on exposure to grain dust, chronic symptoms, grain fever, and symptom complexes and skin reactivity to common allergens or specific allergens.

Section I

2c. SKIN TESTS - DELAYED HYPERSENSITIVITY (Table 43).

There was no difference in the prevalence of positive PPD tests in grain workers and controls. The prevalence of skin reactions to candida and mumps was higher in city workers. Conversely, the prevalence of positive skin tests to Trichophytin and SK/SD was higher in grain workers. Overall, the prevalence of positive tests (2 or more of positive tests) was not significantly different between groups.

2d. SERUM PRECIPITATING ANTIBODIES

The prevalence of precipitins are shown in Table 44. City workers had a greater frequency of precipitins to Trichoderma, T. vulgaris (Greer or Hollisteir strains), T. sacchari or to one or more extracts (#1-33). Conversely, grain workers had a greater frequency of precipitins to durum wheat and rye. The grain workers also had an increased frequency of precipitins to airborne dusts from durum wheat, barley, rye, oats and sunflower seeds.

Relationships between Serum Precipitins and Pulmonary Function.

To evaluate the relationship, we used the prevalence of abnormal functions:

FEV_1/FVC ratio < 70%, $Vmax_{50}$ < 1.65 SD, N2/L > 1.65 SD and D_{LCO} < 80% in subjects with positive or negative precipitins to one or more of the following:

1) Fungal, bacterial, and pigeon sera antigens 1-33 (Table 44)
2) grain dust antigens labeled 42-52 (Table 44)
3) grain, grain dust, insects or mites 34-55 (Table 44)
4) Thermoactinomycetes #17-20 and #27-33 (Table 44)
5) Aspergillus fumigatus #5-10 (Table 44)

There was a significantly higher prevalence of airways obstruction (FEV_1/FVC < 70%) among grain handlers with precipitins to A. fumigatus. A higher prevalence of abnormal slope III or N2/L was observed in grain workers and controls with serum precipitins to one or more fungal antigens. There was no relationship between the presence of precipitins and abnormal $Vmax_{50}$, $Vmax_{75}$, MMF, and DL.

Relationship between Symptoms and Precipitins

The prevalence of symptoms on exposure or grain fever were not different in grain workers with or without precipitins as described above.

Conclusions

7) Serum precipitating antibodies. City workers had a greater prevalence of precipitins to Trichoderma, T. vulgaris, T. sacchari and to one or more fungi than grain workers (Table 44). Conversely, grain workers had a greater prevalence of precipitins to durum wheat, rye, and airborne dusts of wheat, barley, rye, oats and sunflower and to one of the settled dusts than controls. The larger prevalence of

precipitins to some grain dusts among grain workers was not surprising, yet they did not correlate with increased prevalence of symptoms or abnormal lung functions. Hence, the data infer that the respiratory reactions to grain dusts are not precipitin-mediated and that grain fever is not a manifestation of allergic alveolitis type III reaction. Serum precipitins reflect host response to antigens but not necessarily the presence of disease or abnormal pulmonary dysfunction. The reason for the greater prevalence of fungal precipitins among city workers is not clear.

Section I
2e RESULTS - BLOOD CHEMISTRIES, URINALYSIS, HEMOGLOBIN

The mean values for pseudocholinesterase , SGPT and creatinine were higher among grain workers (Table 45). The elevated values observed, however, were not high enough to indicate significant parenchymal liver disease. When the prevalence of abnormal values (larger than the highest range value for the laboratory) was considered, there was a difference only in GGT values.

Follow-up studies of abnormal liver function tests were attempted, but the returns from patients and physicians were not high. Hence, the data were inconclusive.

The presence of protein in urine was more frequent among grain workers when compared to controls.

Discussion - Liver Function Screening

SGPT

Alanine amino transferase (SGPT). The determination of SGPT is a sensitive indicator of minimal hepatocellular injury. Elevated levels may precede other evidence of viral hepatitis by several weeks. The levels may remain elevated following the return to normal of other laboratory parameters which are sensitive indicators of persistent hepatitis. Like other indices of necrosis, the transaminases are inferior to alkaline phosphatase and other cholestatic indicators in detecting infiltrative liver disease or cholestatic injury. The SGPT analysis contributes significantly to the differential diagnosis of hepatobiliary disease: as a general rule, levels greater than ten times the upper normal limits favor acute hepatic cellular injury, lesser elevations favor chronic cell injury, cholestasis or infiltrative liver disease. There are, however, a number of important exceptions. Alcoholic liver disease (severe, acute alcoholic hepatitis) is characterized by transaminase levels less than ten times normal. On the other hand, extremely high values (in excess of ten times normal) may occur in early cholestatic injury due to extra hepatic obstruction. Although the transaminases are sensitive indices of cell injury, the diagnostic accuracy of these determinations are limited by a lack of a specificity. SGPT is widely distributed in the body, but it is predominantly confined to the liver making it more specific than SGOT.

GGT

Gamma glutamyl transpeptidase (GGT) predominates in renal and hepatobiliary tract tissue and was shown by histochemical methods to be located in the endothelial cells of a variety of tissues. However, serum GGT it is believed to originate in the hepatobiliary system. It is regarded as the most sensitive of the cholestatic indicators but has also been reported to be significantly elevated in virtually all hepatocellular conditions, especially in alcoholic liver disease and infiltrative hepatobiliary disease. Since GGT is absent from bone and placenta tissue, children, adolescents, pregnant patients and patients with bone disease show normal or only slightly elevated GGT values. A number of reports demonstrated that GGT was elevated in neurological disease, post-myocardial infarction, alcoholic patients without other evidence of liver disease and patients receiving enzyme-inducing drugs (e.g., anticonvulsants). This suggests that the elevated GGT levels should be interpreted with caution. As with SGPT, slightly elevated levels (i.e., slightly above the range of normal) are less organ specific than high abnormal values, but other organ parenchymal reactions cannot be excluded from consideration. For the purpose of screening for liver disease, the values did not reach levels (ï500) which were indicative of liver disease. Abnormal or elevated GGT values were found in 64 or (21%) of the grain workers and 31 (13%) of the controls. The elevated gamma GT rarely correlated with elevated SGPT or cholinesterase.

Cholinesterase may be an indicator of chronic liver disease but few abnormal values were found in this study. The frequency of abnormal values was not different in grain workers and controls.

CONCLUSION

We did not detect significant differences in the frequency of overt liver disease between grain workers and controls. We used three screening methods to detect liver disease. The questionnaire included a question: "has a physician ever diagnosed liver disease in the patient?" There was no significant difference in the answer to this question between grain workers and controls. Second, in the physical examination the presence of hepatomegaly was determined. There was no significant difference between the two groups, although the prevalence of a palpable liver was different between the two groups. Third, the serum enzymes (SGPT< GT and cholinesterase were not abnormal in the grain workers or controls).

Although the findings are inconclusive, we did find a higher number of abnormal values for GGT, a higher mean value of SSPT, and more palpable livers among grain workers. Since grain workers are occasionally exposed to hepatotoxic grain fumigants we recommend further prospective studies on the potential hepatotoxicity of grain fumigant exposure.

Renal function screening

There were few abnormal creatinine levels (Table 45) in grain workers and controls, but the mean value (t-test) was significantly higher among grain workers than controls (Table 46). The urinalysis revealed no differences in the frequency of blood, glucose and protein the urine when grain workers were compared to city workers. There was, however, a higher percentage of grain workers with a trace of protein in the urine.

CONCLUSION

II) Renal disease screening. The results of the renal function screening tests were inconclusive (Tables 45, 46). We would recommend further prospective studies on the potential renal morbidity of pesticide exposure.

Hemoglobin - hematocrit

The hemoglobin was evaluated: 1) to detect the presence of polycythemia or anemia and 2) for correction of diffusion values if necessary. We found no significant abnormalities in either occupational group.

RESULTS

2f RADIOLOGICAL FINDINGS

The chest-roentgenogram changes found in grain workers and controls are shown in Table 47. The prevalence of abnormal findings was small and most changes, with a few exceptions, were of minor clinical significance. One control subject showed bilateral hilar adenopathies compatible with lymphoma or sarcoidosis. Another control had evidence of coronary bypass surgery and a third subject had a questionable paratracheal node (which in re-examination with other views could not be delineated). Among the grain workers there were three workers with small blebs, one with marked hyperinflation compatible with emphysema, one with a rib resection from a negative exploratory thoracotomy and a worker with bilateral calcified pleura thickening. The apical thickening and costophrenic angle pleural thickening was minimal. There were no cases with diffuse bilateral interstitial infiltration or fibrosis. Old healed rib fractures, degenerative changes of the thoracic spine, basilar bands of fibrosis or plate atelectasis were more commonly seen among grain workers.

Conclusion

Grain dust exposure does not appear to be associated with any specific roentgenographic abnormality.

2g. Immunoglobulin Levels

The levels of IgG and IgA observed in grain workers differed significantly from the city workers (Table 48), whereas the levels of IgM were similar in both groups. Since it was conceivable that differences in age, smoking habit, place of employment or length of employment introduced an inherent bias into the data, the test and control groups were further subdivided.

Table 49 shows the immunoglobulin levels when the test group (grain workers) and controls (city workers) were grouped on the basis of smoking habits. The levels of IgG were significantly higher in the grain workers when compared to city workers in each of the three smoking habit categories. Hence, the data suggest that the increased levels of IgG observed in the grain workers were not a reflection of smoking habit. Conversely, only ex-smoking and nonsmoking grain workers demonstrated elevated serum IgA levels when compared to control values. The data suggest that grain dust normally enhances the levels of serum IgA but that the response was blunted by smoking.